A

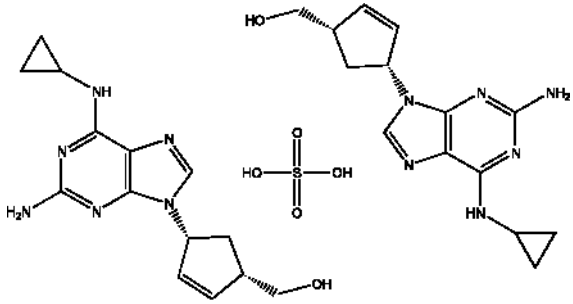
ABACAVIR SULFATE

Therapeutic Function: Antiviral

Chemical Name: 2-Cyclopentene-1-methanol, 4-(2-amino-6-(cyclopropylamino-9H-purin-9-yl), sulfate (salt) (2:1), (1S,4R), sulfate

Common Name: Abacavir sulfate

Structural Formula:



Chemical Abstracts Registry No.: 188062-50-2; 136470-78-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Ziagen	GlaxoSmithKline	-	-
Ziagen	Glaxo Wellcome	-	-
Ziagenavir	Glaxo Wellcome	-	-

Raw Materials

2,5-Diamino-4,6-dihydroxypyrimidine
(Chloromethylene)dimethylammonium chloride
(1S,4R)-4-Amino-2-cyclopentene-1-methanol
Triethylamine
Tartaric acid, dibenzoate, (-)-
Orthoformate or diethoxymethyl acetate
Cyclopropylamine

Manufacturing Process

Treatment of 2,5-diamino-4,6-dihydroxypyrimidine (I) with (chloromethylene)dimethylammonium chloride yielded the dichloropyrimidine with both amino groups derivatized as amidines. Partial hydrolysis with aqueous HCl in hot ethanol gave N-(2-amino-4,6-dichloro-pyrimidin-5-yl)-N,N-dimethylformamidene (II). Subseqent buffered hydrolysis at pH 3.2 yielded the (2-amino-4,6-dichloro-pyrimididin-5-ylamino)acetaldehyde (III). Condensation chloropyrimidine (III) with (1S,4R)-4-amino-2-cyclopentene-1-methanol (IV) in the presence of triethylamine and NaOH gave [2-amino-4-chloro-6-(4-hydroxymethyl-cyclopent-2-enylamino)pyrimidin-5-ylamino]-acetaldehyde (V). The correct enantiomer (IV) of racemic aminocyclopentene was obtained by resolution of diastereomeric salts with D-dibenzoyltartaric acid. Cyclization of (V) to the corresponding purine was accomplished with refluxing triethyl orthoformate or diethoxymethyl acetate to give nucleoside analogue [4-(2-amino-6-chloro-purin-9-yl)-cyclopent-2-enyl]methanol (VI). Displacement of chloride in the purine nucleus with cyclopropyl amine in refluxing butanol afforded abacavir. The structure of obtained compound was confirmed by 1H NMR method and elemental analysis.

In practice it is usually used as sulfate salt.

References

Huff J.R.; Bioorg. Med. Chem., 7, (1999), 2667-2669
Daluga S.M.; European Patent No. 0,434,450; Dec. 12, 1990

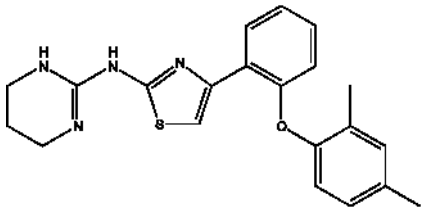
ABAFUNGIN

Therapeutic Function: Antibacterial, Antifungal

Chemical Name: N-{4-[2-(2,4-Dimethylphenoxy)phenyl]thiazol-2-yl}-1,4,5,6-tetrahydro-pyrimidinamine

Common Name: Abafungin; BAY w 6341

Structural Formula:



Chemical Abstracts Registry No.: 129639-79-8

Trade Name	Manufacturer	Country	Year Introduced
Abafungin	York Pharma	-	-

Raw Materials

N-(1,4,5,6-Tetrahydropyrimidinyl)thiourea
2-(2,4-Dimethylphenoxy)phenacyl chloride

Manufacturing Process

15.8 g (0.12 mole) N-(1,4,5,6-tetrahydropyrimidinyl)thiourea were added to 27.45 g (0.1 mole) 2-(2,4-dimethylphenoxy)phenacyl chloride in 100 ml acetone and heated to reflux for 2 hours. On cooling the falling out product was filtered off, washed with acetone and dried. N-[4-[2-(2,4-Dimethylphenoxy)phenyl]-2-thiazolyl]-1,4,5,6-tetrahydro-2-pyrimidinamine hydrochloride was prepared. Yield 91.4%; MP: 160°C.

20.72 g (0.05 mole) above product was stirred with 300 ml 1 N sodium hydroxide for 30 minutes at room temperature. The insoluble product was filtered off, washed and dried. Yield of N-[4-[2-(2,4-dimethylphenoxy)phenyl]-2-thiazolyl]-1,4,5,6-tetrahydro-2-pyrimidinamine was 16.2 g (86%). MP: 191°-192°C.

References

Ippen. Joachim et al.; D.B. Patent No. 3,836,161 A1; Nov. 24, 1988; Bayer AG, 5090 Leverkusen, DE

ABAMECTIN

Therapeutic Function: Antiparasitic

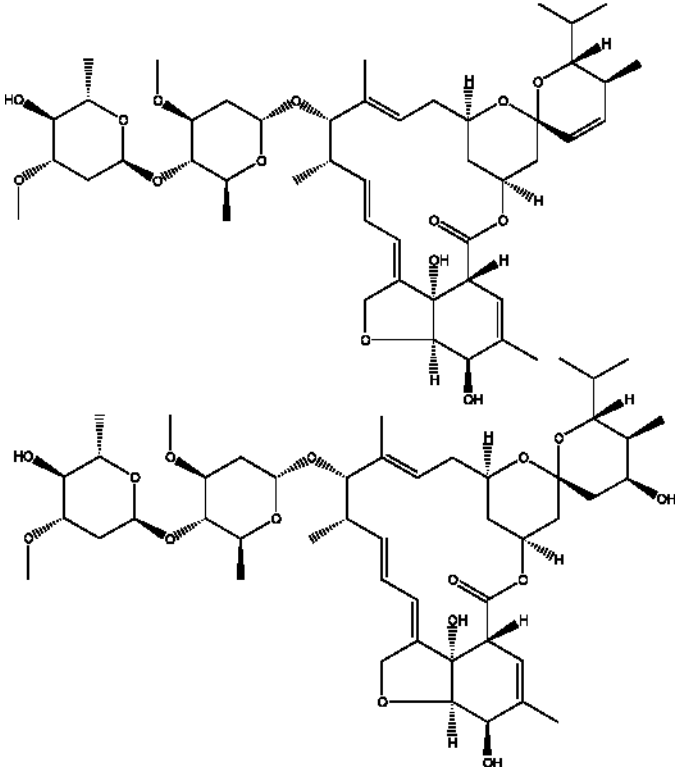
Chemical Name: Avermectin B_1

Common Name: Abamectin; MK-936, Zectin

Chemical Abstracts Registry No.: 71751-41-2; 65195-55-3

Trade Name	Manufacturer	Country	Year Introduced
Abamectin	Yellow River Enterprise Co. (a.k.a Yelori)	-	-
Kraft TM	Cheminova	-	-
Abamectin 1.8%	LIFES Labo	-	-
Abamectin	Ningbo Sega Chemical Company	-	-
Avomec	Institutul Pasteur Romania	-	-
Duotin	Merial	-	-
Enzec	Merck Sharp and Dohme Ltd	-	-

Structural Formula:



Raw Materials

Streptomyces avermitilis MA-4680
Nutrient medium

Manufacturing Process

1. The contents of a lyophilized tube of Streptomyces avermitilis MA-4680 is transferred aseptically to a 250 ml Erlenmeyer flask containing 305 ml of Medium 1: Dextrose 20 g, Peptone 5 g, Meat Extract 5 g, Primary Yeast 3 g, NaCl 5 g, $CaCO_3$ (after pH adjustment) 3 g, Distilled water 1000 ml, pH 7.0. The inoculated flask is incubated for 3 days at 28°C on a rotary shaking machine at a speed of 220 RPM in a 2 inch radius circular orbit. At the end of this time, a 250 ml Erlenmeyer flask containing 50 ml of Medium 2 [Tomato Paste 20 g, Modified Starch (CPC) 20 g, Primary Yeast 10 g, $CoCl_2 \cdot 6H_2O$ 0.005 g, Distilled water 1000 ml, pH 7.2-7.4] is inoculated with a 2 ml sample from the first flask. This flask is incubated for 3 days at 28°C on a rotary shaking machine at a speed of 220 RPM in a 2 inch diameter circular orbit. 50 Ml of the resulting fermentation broth containing C-076 is effective against an N.dubius infection in mice.

2. A lyophilized tube of Streptomyces avermitilis MA-4680 is opened aseptically and the contents suspended in 50 ml of Medium 1 in a 250 ml Erlenmeyer flask. This flask is shaken for 3 days at 28°C on a rotary shaking machine 220 RPM with a 2 inch diameter circular orbit. A 0.2 ml portion of this seed medium is used to inoculate a Slant of Medium 3: Dextrose 10.0 g , Bacto Asparagine 0.5 g, K_2HPO_4 40.5 g, Bacto Agar 15.0 g , Distilled water 1000 ml, pH 7.0. The inoculated slant medium is incubated at 28°C for 10 days and stored at 4°C until used to inoculate 4 more slants of Medium 3. These slants are incubated in the dark for 8 days. One of these slants is used to inoculate 3 baffled 250 ml Erlenmeyer flasks containing 50 ml of No. 4 Seed Medium: Soluble Starch 10.0 g, Ardamine 5.0 g, NZ Amine E 5.0 g, Beef Extract 3.0 g, $MgSO_4 \cdot 7H_2O$ 0.5 g, Cerelose 1.0 g, Na_2HPO_4 0.190 g, KH_2PO_4 182 g, $CaCO_3$ 0.5 g, Distilled water 1000 ml, pH 7.0-7.2. The seed flasks are shaken for 2 days at 27-28°C on a rotary shaking machine at 220 RPM with a 2 inch diameter circular orbit. The contents of these flasks are pooled and used to inoculate (5% inoculum) baffled 250 ml Erlenmeyer flasks containing 40 ml of various production media. Flasks containing media 2, 5 and 6 are incubated for 4 days at 28°C on a rotary shaking machine at 220 RPM with a 2 inch diameter circular orbit. The resulting broth containing C-076 is then harvested and tested for anthelmintic activity. In all cases 6.2 ml of whole broth and the solids obtained from centrifuging 25 ml of whole broth are fully active against N.dubius helminth infections in mice.

3. The one of the four slants of Medium 3 prepared as in Example 2 is used to inoculate a baffled 250 ml Erlenmeyer flask containing 50 ml of Seed Medium No. 4. The seed flask is shaken for 1 day at 27- 28°C on a rotary shaking machine at 220 RPM with a 2 inch diameter circular orbit. The seed flask is then stored stationary at 4°C until it is ready to be used. The contents of this flask are then used to inoculate (5% inoculum) 20 unbaffled 250 ml Erlenmeyer flasks containing 40 ml of Medium No. 2. After 4 days incubation at 28°C on a rotary shaking machine at 220 RPM with a 2 inch diameter circular orbit, 19 of the flasks are harvested and pooled. The combined fermentation broths

containing C-076 are filtered affording 500 ml of filtrate and 84 g of mycelia. 78 G of mycelia are extracted with 150 ml of acetone for ½ hour with stirring and the mixture filtered. The filter cake is washed with 50 ml of acetone and the filtrate and washings are combined and concentrated to 46.5 ml 30 Ml of the concentrate is adjusted to pH 4 with dilute hydrochloric acid and extracted 3 times with 30 ml portions of chloroform. The extracts are dried by filtering through dry Infusorial Earth (Super-Cel) combined and concentrated to dryness in vacuum. The oily residue of C-076 weighing 91.4 mg is dissolved in chloroform sufficient to make 3 ml of solution which represents 1% of broth volume. The C-076 (Abamectin) obtained in this recovery procedure is fully active against N.dubius infections in mice. In addition, the chloroform extraction achieved a 70 fold purification of C-076 from the whole broth.

References

Albers-Schonberg G., Wallick H., Ormond R.E., Miller Thomas W., Burg Richard W.; US Patent No. 4,310,519; Jan. 12, 1982; Assigned to Merck and Co., Inc. (Rahway, NJ)

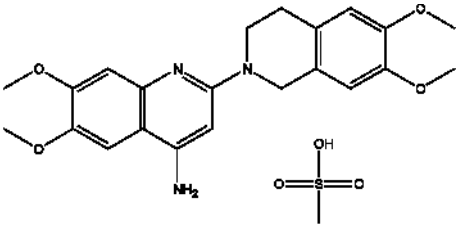
ABANOQUIL MESYLATE

Therapeutic Function: Antiarrhythmic, Coronary vasodilator

Chemical Name: 4-Amino, 2-(3,4-dihydro-6,7-dimethoxy-2(1H)-isoquinolyl)-6,7- dimethoxyquinoline monomethanesulfonate

Common Name: Abanoquil mesylate

Structural Formula:



Chemical Abstracts Registry No.: 118931-00-3; 90402-40-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Abanquil	Onbio Inc.	-	-

Raw Materials

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline
Acetic anhydride
Phosphorus(V) oxychloride
2-Amino-4,5-dimethoxybenzonitrile
Sodium hydroxide
Zinc chloride
Fumaric acid

Manufacturing Process

Synthesis of 1-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)ethanone:

To a stirred solution of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3.00 g, 15.4 mmol, 1.00 equiv.) in anhydrous pyridine (100 mL) under argon at room temperature was added acetic anhydride (14.5 mL, 154 mmol, 10.0 equiv.) over 15 min. The resulting mixture was stirred at room temperature for 2 h, and then at reflux for 6 h. The volatiles were removed by rotary evaporation at 80°C under high vacuum. The residue was flash chromatographed on silica gel (MeOH-CH_2Cl_2 8:92) to afford 3.21 g (89%) of 1-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)ethanone as a viscous brown oil. The H-NMR spectrum reflected the presence of two slowly interconverting conformers in a ratio of 1.2:1 at room temperature.

Synthesis of 2-[1-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)ethylidineamino]-4,5-dimethoxybenzonitrile:

To a stirred solution of 1-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)ethanone (1.00 g, 4.25 mmol, 1.00 equiv.) in $CHCl_3$ at room temperature under argon was added $POCl_3$ (143 µL, 1.53 mmol, 0.36 equiv.). After 10 min, 2-amino-4,5-dimethoxybenzonitrile (763 mg, 4.28 mmol, 1.01 equiv.) was added and the mixture was heated at reflux overnight. The mixture was cooled to room temperature and poured into 1 M aq. NaOH solution (50 mL), and the aqueous phase was extracted with CH_2Cl_2. The combined organic solutions were dried over MgSO4 and concentrated. The residue was flash chromatographed on silica gel (MeOH-CH_2Cl_2, 2 5:95) to afford 482 mg (28%) of 2-[1-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)ethylidineamino]-4,5-dimethoxybenzonitrile as an yellow solid.

Synthesis of 2-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-6,7-dimethoxyquinolin-4-ylamine hemifumarate hydrate (abanoquil):

To a stirred solution of 2-[1-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)ethylidineamino]-4,5-dimethoxybenzonitrile (471 mg, 1.19 mmol, 1.00 equiv.) in refluxing anhydrous N,N-dimethylacetamide (24 mL) under argon was added $ZnCl_2$ (339 mg, 2.49 mmol, 2.10 equiv.) in three portions over 1 h. The solvent was removed by distillation at 70°C under high vacuum. Ether (40 mL) was added to the residue, which was broken up with a stirring rod, and the mixture was stirred at 0°C to precipitate the product. The supernatant was discarded, and the precipitate was washed twice more at 0°C with ether. The solid residue was stirred with 1 M aq. NaOH (25 mL) and CH_2Cl_2 (25 mL) for 10 min, and the aqueous phase was extracted with CH_2Cl_2. The combined organic solutions were dried over $MgSO_4$ and concentrated to give 493 mg of brown oil, which was flash chromatographed on silica gel (MeOH-CH_2Cl_2,12:88 followed by 2-propylamine-CH_2Cl_2, 5:95) to afford 151 mg (38%) of 2-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-6,7-dimethoxyquinolin-4-ylamine as a tan solid.

To a solution of 2-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-6,7-dimethoxyquinolin-4-ylamine (150 mg) in hot CH_2Cl_2 (4.5 mL) and MeOH (1.5 mL) was added a solution of fumaric acid (22.8 mg, 0.196 mmol, 0.50 equiv.) in hot MeOH (3.0 mL). The resulting mixture was concentrated and the product was recrystallized from MeOH with hot filtration to afford, after filtration, 85 mg of light brown solid: m.p. 239-240°C.

In practice it is usually used as mesylate.

References

Craig D.A., Forrey C.C., Gluchovski Ch., Branchek T.A.; US Patent No. 5,610,174; March 11, 1997; Assigned to Synaptic Pharmaceutical Corporation (Paramus, NJ)

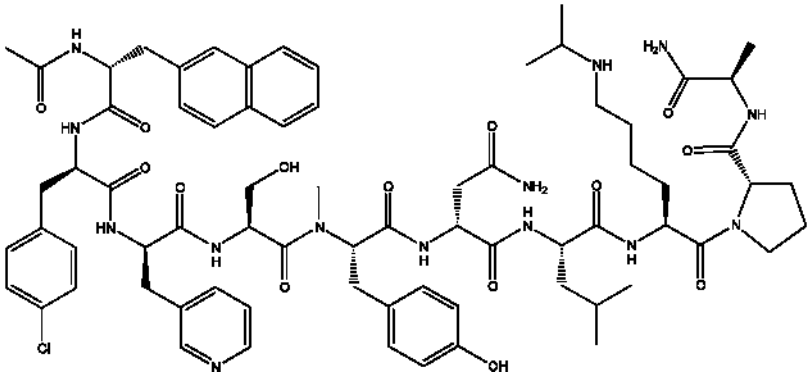
ABARELIX

Therapeutic Function: LHRH antagonist

Chemical Name: D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-N-methyl-L-tyrosyl-D-asparaginyl-L-leucyl-N^6-(1-methylethyl)-L-lysyl-L-prolyl-

Common Name: Abarelix; PPI-149

Structural Formula:



Chemical Abstracts Registry No.: 183552-38-7

Trade Name	Manufacturer	Country	Year Introduced
Plenaxis	Praecis Pharmaceuticals	-	-

Raw Materials

Thioanisole
Trifluoroacetic acid
1-Hydroxybenzotriazole
Dicyclohexylcarbodiimide
2-Iodopropane
Methylbenzyhydramine resin
Diisopropylethylamine
Boc-protected amino acids
Silver(I) oxide
m-Chloroperbenzoic acid
Boc-D-Pal (Boc-D- 3-(3'-pyridyl)alanine)

Manufacturing Process

Abbreviation Residue or moiety:

Nal - 3-(2-naphthyl)alaninyl

4-Cl-Phe - (4'-chlorophenyl)alaninyl

Pal - 3-(3'-pyridyl)alaninyl

Pal(N-O) - 3-(3'-pyridine-N-oxide)alaninyl

Pal(iPr) - 3-N-(2-propyl)-3'-pyridinium)alaninyl

BOC - N-t-butyoxycarbonyl

DCC - dicyclohexylcarbodiimide

Abarelix was synthesized by the solid phase method using an automated synthesizer (e.g. Beckman Model 990). The amino acid residues used can be purchased from commercial sources (e.g. Aldrich Chemical Co., Milwaukee, Wis.), or can be produced from commercially available starting materials according to known methods. Amino acids which are not obtained commercially can be synthesized in a protected form for coupling, or, if appropriate, can be coupled to form a peptide and subsequently modified to the desired form.

For example, Boc-D-Pal(iPr) was prepared next way:

Boc-D-Pal (4.0 g, 17.7 mmol) and Ag_2O (8.0 g, 34.4 mmol) in 22 ml water was stirred at room temperature for 4 hours. The reaction vessel was cooled to 0°C, and 2-iodopropane (20.4 g, 120 mmol) in 40 ml 2-propanol was added. After addition was complete, the mixture was allowed to warm to room temperature and stirred for 4 days. Additional Ag_2O (2 g) and 2-iodopropane (2 g) were added after 24 hours and again after 48 hours. The mixture was filtered, and the precipitate was washed with ethanol (2x15 ml). The filtrate was evaporated to yield 4.3 g of a yellow oil. Crystallization from ethanol/ethyl acetate gave light yellow crystals (3.0 g); Yield: 63%; m.p. 182°-185°C.

Synthesis of Boc-D-Pal(N-O):

Boc-D-Pal (2.0 g, 7.5 mmole) was dissolved in 40 ml acetone and 2.48 g (16.5 mmol) of m-chloroperbenzoic acid (MCPBA) (57-86%; purchased from Aldrich and used as received) in 80 ml acetone was added in one portion. The mixture was stirred at room temperature for 40 hours; a small amount of white precipitate formed as the reaction proceeded. The precipitated was filtered and the mother liquor evaporated to yield a white precipitate. The combined solids were washed with ether (to remove chlorobenzoic acid) and recrystallized from ethyl acetate/hexane. Yield: 1.7 g (80%); m.p. 155°-157°C.

A typical coupling cycle for peptide synthesis with Boc-amino acids on a peptide synthesizer (Beckman Model 990) was as follows:

Methylbenzyhydramine (MBHA) resin (1.18 g, 0.85 meq amino groups/g resin) was weighed into the reaction vessel and washed with two portions of chloroform (26 ml each). The resin was prewashed with 22% thioanisole (5 ml)/66% trifluoroacetic acid (TFA) in 14 ml dichloromethane (DCM) for 5 minutes, and then deprotected for 30 minutes with the same thioanisole/TFA mixture. The resin was washed with three portions of chloroform (20 ml each), two portions of 2-propanol (26 ml each) and two portions of DCM (26 ml each). The resin was neutralized with two portions of 12% diisopropylethylamine (DIPEA) (26 ml each), and then washed with four portions of DCM (26 ml each), followed by two portions of 1:1 DCM:dimethylformamide (DMF) (26 ml each). A solution of a Boc-protected amino acid (2.5 mole equivalents) and 1-hydroxybenzotriazole (HOBt) (2.5 mole equivalents) was introduced as a solution in 10 ml DMF, and DCC was added (256 mg in 6 DMF). Coupling was allowed to proceed for three hours,

or overnight. Hindered residues (e.g. backbone N-methyl amino acids) required longer coupling times. The resin was washed with two 26 ml portions of DMF, followed by two 26 ml portions of 2-propanol and then two 26 ml portions of DCM. Completion of coupling was assessed by Kaiser's test (ninhydrin test). If coupling is not complete, a double coupling was performed (i.e. the resin was neutralized as above and the coupling step repeated). When complete coupling is achieved, the cycle was repeated with the next amino acid.

Upon completion of the synthesis, the peptide was cleaved from the resin by treatment with liquid hydrofluoric acid (HF) for 45 minutes at 0°C. The HF was evaporated and the peptide treated with aqueous acetic acid and lyophilized. The crude peptide was then purified by high performance liquid chromatography (HPLC) on a C18 column, eluting with a mixture of acetonitrile and 0.1% TFA in water. Purified fractions (homogeneous by UV and TLC analysis) were combined and lyophilized. Analytical HPLC was used to determine the purity of the final product; peptides synthesized was at least 98% pure.

References

Folkers K. et al.; 1986; "Increased Potency of Antagonists of the Luteinizing Hormone Releasing Hormone Which Have D-3 Pal in Position 6"; Biochem. Biophys. Res. Comm.; 137(2):709-715

Tian, Z.P. et al.; 1994; "Design and synthesis of highly water soluble LHRH antagonists"; Pept.: Chem., Struct. Biol., Proc. Am. Pept. Symp.; 13th; 562-564

Roeske R. W.; US Patent No. 5,843,901; Dec. 1, 1998; Assigned to Advanced Research and Technology Institute, Bloomington, Ind.

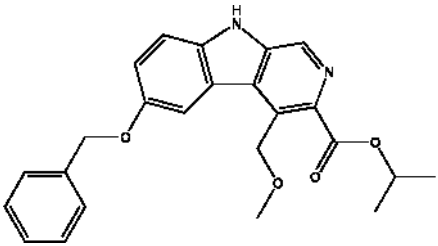
ABECARNIL

Therapeutic Function: Anticonvulsant, Anxiolytic

Chemical Name: 9H-Pyrido[3,4-b]indole-3-carboxylic acid, 4-(methoxymethyl)-6-(phenylmethoxy)-, 1-methylethyl ester

Common Name: Abecarnil; SH 524

Structural Formula:



Chemical Abstracts Registry No.: 111841-85-1

Trade Name	Manufacture	Country	Year Introduced
Abecarnil	Schepa	-	-

Raw Materials

Potassium carbonate
Anisaldehyde
Sodium hydroxide
Hydrochloric acid
Triethylamine
Hydrochloric acid
Glycine isopropyl ester
Paraformaldehyde
tert-Butyl hypochlorite
5-Benzyloxy-3-(1-isopropylamino-2-methoxyethyl)indole

Manufacturing Process

Under nitrogen, 6 g (43.5 millimoles) of finely pulverized potassium carbonate is stirred for 10 min at 95°C in 25 ml of absolute dimethylformamide. Then, while the mixture is hot, 10 g (29.6 mmol) of 5-benzyloxy-3-(1-isopropylamino-2-methoxyethyl)indole is added and the mixture is stirred approximately 10 min at 95°C until the compound has been dissolved. Thereupon, likewise at 95°C, a solution of 34.5 mmol of glycinimine (prepared from anisaldehyde and glycine isopropyl ester) in 25 ml of dimethylformamide is added dropwise in a time period of 30 min. The solution is agitated until the starting indole can no longer be detected in a thin-layer chromatogram. After cooling, the product is filtered off by suction from potassium carbonate and rinsed with toluene. After adding 100 ml of toluene, 200 ml of 1 N hydrochloric acid is added and the mixture stirred for 3 hours at room temperature. The toluene phase is separated, and the aqueous acidic phase is extracted by shaking with 100 ml of toluene. The organic phase is discarded. The acidic phase is cooled to 5°C, combined with 100 ml of toluene, and adjusted to pH 10-12 with 4 N sodium hydroxide solution. After extraction by shaking, the mixture is again extracted by shaking with 100 ml of toluene, and the combined organic phase is washed with 50 ml of water, dried, filtered, and concentrated, thus obtaining 70% 2-amino-3-(5-benzyloxyindol-3-yl)-4-methoxybutyric acid isopropyl ester as an oil.

A solution is prepared from 3.8 g of 2-amino-3-(5-benzyloxyindol-3-yl)-4-methoxybutyric acid isopropyl ester (10 mmol) in 80 ml of xylene and added dropwise to a suspension of 360 mg of paraformaldehyde in 60 ml of xylene heated for 45 min to 100°C. The mixture is then refluxed for 2 hours on a water trap. After concentration, the residue is chromatographed over silica gel with methylene chloride:acetone=1:1 as the eluent, yielding 2.5 g of 6-benzyloxy-4-methoxymethyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid isopropyl ester (65% yield as an oil); or a suspension of 2.56 g of paraformaldehyde in 8 ml of water and 0.8 ml of concentrated hydrochloric acid is refluxed at 80°C for 1 hour. One-tenth of the thus-obtained clear solution is added dropwise, after cooling to room temperature, to a solution of 3.8 g (10 mmol) of 2-amino-3-(5-benzyloxyindol-3-yl)-4-methoxybutyric acid isopropyl ester in 500 ml of water and 10 ml of concentrated hydrochloric acid (pH=3). After ½ hour of agitation, an estimate of the amount of amino compound still remaining is made by thin-layer chromatography, and a corresponding quantity of formaldehyde solution is added. Thereupon, the mixture is stirred for another hour and then extracted twice by shaking with 50 ml of toluene, respectively. The organic phase is discarded. The aqueous phase is adjusted, after adding 100 ml of toluene, to a pH of 5.3 with 27%

strength sodium hydroxide solution. After extraction by shaking, the mixture is additionally extracted by shaking twice with 50 ml of toluene; these 3 organic phases are combined, dried over sodium sulfate, filtered, and concentrated, thus obtaining 3.3 g (85%) of 6-benzyloxy-4-methoxymethyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid isopropyl ester as an oil.

A solution is prepared from 3.3 g (8.5 mmol) of 6-benzyloxy-4-methoxymethyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid isopropyl ester in 150 ml of methylene chloride, combined under argon with 3.9 ml of triethylamine, and cooled to -15°C. At this temperature, a solution of 3.2 ml (25.6 mmol) of t-butyl hypochlorite in 50 ml of methylene chloride is added dropwise without delay to this solution. After the adding step is completed, the mixture is stirred for another 10 min, combined with 2.6 ml of triethylamine, and agitated for 2 hours at room temperature. Subsequently, the mixture is concentrated to one-half thereof and extracted once by shaking with dilute ammonia solution. The organic phase is dried, filtered, and concentrated. The residue is chromatographed over silica gel with methylene chloride:acetone=4:1 as the eluent. Recrystallization from ethyl acetate gives 1.1 g (35% yield) of 6-benzyloxy-4-methoxymethyl-β-carboline-3-carboxylic acid isopropyl ester, m.p. 150-151°C.

References

Biere H., Huth A., Rahtz D. et al.; US Patent No. 5,414,002; May 9, 1995; Assigned to Schering Aktiengesellschaft, Berlin and Bergkamen, Germany

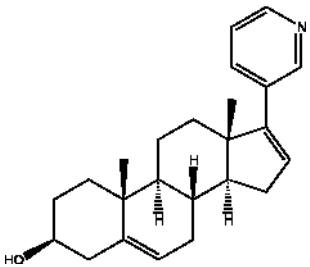
ABIRATERONE

Therapeutic Function: Antiandrogen

Chemical Name: Androsta-5,16-dien-3-ol, 17-(3-pyridinyl)-, (3β)-

Common Name: Abiraterone; CB 7598; Piraterone

Structural Formula:



Chemical Abstracts Registry No.: 154229-19-3

Trade Name	Manufacturer	Country	Year Introduced
Abiraterone	Cougar	-	-

Raw Materials

Diethyl(3-pyridyl)borane
3β-Acetoxyandrosta-5,16-dien-17-yl trifluoromethanesulphonate
Bis(triphenylphosphine)palladium(II) chloride
Sodium carbonate
Sodium hydroxide
Hydrochloric acid

Manufacturing Proces

Diethyl(3-pyridyl)borane (3.38 g, 23 mmol) from Aldrich Chemical Co. Ltd. was added to a stirred solution of 3β-acetoxyandrosta-5,16-dien-17-yl trifluoromethanesulphonate (6.94 g, 15 mmol) in THF (75 ml) containing bis(triphenylphosphine)palladium(II) chloride (0.105 g, 0.15 mmol). An aqueous solution of sodium carbonate (2 M, 30 ml) was then added and the mixture heated, with stirring, by an oil bath at 80°C for 1 h, and allowed to cool. The mixture was partitioned between diethyl ether and water, the ether phase was dried (Na_2CO_3), filtered through a short plug of silica, and concentrated. Chromatography, on elution with light petroleum-diethyl ether (2:1), afforded the 3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene (4.95 g, 84%) which crystallised from hexane, m.p. 144-145°C.

To a solution of 3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene (4.90 g, 12.5 mmol) in methanol (50 ml) was added an aqueous solution of sodium hydroxide (10% w/v, 10 ml) and the mixture heated, with stirring, on an oil bath at 80°C for 5 min, then allowed to cool. The mixture was poured into water, neutralised with hydrochloric acid (1 M), rebasified with saturated sodium bicarbonate solution, and extracted with hot toluene. The toluene extracts were combined, dried (Na_2CO_3), and concentrated. Chromatography, on elution with toluene-diethyl ether (2:1) afforded the 17-(3-pyridyl)androsta-5,16-dien-3β-ol (3.45 g, 79%) which crystallised from toluene, m.p. 228-229°C.

References

Barrie S.E., Jarman M., Potter G.A., Hardcastle Ian R.; US Patent No. 5,604,213; Feb. 18, 1997; Assigned to British Technology Group Limited (London, GB2)

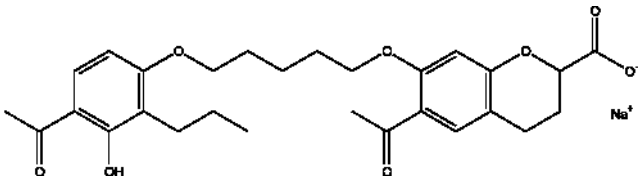
ABLUKAST SODIUM

Therapeutic Function: Antiallergic, Anti-asthmatic

Chemical Name: 2H-1-Benzopyran-2-carboxylic acid, 6-acetyl-7-[[5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentyl]oxy]-3,4-dihydro-, sodium salt

Common Name: Ablukast sodium

Structural Formula:



Chemical Abstracts Registry No.: 96565-55-8; 96566-25-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Ulpax	Roche	-	-

Raw Materials

Diethyl oxalate	2',4'-Dihydroxyacetophenone
Sodium ethylate	Hydrochloric acid
Palladium on charcoal	Hydrogen
4-Toluenesulfonic acid	Boron trifluoride diethyl etherate
5-Bromo-1-pentanyl acetate	Tetrabutylammonium hydroxide
Acetic acid	Triethylamine
Methanesulfonyl chloride	Tris(3,6-dioxahepyl)amine
Sodium hydroxide	

Manufacturing Process

A solution of 109.8 g (0.75 mol) of diethyl oxalate and 65 g (0.427 mol) of 2',4'-dihydroxyacetophenone in 100 mL of EtOH was added slowly under Ar, with cooling, to a stirred solution of NaOEt (from 40 g of Na and 550 mL of EtOH). The mixture was stirred at 50°C for 3 h, cooled to room temperature, and poured into a separatory funnel containing 500 mL of 2 N HCl. It was extracted with CH_2CH_2 washed with 500 mL of saturated $NaHCO_3$, dried and evaporated to give a red oil, which was dissolved in 250 mL of EtOH and 10 mL of conc. HCl. The mixture was boiled under reflux for 1 h, cooled to ca. 10°C and the product was collected by filtration. It was washed with some EtOH followed by hexane to give 86.0 g (86% yield) of ethyl 7-hydroxy-4-oxo-4H-1-benzopyran-2-carboxylate: m.p. 218-223°C. Crystallization of a portion from hot AcOH gave an analytical sample: m.p. 221-223°C.

A solution of 80 g (0.34 mol) of ethyl 7-hydroxy-4-oxo-4H-1-benzopyran-2-carboxylate in 60 mL of AcOH and 275 mL of THF was hydrogenated over 4.0 g of 10% Pd on charcoal at 45°C and 65 psi. After hydrogen absorption ceased, the catalyst was removed by filtration and the solvents were evaporated under reduced pressure. Crystallization from CCl4 gave 65 g (85%) of ethyl (R,S)-3,4-dihydro-7-hydroxy-2H-1-benzopyran-2-carboxylate: m.p. 80-82°C.

A stirred mixture of 65 g (0.293 mol) of ethyl (R,S)-3,4-dihydro-7-hydroxy-2H-1-benzopyran-2-carboxylate in 650 mL of AcOH, 1.5 mL of acetic anhydride, and 65 mL of $BF_3 \cdot OEt_2$ was heated at reflux for 18 h and evaporated. To the residue was added 700 mL of water, and the mixture was stirred at room temperature for 1.0 h. The product was collected by filtration

and washed with hexane. It was then dissolved in 900 mL of MeOH, treated with 6.6 g of p-toluenesulfonic acid, boiled under reflux for 18 h, and cooled to 0°C. The product was collected by filtration to give 52 g (70% yield) of ethyl (R,S)-3,4-dihydro-7-hydroxy-2H-1-benzopyran-2-carboxylate: m.p. 140-142°C.

A 1 L, 3-necked, round-bottomed flask equipped with a mechanical stirrer and an Ar bubbler was charged with 37.5 g (0.179 moles) of 5-bromo-1-pentanyl acetate, 350 mL of anhyd. DMSO, 40.7 g (0.163 mol) of ethyl (R,S)-3,4-dihydro-7-hydroxy-2H-1-benzopyran-2-carboxylate, and 51.0 g (0.369 mol) of powdered potassium carbonate. The mixture was stirred at room temperature for 18 h, poured into 1.0 L of water and extracted into EtOAc (2*1 L). The extract was washed with 1 L of brine, dried and evaporated. The residue was dissolved in 200 mL of ether, cooled to 57°C and, with stirring, diluted with petroleum ether. The product was collected by filtration, washed with a little 1:1 ether-petroleum ether (b.p. 40-60°C) and dried to give 60.0 g (97%) of methyl (R,S)-6-acetyl-3,4-dihydro-7-((5-acetoxypentyl)oxy-2H-1-benzopyran-2-carboxylate: m.p.51-53°C.

A solution of 72.08 g (0.19 mol) of 5-bromo-1-pentanyl acetate in 1.4 L of MeOH was treated with 38 mL of a 1.0 molar solution of tetrabutylammonium hydroxide and the mixture was stirred at room temperature for 3.0 h, 3.0 mL of AcOH was added and the solution was evaporated at 35°C. The residue was dissolved in 400 mL of EtOAc and the solution was washed with saturated $NaHCO_3$, brine, dried, and evaporated to give 60.45 g (94% yield) of the intermediate hydroxy ester (an analytical sample may be obtained by crystallization from 70% EtOAc in hexane, m.p. 58-61°C. A stirred solution of 60.25 g of the hydroxyester in 700 mL of EtOAc was cooled to 5°C and treated with 75.5 mL (3 equiv.) of triethylamine and 32.6 mL (2.35 equiv.) of methanesulfonyl chloride. The mixture was stirred at 6°C for 2.0 h, transferred to a separatory funnel and washed sequentially with water, 2 N HCl, and brine. Concentration of the EtOAc to ca. 300 mL and dilution cooled to 0°C and treated with 75.5 mL (3 equiv.) of triethylamine and 32.6 mL (2.35 equiv.) of methanesulfonyl chloride. The mixture was stirred at 6°C for 2.0 h transferred to a separatory funnel and washed sequentially with water, 2 N HCl, and brine. Concentration of the EtOAc to ca. 300 mL and dilution with 250 mL of hexane led to crystallization (0°C, 18 h). The product was collected by filtration and washed with some cold hexane - EtOAc (1:1) to give 66 g (84% yield) of methyl (R,S)-6-acetyl-3,4-dihydro-7-[5-[(methylsufonyl)oxy]pentyloxy]-2H-1-benzopyran-2-carboxylate: m.p. 73-76°C.

A mixture of 66.13 g (0.159 mol) of methyl (R,S)-6-acetyl-3,4-dihydro-7-[5-[(methylsufonyl)oxy]pentyloxy]-2H-1-benzopyran-2-carboxylate, 30.99 g (0.159 mol) of 1-[2,4-dihydroxy-3-propylphenyl)ethanone, 33.07 g (0.239 mol) of pulverized potassium carbonate, 5.16 g (15.9 mmol) of tris(3,6-dioxahepyl)amine in 900 mL of toluene was stirred under Ar at reflux for 6 h and then at room temperature overnight. The mixture was poured into 300 mL of water and the organic phase was separated, washed with brine, dried and evaporated to give 84.3 g of methyl (R,S)-6-acetyl-7-[5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentoxy]-3,4-dihydro-2H-1-benzopyran-2-carboxilate. Crystallization from MeOH (0°C, 18 h) gave 66 g (81% yield), m.p. 77-80°C.

A stirred solution of 55.82 g (0.109 mol) of methyl (R,S)-6-acetyl-7-[5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentoxy]-3,4-dihydro-2H-1-benzopyran-2-carboxylate in 725 mL of MeOH was treated with 4.45 g (0.111 mol) of NaOH in 20 mL of water and the mixture was stirred at reflux for 1.25 h. It was cooled, concentrated to a volume of ca 360 mL, diluted with 310 mL of ether and left at 0°C overnight. The product was collected by filtration, dried in to give 45.76 g of (R,S)-6-acetyl-7-[[5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentyl]oxy]-3,4-dihydro-2H-H-benzopyran-2-carboxylic acid sodium salt (Ablukast) as the monohydrate. A further 12.27 g of product was obtained from the mother liquor to give a total yield of 99%.

References

Manchand P.S., Micheli R.A., Saposnik S.J.; Tetrahedron; 1992; 48, 43, 9391

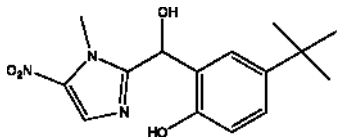
ABUNIDAZOLE

Therapeutic Function: Antiprotozoal

Chemical Name: α-[5-(1,1-Dimethylethyl)-2-hydroxyphenyl]-1-methyl-5-nitro-1H-imidazole-2-methanol

Common Name: Abunidazole; PN 4478846

Structural Formula:



Chemical Abstracts Registry No.: 91017-58-2

Trade Name	Manufacturer	Country	Year Introduced
Abunidazole	ZYF Pharm Chemical	-	-

Raw Materials

p-tert-Butylphenol
Hydrogen chloride
Ethylmagnesium bromide
1-Methyl-5-nitroimidazolyl-2-carboxyaldehyde

Manufacturing Process

150.0 g (1 mol) of p-tert-butylphenol are dissolved in 1200 ml of anhydrous ethyl ether and the thus obtained solution is added to a 10% solution of ethylmagnesium bromide in 1000 ml of anhydrous ether, at room temperature, under stirring.

After having evaporated the ether, 1000 ml of anhydrous benzene are added

and the mixture is distilled, at normal pressure, until its volume is about 2/3 of the original volume. After cooling at room temperature, 1 mol of 1-methyl-5-nitroimidazolyl-2-carboxyaldehyde in 1000 ml of anhydrous benzene is added.

The whole is boiled for 1 h, is cooled to about 10°C and is added with 8% HCl to adjust the pH to 7. Benzene layer is dried and concentrated up to 2/3 of the volume. The 2-(1-methyl-5-nitro)imidazolyl-1-(2-hydroxy-5-tert-butylphenylcarbinol is allowed to crystallize, melting point 158°-160°C; yield 0-60%.

References

Tessitore P.T.; US Patent No. 4,478,846; Oct. 23, 1984

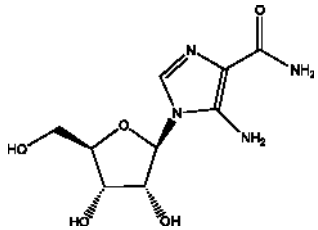
ACADESINE

Therapeutic Function: Cardiotonic, Platelet aggregation inhibitor

Chemical Name: 1H-Imidazole-4-carboxamide, 5-amino-1β-D-ribofuranosyl-

Common Name: Acadesine; AICA riboside; Arasine

Structural Formula:



Chemical Abstracts Registry No.: 2627-69-2

Trade Name	Manufacturer	Country	Year Introduced
AICA	BIOMOL	-	-

Raw Materials

Sodium hydroxide
Methyl iodide
Formic acid
Hydrogen
Ammonium hydroxide
Adenosine 3', 5'-cyclic phosphate N'-oxide
Sodium bicarbonate
Nickel
1,5-Diazabicyclo[5.4.0]undec-5-ene

Manufacturing Process

Adenosine 3', 5'-cyclic phosphate N'-oxide (76.0 g, 0.200 mole) as the

dihydrate was dissolved in a solution of 400 ml DMSO and 31.0 g (0.204 mole) 1,5-diazabicyclo[5.4.0]undec-5-ene. The solution was cooled to 15°C and 40 ml methyl iodide was added with stirring at room temperature. After 30 min, the mixture had gelled; 1.5 L ethanol was added and the solid was thoroughly homogenized by vigorous stirring. The solid was filtered, and the resulting paste was resuspended in 2 L ethanol and homogenized. The product was again filtered, washed with ethanol and ether, and dried, giving 80.4 g of 1-methoxyadenosine 3',5'-cyclic phosphate suitable for further transformation (recrystallization from aqueous methanol with ether).

A solution of 30.0 g 1-methoxyadenosine 3',5'-cyclic phosphate (81.5 mmole), 20.0 g $NaHCO_3$ (238 mmole), and 300 ml H_2O was refluxed 45 mm. The pH of the solution was adjusted to 2.5 with Dowex 50x8 $(H)^+$ while warm, and a water pump vacuum was applied to mixture to remove CO_2. The pH was readjusted to 9-10 with NaOH, and the resin was removed by filtration. The solution was passed onto a column containing 400 ml Dowex 1x2 (formate, 100-200 mesh), and the column was washed well with water. The column was eluted with a gradient of 4 L water in the mixing chamber and 4 L 4 N formic acid in the reservoir. The first major product, coming after about 2 L eluate, was 5-amino-N-methoxy-1-β-D-ribofuranosylimidazole-4-carboxamidine 3',5'-cyclic phosphate, giving 5.4 g (19%) after evaporation of the solvent and trituration of the residue with ethanol (recrystallization from water).

A solution of 5.0 g (14.3 mmoles) 5-amino-N-methoxy-1-β-D-ribofuranosylimidazole-4-carboxamidine 3',5'-cyclic phosphate in 200 ml H_2 preheated to 60°C and containing approximately 5.0 g moist sponge nickel catalyst, was shaken with 2-3 atm. H_2 at 60°C for 2 h. The filtered solution was evaporated to dryness to give 3.75 g of 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamidine 3',5'-cyclic phosphate (82%), (recrystallization from water).

A mixture of 4.0 g (12.5 mmole) 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamidine 3',5'-cyclic phosphate and 100 ml conc. NH_4OH was heated in a bomb at 100°C for 16 h, then cooled and evaporated in vacuum. The residue was taken up in 100 ml H_2O and applied to a 2.5x20 cm column of Dowex 1x2 (formate form, 100-200 mesh). After washing well with H_2O the column was eluted with a gradient of 1 L H_2O in the mixing chamber and 1 L 3 N formic acid in the reservoir. Fractions containing the product, appearing near the end of the elution, were evaporated. Trituration of the residue with EtOH gave 2.90 g (68%) of 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide 3',5'-cyclic phosphate.

The 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide may be produced by hydrolysis of 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide 3',5'-cyclic phosphate with NaOH.

References

Meyer R.B., Shuman D.A.; US Patent No. 3,919,192; Nov. 11, 1975; Assigned: ICN Pharmaceuticals, Irvine, Calif.

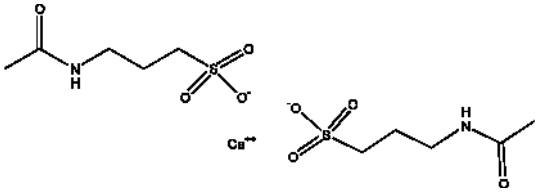
ACAMPROSATE CALCIUM

Therapeutic Function: Psychotropic

Chemical Name: 3-(Acetylamino)-1-propanesulfonic, calsium salt (2:1)

Common Name: Acamprosate; N-Acetylhomotaurine

Structural Formula:



Chemical Abstracts Registry No.: 77337-73-6; 77337-76-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Campral	Merck	-	-
Campral	Forest Pharm	-	-

Raw Materials

Sodium hydroxide	Acetic anhydride
Aminopropanesulfonic acid	Hydrochloric acid

Manufacturing Process

In a 4 liter flask provided with stirring means, a bromine funnel and a thermometer, 17.5% sodium hydroxide solution and aminopropanesulfonic acid (homotaurine) are added.

After complete dissolution, at a temperature of between 25°-40°C, acetic anhydride are added so as not to exceed a temperature of between 30°-40°C. The mixture is then maintained at this temperature by heating for at least 1 h.

The solution is then concentrated in vacuum, the residue is redissolved in 2.5 L of distilled water and the mixture is concentrated again. The residue is then dissolved in 1.6 L of distilled water, filtered, then concentrated almost completely. Drying is terminated in an oven in vacuum. A colorless crystalline powder of 3-acetylaminopropanesulfonate of sodium (sodium N-acetylhomotaurinate) is obtained.

The 3-acetylaminopropanesulfonic acid may be produced by treatment of 3-acetylaminopropanesulfonate of sodium with hydrochloric acid.

In practice it is usually used as calcium salt.

References

Durlach J.P.; US Patent No. 4,355,043; Oct. 19, 1982; Assigned: Les Laboratores Meram, France

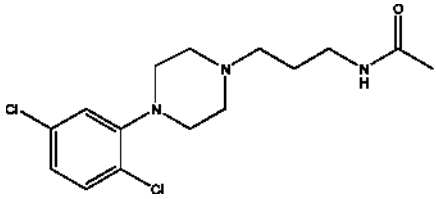
ACAPRAZINE

Therapeutic Function: Adrenergic blocker, Tranquilizer

Chemical Name: Acetamide, N-(3-(4-(2,5-dichlorophenyl)-1-piperazinyl) propyl)-

Common Name: Acaprazine

Structural Formula:



Chemical Abstracts Registry No.: 55485-20-6

Trade Name	Manufacturer	Country	Year Introduced
Acaprazine	ZYF Pharm Chemical	-	-

Raw Materials

Nickel Raney	N-(3-Chloropropyl)phthalimide
Sodium hydroxide	1-(2,5-Dichlorophenyl)piperazine
Sodium carbonate	Hydrogen chloride
Potassium phthalimide	Hydrazine hydrate
4-(m-Chloropheny1)-1-piperazinopropionitrile	1-(3-Chloropropyl)-4-(2,5-dichlorophenyl) piperazine
Acetic anhydride	Chlorosuccinimide
Triethylamine	Hydrogen

Manufacturing Process

2 methods of producing of 1-(3-acetylaminopropyl)-4-(2,5-dichlorophenyl) piperazine:

1. A mixture formed by N-(3-chloropropyl)phthalimide (23.0 g), 1-(2,5-dichlorophenyl)piperazine (24.0 g), anhydrous sodium carbonate (14.0 g) and toluene (130 ml) is boiled under stirring for 30 h. The solution is then cooled, filtered, concentrated to dryness, and the residue is treated with water and ether. The ethereal extract is washed, dried and concentrated to dryness. The

residue is treated with ethyl acetate and transformed into hydrochloride with ethanolic HCl. N-[3-[4-(2,5-Dichlorophenyl)-1-piperazinyl]propyl]phthalimide hydrochloride (30.0 g) is obtained, melting point 233°C (dec.).

N-[3-[4-(2,5-Dichlorophenyl)-1-piperazinyl]propyl]phthalimide (15.0 g) and 99% hydrazinehydrate (2 ml) are heated, under reflux, for 90 min. 5 N HCl (115 ml) is then added and the solution is heated for 30 min under reflux. The solution is cooled, filtered and concentrated to small volume. The residue is diluted with water, made alkaline by means of a solution of NaOH and extracted with CH_2Cl_2. The organic layer is dried, evaporated and distilled under reduced pressure. 7.0 g of 1-(3-aminopropyl)-4-(2,5-dichlorophenyl) piperazine are obtained.

1-(3-Aminopropyl)-4-(2,5-dichlorophenyl)piperazine (50.0 g) is dissolved in CH_2Cl_2, and the solution is heated under reflux. Acetic anhydride (25 ml) dissolved in CH_2Cl_2, (500 ml) is introduced under stirring in about 1 h. The solution is heated for 1 h and is evaporated to dryness in a rotating evaporator. The is treated with H_2O, thus obtaining a solid which is separated, washed and dried at 50°C. This solid is then dissolved in ethyl acetate (about 350 ml), treated with charcoal and crystallized. 1-(3-Acetylaminopropyl)-4-(2,5-dichlorophenyl)piperazine is obtained in an almost quantitative yield, melting point 114°C.

2. Chlorosuccinimide (5.4 g) is added to a solution of 4-(m-chlorophenyl)-1-piperazinopropionitrile (5.0 g) in CH_2Cl_2 (100 ml). The solution is heated for a few hours and, after removal of the solvent, it is chromatographed on an alumina column. The solution is eluted with a 1:1 mixture of cyclohexane and benzene containing 0.3 % of triethylamine. 4-(2,5-Dichlorophenyl)-1-piperazinopropionitrile (2.0 g) is thus obtained.

4-(2,5-Dichlorophenyl)-1-piperazinopropionitrile (20.0 g), acetic anhydride (100 ml), anhydrous sodium sulfate (12.0 g) and a 50% solution of Ni-Raney (6 ml) are hydrogenated at 60.0 pounds per inch at 60°C in a Parr apparatus. After about half an absorption of hydrogen is complete. The reaction mixture is cooled, the is filtered and the solution is concentrated to small volume in a rotating evaporator. The residue is treated with NaOH solution and extracted several times CH_2Cl_2. The organic layer is washed, dried and evaporated. The residue is crystallized from ethyl acetate. 14.0 g of the 1-(3-acetylaminopropyl)-4-(2,5-dichlorophenyl)piperazine are obtained, melting point 114°C.

References

GB Patent No. 1,443,598; July 21, 1976; Assigned: Aziende Chemiche Riunite Angelini Franceso A.C.R.A.F. S.p.A., Italy

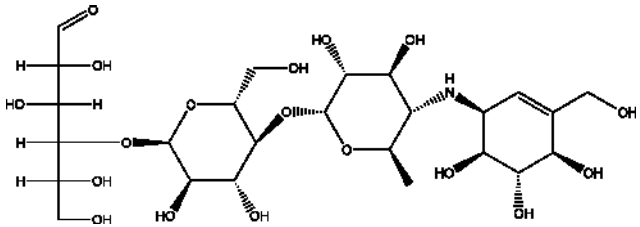
ACARBOSE

Therapeutic Function: Antidiabetic

Chemical Name: D-Glucose, O-4,6-dideoxy-4-(((1S-(1α,4α,5β,6α))-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl)amino)-α-D-glucopyranosyl-(1-4)-O-α-D-glucopyranosyl-(1-4)-

Common Name: Acarbose

Structural Formula:



Chemical Abstracts Registry No.: 56180-94-0

Trade Name	Manufacturer	Country	Year Introduced
Glicobase	Formenti	Italy	-
Glucobay	Bayer Limited	India	-
Glucor	Laboratoires Bayer Pharma	France	-
Glumida	Pensa	Spain	-
Prandase	Yno	-	-
Precose	Bayer	Germany	-
Precose	Cheshire Drugs	-	-
Precose	Allscripts	-	-
Precose	Physicians TC.	-	-

Raw Materials

Microorganisms of family *Actinoplanacease* (by fermentation)
Commercial cation exchanger based on polystyrene with a degree of crosslinking 3-4%
Solution of saccharase inhibitor
Lewatit

Manufacturing Process

The title compound was obtained from a cultural broth of fermenting a microorganism of family Actinoplanaceae in particular of strain genus Actinoplanes, according to DT-OS (German Published Specification) No. 2,347,782.

50 g of cation exchange resin (Lewatit S 1040W) in the H^+ form and 30 g an anion exchanger (Lewatit M 600) in OH form were added to 300 ml of a culture broth with mycelium content of 25% and an inhibitor content of 50 SIU/ml in solution. The mixture was stirred at room temperature for 50 minutes. The solution, containing a sieving nozzle with 0.1 mm slits. For

testing, a sample of filtered broth was centrifuged and was examined for saccharase inhibitor in the supernatant liquor. The solution contained 2.5 SIU/ml, that is to say 5%, of starting activity. This procedure improved the yield of the aminosugar from 20% in the procedure known from DT-OS (German Published Specification) No. 2,347,782, to 50-60%. It has now found that cation exchangers based on styrene, divinylbenzene and methoxymethylmethacrylamide, oxyethyl(meth)acrylic acid amide (ester), dimethylaminoethyl(meth)acrylic acid amide (ester) or oxypropyl(meth)acrylic acid amide(ester) are preferred in industrial separation procedure of acarbose. This exchanger gave a very sharp separation of the individual homologues and impurities. And it has now found the new biosynthesis of acarbose by using of gen engineering methods.

References

Rauenbusch E. et al.; US Patent No. 4,174,439, Nov. 13, 1979, Assigned: Bayer Aktiengesellschaft (Leverkusen, DE)

Lange P.M. et al.; US Patent No. 4,666,776, May 19, 1987, Assigned: Bayer Aktiengesellschaft (Leverkusen, DE)

Deutsches Patent and Markenamt, Offenlegungsschrift DE 100 21 667 A1, 8. 11.2001

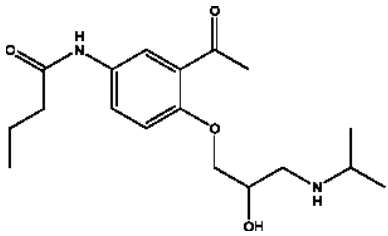
ACEBUTOLOL

Therapeutic Function: beta-Adrenergic blocker

Chemical Name: N-[3-Acetyl-4-[2-hydroxy-3-[(1-methylethyl)-amino] propoxy]phenyl]butanamide

Common Name: 5'-Butyramido-2'-(2-hydroxy-3-isopropylaminoprop-oxy)acetophenone

Structural Formula:



Chemical Abstracts Registry No.: 37517-30-9; 34381-68-5 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Sectral	May and Baker	UK	1975
Sectral	Specia	France	1976
Prent	Bayer	W. Germany	1977

Trade Name	Manufacturer	Country	Year Introduced
Neptall	Rhodia Pharma	W. Germany	1977
Sectral	May and Baker	Switz.	1980
Sectral	Roger Bellon	Italy	1980
Sectral	RBJ Pharma	Italy	1980
Acetanol	Kanebo, Ltd.	Japan	1981
Prent	Bayer	Italy	1981
Acecor	S.P.A.	Italy	-
Diasectral	Rhone Poulenc	-	-
Neptal	Rohm Pharma	-	-
Secradex	May and Baker	UK	-
Sectral	Wyeth	US	-

Raw Materials

Butyramidophenol
Aluminum chloride
Sodium ethoxide
Acetyl chloride
Epichlorohydrin
Isopropylamine

Manufacturing Process

Crude 5'-butyramido-2'-(2,3-epoxypropoxy)acetophenone (16 g), isopropylamine (20 g) and ethanol (100 ml) were heated together under reflux for 4 hours. The reaction mixture was concentrated under reduced pressure and the residual oil was dissolved in N hydrochloric acid. The acid solution was extracted with ethyl acetate, the ethyl acetate layers being discarded. The acidic solution was brought to pH 11 with 2 N aqueous sodium hydroxide solution and then extracted with chloroform. The dried chloroform extracts were concentrated under reduced pressure to give an oil which was crystallized from a mixture of ethanol and diethyl ether to give 5'-butyramido-2'-(2-hydroxy-3-isopropylaminopropoxy)acetophenone (3 g), MP 119-123°C.

Crude 5'-butyramido-2'-(2,3-epoxypropoxy)acetophenone used as starting material was prepared as follows: p-butyramidophenol (58 g; prepared according to Fierz-David and Kuster, Helv. Chim. Acta 1939,2282), acetyl chloride (25.4 g) and benzene (500 ml) were heated together under reflux until a solution formed (12 hours). This solution was cooled and treated with water. The benzene layer was separated and the aqueous layer was again extracted with benzene.

The combined benzene extracts were dried and evaporated to dryness under reduced pressure to give p-butyramidophenyl acetate (38 g) as an off-white solid, MP 102-103°C. A mixture of p-butyramidophenyl acetate (38 g), aluminum chloride (80 g) and 1,1,2,2-tetrachloroethane (250 ml) was heated at 140°C for 3 hours. The reaction mixture was cooled and treated with iced water. The tetrachloroethane layer was separated and the aqueous layer was extracted with chloroform. The combined organic layers were extracted with 2 N aqueous sodium hydroxide and the alkaline solution was acidified to pH 5 with concentrated hydrochloric acid. The acidified solution was extracted with chloroform and the chloroform extract was dried and concentrated under reduced pressure to give 5'-butyramido-2'-hydroxyacetophenone (15.6 g), MP 114-117°C. A solution of 5'-butyramido-2'-hydroxyacetophenone (15.6 g) in

ethanol (100 ml) was added to an ethanolic solution of sodium ethoxide which was prepared from sodium (1.62 g) and ethanol (100 ml). The resulting solution was evaporated to dryness under reduced pressure and dimethylformamide (100 ml) was added to the solid residue. Approximately 10 ml of dimethylformamide was removed by distillation under reduced pressure. Epichlorohydrin (25 ml) was added and the solution was heated at 100°C for 4 hours. The solution was concentrated under reduced pressure to give a residual oil which was treated with water to give a solid. The solid was dissolved in ethanol and the resulting solution was treated with charcoal, filtered and concentrated under reduced pressure to give crude 5'-butyramido-2'-(2,3-epoxypropoxy)acetophenone (16 g), MP 110-116°C.

The crude compound may be purified by recrystallization from ethyl acetate, after treatment with decolorizing charcoal, to give pure 5'-butyramido-2'-(2,3-epoxypropoxy)acetophenone, MP 136-138°C.

References

Merck Index 13
Kleeman and Engel p. 1
PDR p. 1978
OCDS Vol. 2 p. 109 (1980)
DOT 11 (7) p. 264 (1975)
I.N. p. 2
Wooldridge, K.R.H. and Basil, B.; US Patent 3,857,952; Dec. 31,1974; Assigned to May and Baker, Ltd.

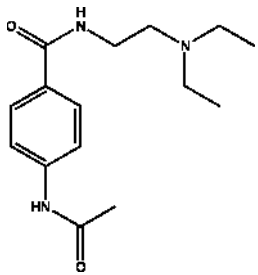
ACECAINIDE

Therapeutic Function: Antiarrhythmic

Chemical Name: Benzamide, 4-(acetylamino)-N-(2-(diethylamino)ethyl)-

Common Name: Acecainide; NAPA

Structural Formula:



Chemical Abstracts Registry No.: 32795-44-1

Trade Name	Manufacturer	Country	Year Introduced
Acecainide	ZYF Pharm Chemical	-	-

Raw Materials

Acetyl chloride
p-Amino-N-(2-diethylaminoethyl)benzamide
Sodium hydroxide

Manufacturing Process

1.0 g of p-amino-N-(2-diethylaminoethyl)benzamide is dissolved in chloroform. A few ice cubes are added to the solution. Acetyl chloride is added dropwise with stirring until no more white precipitate forms; the latter is separated by filtering under suction. The precipitate is washed with cold acetone and dried overnight in a vacuum oven at room temperature. The product is dissolved in a minimum amount of hot isopropanol and allowed to precipitate in the cold. The p-acetamido-N-(2-diethylaminoethyl)benzamide hydrochloride, is recrystallized a second time from hot isopropanol, melting point 190°-193°C.

The free base is obtained from the hydrochloride by dissolving the latter in water, adjusting the pH to greater than 10 with dilute sodium hydroxide, and adding an equal volume of benzene. After shaking in a separatory funnel, the benzene layer is recovered and evaporated to dryness. So the p-acetamido-N-(2-diethylaminoethyl)benzamide is obtained.

References

GB Patent No. 1,319,980; June 13, 1973; Assigned: E.R. Squibb and Sons, Inc., a corporation organized and existing under the laws of the State of Delaware, USA

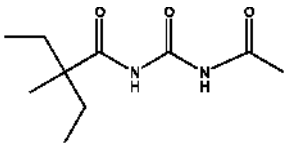
ACECARBROMAL

Therapeutic Function: Sedative, Hypnotic

Chemical Name: Butanamide, N-((acetylamino)carbonyl)-2-bromo-2-ethyl-

Common Name: Acecarbromal; Acetcarbromal; Acetylcarbromal; Sedacetyl

Structural Formula:



Chemical Abstracts Registry No.: 77-66-7

Trade Name	Manufacturer	Country	Year Introduced
Acetylcarbromal	Pfaltz and Bauer	-	-
Afrodor 2000	Farco-Pharma	-	-
Afrodor 2000	Biomenta	-	-
Paxarel	Circle Pharmaceuticals	-	-

Raw Materials

Urea
Bromine
Zinc chloride
Diethylacetic acid anhydride
Acetic anhydride

Manufacturing Process

It was mixed 120 parts of urea and 258 parts of bromodiethylacetylbromide (prepared from diethylacetic acid anhydride and bromine). After 12 hours the mixture was heated for 3 hours at 100°C. The product was mixed with an aqueous solution of sodium bicarbonate and then was filtered. The obtained bromodiethylacetylurea was crystallized from diluted ethanol; melting point 114-118°C. The mixture of 474 parts of bromodiethylacetylurea, 1000 parts of acetic anhydride and 75 parts $ZnCl_2$ was heated at 60°C for 1 hour. The product was stirred with 3000 parts of ice-water and then 1-acetyl-3-(α-bromo-α-ethylbutyryl)urea was filtered; melting point 108-109°C.

References

Merck Index, Monograph number: 18, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
DE Patent 286,760, 1913; Bayer and Co. In Elberfeld
DE Patent 327,129, 1917; Bayer and Co., Leverkusen

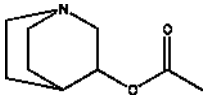
ACECLIDINE

Therapeutic Function: Miotic, Cholinomimetic

Chemical Name: 1-Azabicyclo[2.2.2]octan-3-ol acetate

Common Name: 3-Quinuclidinol acetate

Structural Formula:



Chemical Abstracts Registry No.: 827-61-2; 6109-70-2 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Glacostat	MSD-Chibret	France	1966
Glaunorm	Farmigea	Italy	1969
Glaudin	Sifi	Italy	-

Raw Materials

Methyl isonicotinate
Potassium
Ethyl bromoacetate
Hydrogen

Manufacturing Process

A mixture of 274 g of methyl isonicotinate, 367 g of ethyl bromoacetate and 125 cc of ethyl alcohol was stirred without heating for 4 hours in a flask equipped with a reflux condenser. (The reaction was exothermic and precautions were taken to keep the temperature below 70°C.) The reaction mixture was then left for 15 hours at room temperature.

The reaction product (1-carbethoxymethyl-4-carbornethoxy-pyridinium bromide) was obtained in crystalline form. (It formed prisms melting at 166-169°C after recrystallization from a mixture of isopropanol and acetone.) It was not necessary to isolate it. For the following reduction step, the reaction mixture was brought into solution by the addition of about 1 liter of warm ethyl alcohol. It was then hydrogenated at about 30 atm pressure in the presence of 2 g of platinum oxide. The temperature rose during this reaction to about 40°C. After the calculated amount of hydrogen had been absorbed, the catalyst was filtered off, the solution was concentrated in vacuum, and the residual syrup was dissolved in ice water. Benzene was added and the mixture was made alkaline with an excess of concentrated ice cold potassium carbonate solution. The temperature was kept low by continuous addition of ice, and the benzene layer was separated and dried with sodium sulfate. The dried benzene solution was concentrated in vacuum and the residual oil was distilled in vacuum. BP 30 mm = 175-182°C, n_D^{25}= 1.4613-1.4628. During the reduction, partial alcoholysis occurred, and the product isolated was 1-carbethoxymethyl-4-"carbalkoxy"-piperidine, wherein "carbalkoxy" represents a mixture of carbomethoxy and carbethoxy.

100 g of potassium were pulverized in 200 cc of hot toluene in a heated three-neck flask equipped with an efficient condenser, stirrer and dropping funnel. To the refluxing potassium suspension were added in small portions 229 g of the product of the previous step and about 700 cc of toluene. This addition had to be carried out very cautiously; the onset of the exothermic reaction is sometimes delayed. The addition was finished in about 1 hour. To complete the reaction, the refluxing and stirring were continued for about 4 hours. The reaction mixture was then cooled to about +5°C and about 50 cc isopropanol were added to decompose unreacted potassium. Then 2.5 liters of concentrated hydrochloric acid were added and the mixture was refluxed for 15 hours, and then concentrated in vacuum to dryness. To the residue was added with cooling an excess of 50% potassium hydroxide. Ether was then added and the resulting mixture was filtered through a fritted glass funnel, thus removing the precipitated potassium chloride. The ethereal and aqueous layers were separated, and the aqueous layer was extracted repeatedly with 500 cc portions of ether. The organic solutions were combined, dried over

sodium sulfate and concentrated in vacuum. Aqueous hydrochloric acid was added to the residue until the solution became acid. The mixture was then diluted with distilled water to about 300 cc, heated with decolorizing charcoal, filtered and concentrated in vacuum to dryness. The residue was treated with isopropanol, and the precipitated crystalline product was filtered off. The product was recrystallized from a mixture of water and isopropanol and was identified as 1-azabicyclo[2.2.2]-3-octanone hydrochloride; prisms, MP 311-313°C, with decomposition.

A solution of 50 g of the above ketone-hydrochloride in 30 cc of water was made alkaline by the addition of 30 g of potassium hydroxide. After the alkali was dissolved, 35 g of granular potassium carbonate were added. The free basic ketone was then extracted from the viscous mixture by shaking with 4 portions of hot benzene (300 cc in each portion). The benzene extracts were decanted, filtered over sodium sulfate in order to remove any suspended alkali, and concentrated in vacuum. The residual lszabicyclo[2.2.2]-3-octanone was purified by sublimation (50-70°C/0.5 mm Hg); it can also be purified by recrystallization from petroleum ether. It formed feathery crystals melting at 147-148°C.

The product was reduced as follows:

A solution of 50 g of 1-azabicyclo[2.2.2]-3-octanone hydrochloride in 200 cc of water was hydrogenated at room temperature and 50 atm pressure with 1 g of platinum oxide as catalyst. After the calculated amount of hydrogen had been absorbed, the mixture was filtered and concentrated in vacuum to dryness. The residual product was recrystallized from a mixture of methanol and acetone and formed prisms melting above 300°C. It was identified as 1-azabicyclo[2.2.2]-3-octanol hydrochloride.

A solution of 50 g of 1-azabicyclo[2.2.2]-3-octanol hydrochloride in 30 cc water was made alkaline with 30 g of potassium hydroxide. After the alkali was dissolved 35 g of granular potassium carbonate were added. The free basic alcohol was then extracted from the viscous mixture by shaking with four portions of boiling benzene (300 cc in each portion). The benzene extracts were decanted and filtered over anhydrous sodium sulfate, to remove any suspended alkali. The combined benzene solutions were concentrated in vacuum. The residue was recrystallized from benzene and identified as lszabicyclo[2.2.2]-3-octanol, MP 221-223°C. The product can also be purified by recrystallization from acetone, or by sublimation in vacuum (120°C/20 mm Hg). The alcohol was reacted with acetic anhydride to give the product aceclidine.

References

Kleeman and Engel p. 2
OCDS Vol. 2 p. 295 (1980)
I.N. p. 2
Sternbach, L.H.; US.Patent 2,648,667; Aug. 11,1953; Assigned to Hoffman - La Roche Inc.

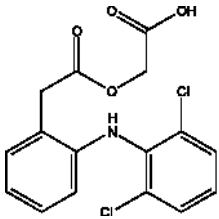
ACECLOFENAC

Therapeutic Function: Analgesic, Antiinflammatory

Chemical Name: Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, carboxymethyl ester

Common Name: Aceclofenac; Locomin

Structural Formula:



Chemical Abstracts Registry No.: 89796-99-6

Trade Name	Manufacturer	Country	Year Introduced
Reservix	Incepta	-	-
Aceclofenac	Xian HaiXin pharmaceutical Co., Ltd.	-	-
Airtal	Almirall	-	-
Kafenac	Almirall	-	-
Zurem	ABIOGEN PHARMA srl	-	-
Beofenac	Almirall	-	-
Bristaflam	Egypt Company Co.	-	-
Bristaflam	BMS Co.	-	-
Berlofen	Elea	-	-
Bristaflam	Bristol	-	-
Biofenac	UCB	-	-
Biofenac	BERAGENA	-	-
Biofenac	EMRA-MED ARZNEIM	-	-
Locomin	UCB	-	-
Proflam	Eurofarma	-	-

Raw Materials

Benzyl bromoacetate Sodium 2-[(2,6-dichlorphenyl)amino]phenylacetate Palladium on carbon Hydrogen

Manufacturing Process

50 g of sodium 2-[(2,6-dichlorphenyl)amino]phenylacetate were dissolved in 300 ml of N,N-dimethylformamide under heating to 50°C, and 44.22 g of benzyl bromoacetate were added thereto. Under these condition stirring was

continued for 9 hours. Upon completion of the reaction, the solvent was removed at reduced pressure, and the sodium salt were precipitated with addition of 400 ml of ether. The solution was then filtered and the ether phase was washed twice time with 100 ml of hexane. The resulting product was crystallized from the hexane/ether and then from acetone/chloroform (1:9) thus obtaining 44.1 g (61%) of benzyl 2-[(2,6-dichlorphenyl)amino]phenylacetoxyacetate in the form of white crystals having a melting point of 67-69°C.

45.28 g of benzyl 2-[(2,6-dichlorphenyl)amino]phenylacetoxyacetate were dissolved in 1500 ml of ethyl acetate, and the resulting solution was mixed with 7 g of Pd/C 10% and then hydrogen ted at atmospheric pressure for 14 hours. The solution was filtered, concentrated and crystallized; thereby obtaining 23.51 g (65%) of 2-[(2,6-dichlorphenyl)amino]phenylacetoxyacetic acid; melting point 149-150°C.

References

Casas A.V.; US Patent No. 4,548,952; Oct. 22, 1985; Assigned to Prodes, S.A., San Justo Desvern, Spain

Schickaneder H., Nikolopoulos A., Murphy T.; WO Patent No. 9,955,660; 1999-11-04; Assigned to Russinsky Ltd (IE), Schickaneder Helmut (IE), Nikolopoulos Aggelos (IE), Murphy Trevor (IE)

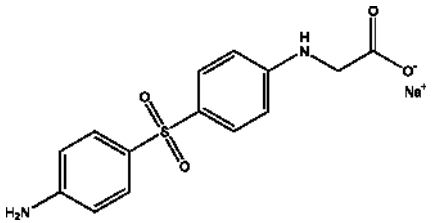
ACEDIASULFONE SODIUM

Therapeutic Function: Antibacterial

Chemical Name: N-p-Sulfanilylphenylglycine sodium

Common Name: Acediasulfone sodium; Glycinodiasulfone sodium

Structural Formula:



Chemical Abstracts Registry No.: 127-60-6; 80-03-5 (Base)

Raw Materials

Methyl chloroacetate
Lithium hydroxide
Sodium hydroxide
4,4'-Diaminodiphenyl sulfone
Hydrochloric acid

Trade Name	Manufacturer	Country	Year Introduced
Solfone	Bracco	-	-

Manufacturing Process

24.8 g of 4,4'-diaminodiphenyl sulfone, 150 g of methyl chloroacetate and 150 ml of ethanol are refluxed together and refluxed for 24 hours. The alcohol and excess methyl chloroacetate are then distilled off on a steam bath under reduced pressure. The residue consisting of the hydrochloride salt of 4-amino-4'-(carbomethoxymethylamino)diphenyl sulfone is mixed with of alcoholic solution containing 2.5 g lithium hydroxide and refluxed for 4 hours on the steam bath. Most of the alcohol is removed by distillation and the residual lithium salt of 4-amino-4'-(carboxymethylamino)diphenyl sulfone taken up water. The solution is filtered and dilute HCl added until no more separation occurs. The 4-amino-4'-(carboxymethylamino)diphenyl sulfone thus obtained is collected and dried.

The sodium salt of 4-amino-4'-(carboxymethylamino)diphenyl sulfone is prepared by dissolving the free acid in an aqueous solution containing one equivalent of sodium hydroxide and evaporating the solution to dryness in vacuo.

References

Merck Index, Monograph number: 21, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Rawlins A.L.; US Patent No. 2,589,211; Mar. 18, 1952; Assigned to Parke, Devis and Co., Detroit, Michigan
Martin H., Habicht E.; US Patent No. 2,751,382; June 19, 1956; Assigned to Cilag Ltd., Schaffhausen, Switzerland

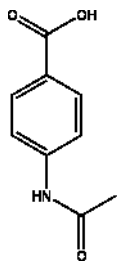
ACEDOBEN

Therapeutic Function: Antiviral

Chemical Name: Benzoic acid, p-acetamido-

Common Name: Acedoben

Structural Formula:



Chemical Abstracts Registry No.: 556-08-1

Trade Name	Manufacturer	Country	Year Introduced
4-Acetamidobenzoic acid	ARIAC	-	-
p-Acetamidobenzoic Acid	Chembay Chemical Co., LTD	-	-
p-Acetamidobenzoic Acid	Sigma-Aldrich	-	-

Raw Materials

Magnesium sulfate
N-p-Tolylacetamide
Hydrochloric acid
Sodium acetate
Potassium permanganate

Manufacturing Process

Into a 2 L, 3-necked flask set in a tub and equipped with a stirrer, an air condenser (drying tube), thermometer, was placed 860 ml of water, 43.0 g of $MgSO_4$ and 43.0 g of sodium acetate and heated on water bath. Into heated solution to 70°C stirring 43.0 g of N-p-tolylacetamide were added. Then 136.0 g of $KMnO_4$ by small portions were added at 75°-80°C. The reaction mixture allow to stand for 6 h and stirring was continue till the solution became colorless. Hot solution was filtered and filtrate treated hydrochloric acid to slightly acidic pH. After that 44.0 g (85%) of p-acetoaminobenzoic acid was obtained as white precipitate, melting point 250°C.

References

Berkengame A.M.; Chemistry and Technology of synthetic drugs; 1935; Moscow

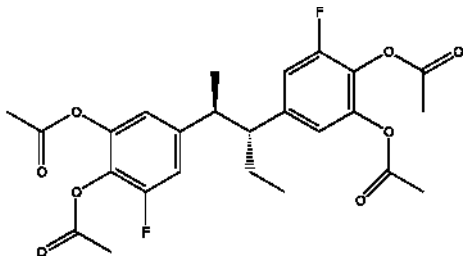
ACEFLURANOL

Therapeutic Function: Antiestrogen

Chemical Name: (1RS,2SR)-4,4'-(1-Ethyl-2-methyl-1,2-ethanediyl)bis[6-fluoro-1,2-benzenediol] tetraacetate

Common Name: Acefluranol; BX 591

Structural Formula:



Chemical Abstracts Registry No.: 80595-73-9

Trade Name	Manufacturer	Country	Year Introduced
Acefluranol	ZYF Pharm Chemical	-	-

Raw Materials

erythro-3,3'-Difluoro-4,4'-dihydroxy-α-ethyl-α'-methylbibenzyl
Pyridine
Acetic anhydride
Aluminum chloride
Sodium hydroxide
Hydrogen peroxide
Sodium borohydride
Hydrochloric acid

Manufacturing Process

4.5 g erythro-3,3'-difluoro-4,4'-dihydroxy-α-ethyl-α'-methylbibenzyl in 30 ml pyridine and 10 ml acetic anhydride were left to stand for 24 h at room temperature, thereafter the reaction mixture was worked up to give a crude product, recrystallisation of which from chloroform-diethyl ether (1:4 v/v) gave 5.5 g erythro-3,3'-difluoro-4,4'-diacetoxy-α-ethyl-α'-methylbibenzyl, melting point 118°-120°C.

5.0 g of the erythro-3,3'-difluoro-4,4'-diacetoxy-α-ethyl-α'-methylbibenzyl were ground with 10.0 g aluminum chloride and the mixture was heated at 150°C for 30 min. After cooling, the mass was added portion-wise to ice, stirred and extracted with chloroform. The chloroform solution was washed with water, dried with anhydrous sodium sulfate and concentrated to half its volume. An equal volume of diethyl ether was added thereto and the solution was treated with charcoal and filtered. The filtrate was evaporated and the residue obtained was crystallized from chloroform-diethyl ether (1:1 v/v) to give 2.6 g erythro-3,3'-diacetyl-4,4'-dihydroxy-5,5'-difluoro-α-ethyl-α'-methylbibenzyl, melting point 194°-196°C.

0.9 g erythro-3,3'-diacetyl-4,4'-dihydroxy-5,5'-difluoro-α-ethyl-α'-methylbibenzyl were suspended in a mixture of 10 ml dioxan and 6 ml 1 N aqueous sodium hydroxide solution. The solution was cooled to 10°C and 0.8 ml 30% hydrogen peroxide added dropwise thereto. The reaction mixture was stirred at 20°C for 1.5 h and then poured into a mixture of dilute hydrochloric acid and ice. The product was extracted with peroxide-free diethyl ether, the extract was evaporated and the residue was crystallized from benzene to give a yellow solid. This was treated in 5 ml ethanol with 2.0 mg sodium borohydride, followed by acidification with hydrochloric acid, rapid extraction with diethyl ether, evaporation of the extract and immediate crystallization from benzene to give 350.0 mg of pure erythro-4,4',5,5'-tetrahydroxy-3,3'-difluoro-α-ethyl-α'-methyldibenzyl, melting point 143°-145°C.

1.0 g erythro-3,3'-difluoro-4,4',5,5'-tetrahydroxy-α-ethyl-α'-methyldibenzyl in a mixture of 10 ml pyridine and 5 ml acetic anhydride was left to stand at 20°C for 20 h and at 60°-80°C for 1 h. The reaction mixture was then poured into a mixture of dilute hydrochloric acid and ice, stirred for several h and filtered. The filtrate was evaporated and the residue was taken up in

chloroform and the chloroform solution was washed with dilute hydrochloric acid and water, dried over anhydrous sodium sulfate and the solvent removed. The gummy residue was taken up with benzene and the benzene solution filtered through a neutral alumina. The benzene was removed from the filtrate to give 1.0 g pure erythro-3,3'-difluoro-4,4',5,5'-tetraacetoxy-α-ethyl-α'-methyldibenzyl; melting point 160°-162°C (crystallised from diethyl ether).

References

Chan R.P.K.; US Patent No. 4,427,697; Jan. 24, 1984; Assigned: Biorex Laboratories Limited, England

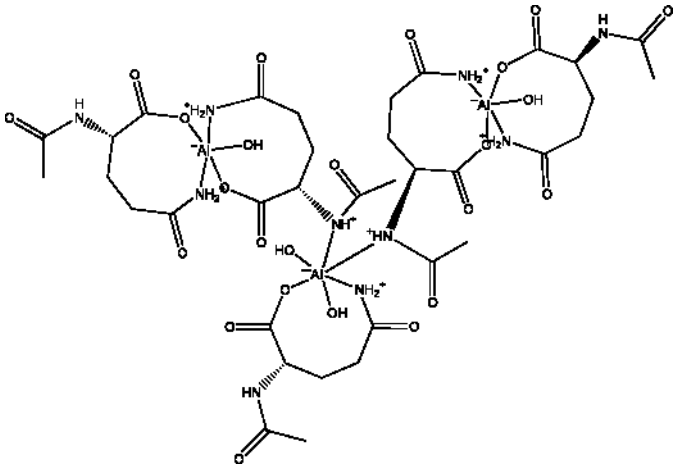
ACEGLUTAMIDE ALUMINUM

Therapeutic Function: Antiulcer

Chemical Name: Pentakis(N^2-acetyl-L-glutaminato)tetrahydroxytrialuminum

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 12607-92-0

Trade Name	Manufacturer	Country	Year Introduced
Glumal	Kyowa Hakko	Japan	1978
Glumal	Liade	Spain	-

Raw Materials

N-Acetyl-L-glutamine
Aluminum isopropoxide

Manufacturing Process

A mixture of 37.6 g of N-acetyl-L-glutamine and 1,000 ml of water is heated to 40°C, and 900 ml of an isopropanol solution containing 40.8 g of aluminum isopropoxide is added to the warm mixture with stirring. The stirring is continued for 10 minutes. The reaction mixture is filtered and the filtrate is concentrated under reduced pressure. Isopropanol is added to the aqueous solution and the salt precipitates in the solution. The precipitates are collected by filtration and upon drying, 48.5 g of the crystalline-like aluminum salt of N-acetyl-L-glutamine are obtained.

References

Merck Index 20
Kleeman and Engel p. 32
DOT 14 (2) p. 54 (1978)
I.N. p. 3
Kagawa, T., Fuji, K., Tanaka, M. and Tanaka, H.; US Patent 3,787,466; Jan. 22,1974; Assigned to Kyowa Hakko Kogyo Co., Ltd.

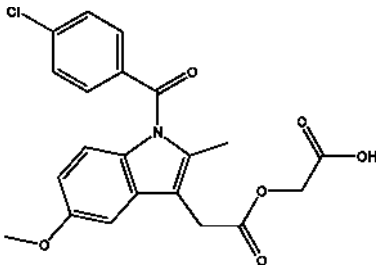
ACEMETACIN

Therapeutic Function: Antiinflammatory

Chemical Name: 1-(p-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetoxyacetic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 53164-05-9

Trade Name	Manufacturer	Country	Year Introduced
Rantudil	Bayer	W. Germany	1980
Rantudil	Tropon	W. Germany	-

Raw Materials

N-(p-Methoxybenzyl)-p-chlorobenzhydrazide HCl
Benzyl levulinoyloxyacetate
Hydrogen

Manufacturing Process

25.4 g (0.050 mol) of [1-(p-chlorobenzoyl)-5-methoxy-2-methyl-3-indoleacetoxy]-benzyl acetate were dissolved in 400 ml of glacial acetic acid and hydrogenated on 2.0 g of palladium carbon at room temperature. After the absorption of hydrogen had finished (1 hour), the catalyst was filtered off, the filtrate was concentrated by evaporation under vacuum and the compound was caused to crystallize by adding petroleum ether. The compound melted at 149.5-150.5°C (determined on the micro-Kofler bench); the yield was 19.4 g which corresponds to 93% of the theoretical yield.

The starting material for the above step may be prepared as follows: 5 g (0.016 mol) of N^1-(p-methoxyphenyl)-p-chlorobenzhydrazide hydrochloride and 4.75 g (0.018 mol) of benzyl levulinoyloxyacetate were heated in 25 ml of glacial acetic acid for 3 hours at 80°C. The solvent was then evaporated off under vacuum. The residue was taken up in chloroform and the solution was washed neutral by shaking with sodium bicarbonate solution and thereafter with water. After drying the chloroform solution, this was subjected to chromatography on aluminium oxide, the eluate was concentrated by evaporation and the viscous oil remaining as residue was crystallized by adding ether. The compound melted at 94-95°C. The yield was 4.1 g which corresponds to 50.7% of the theoretical yield.

References

Merck Index 21
DFU 2 (7) p.423 (1977)
Kleeman and Engel p. 3
DOT 17 (7) p.279 (1981)
I.N. p. 3
Boltze, K.H., Brendler, O., Dell, H.D. and Jacobi, H.; US Patent 3,910,952; October 7,1945; Assigned to Tropenwerke Dinklage and Co.
Boltze, K.H., Brendler,O., Dell, H.D. and Jacobi, H.; US Patent 3,966,956; June 29,1976; Assigned to Tropenwerke Dinklage and Co.

ACENOCOUMAROL

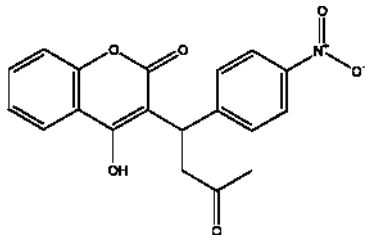
Therapeutic Function: Anticoagulant, Vitamin

Chemical Name: 3-(α-Acetonyl-p-nitrobenzyl)-4-hydroxycoumarin

Common Name: Nicoumalone

Chemical Abstracts Registry No.: 152-72-7

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Sintrom	Geigy	US	1957
Sintrom	Geigy	W. Germany	-
Sintrom	Ciba Geigy	Switz.	-
Sintrom	Ciba Geigy	France	1959
NeoSintrom	Geigy	-	-
Ascumar	Star	Finland	-
Syncumar	EGYT	Hungary	-
Synthrome	Geigy	UK	-
Sintrom	Ciba Geigy	Japan	-

Raw Materials

4-Hydroxycoumarin
Nitrobenzalacetone

Manufacturing Process

16 parts of 4-hydroxycoumarin and 19 parts of 4-nitrobenzalacetoneare thoroughly mixed and heated for 12-14 hours in an oil bath, the temperature of which is between 135°C and 140°C. After cooling, the melt is dissolved in a little acetone. The solution is slowly added to a lye made up from 6 parts of sodium hydroxide in 400 parts of water while stirring and then the mixture is stirred for 30 minutes. A little animal charcoal is then added, the mixture is stirred for a further 15 minutes, 400 parts of water are added and the charcoal and undissolved components are separated by filtration under suction. The clear solution is made acid to Congo red paper with hydrochloric acid and the product which is precipitated is filtered off under suction. 3-[α-(4'-Nitrophenyl)-β-acetylethyl]-4-hydroxycoumarin is obtained. MP 196-199°C.

It should be noted that the process is akin to that for Warfarin except that 4-nitrobenzalacetone replaces benzalacetone as a raw material.

References

Merck Index 23
Kleeman and Engel p. 4
OCDS Vol. 1 p. 331 (1977)
I.N. p.3
Stoll, W. and Litvan, F.; US Patent 2,648,682; August 11, 1953; Assigned to J.R. Geigy A.G., Switzerland.

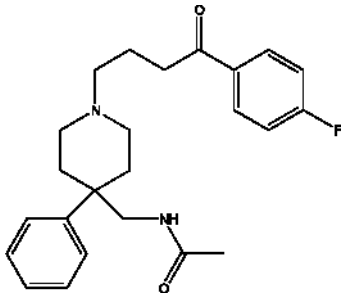
ACEPERONE

Therapeutic Function: Vasodilator, Antihypertensive, Neuroleptic

Chemical Name: Acetamide, N-((1-(4-(4-fluorophenyl)-4-oxobutyl)-4-phenyl-4-piperidinyl)methyl)-

Common Name: Aceperone; Acetabutone

Structural Formula:



Chemical Abstracts Registry No.: 807-31-8

Trade Name	Manufacturer	Country	Year Introduced
Aceperone	ZYF Pharm Chemical	-	-
Aceperone	Vasudha Pharma Chem Limited.	-	-

Raw Materials

1-Benzyl-4-(4-phenyl)-4-(acetaminomethyl)piperidine
Sodium bicarbonate
3-(4-Fluorobenzoyl)propyl bromide
Thiophenol
Sodium hydroxide

Manufacturing Process

A mixture of 1-benzyl-4-(4-phenyl)-4-(acetaminomethyl)piperidine, 3-(4-fluorobenzoyl)propyl bromide, sodium bicarbonate and anhydrous acetone was stirred and heated under reflux. The resulting mixture was filtered while still hot, and the filtrate was concentrated to dryness under reduced pressure. The residue was washed with ether to give 1-benzyl-1-[3-(4-fiuorobenzoyl)propyl]-(4-phenyl-4-acetaminomethyl)piperidinium bromide.

To a stirred mixture of thiophenol and 15% (W/W) aqueous sodium hydroxide was added the 1-benzyl-1-[3-(4-fluorobenzoyl)propyl]-(4-phenyl-4-acetaminomethyl)piperidinium bromide and the mixture was heated to 85°-90°C for 2 h. After cooling, solid matter precipitated was collected by filtration and washed with water to give 1-[3-(4-fluorobenzoyl)propyl]-4-(acetaminomethyl)-4-phenylpiperidine, melting point 111°-112°C.

References

Nakao M. et al.; US Patent No. 3,850,935; Nov. 26, 1974; Assigned: Sumitomo Chemical Company, Limited, Osaka, Japan

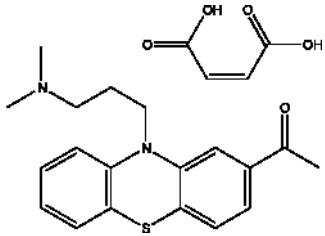
ACEPROMAZINE MALEATE

Therapeutic Function: Neuroleptic, Antiemetic

Chemical Name: Ethanone, 1-(10-(3-(dimethylamino)propyl)-10H-phenothiazin-2-yl)-, maleate (1:1)

Common Name: Acepromazine maleate; Acetopramazine maleate; Notensil

Structural Formula:



Chemical Abstracts Registry No.: 3598-37-6; 61-00-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Sedaject	Bayer Korea Co.	-	-
Anatran	Ayerst	-	-
Sedalin	Chassot	-	-

Raw Materials

3-Acetylphenothiazine
Phosgene
γ-Dimethylaminopropyl alcohol

Manufacturing Process

120 g 3-acetylphenothiazine (0.479 mol) are heated to the boil in 1.2 L xylene and a rapid stream of phosgene then passed in for a period of 12 hours. The solvent is then removed by distillation and the residue taken up in 1 L benzene. The benzene solution is heated to the boil and 112 g of γ-dimethylaminopropyl alcohol (1.09 mol) are added within a period of 15 min and the reaction mixture boiled for a further 2 hours. After cooling, the precipitated hydrochloride of the γ-dimethylaminopropyl alcohol washed with benzene and the combined benzene solutions rapidly washed with water in order to remove excess basic alcohol. The material is dried over potash and the hydrochloride precipitated by means of ethereal hydrochloric acid. The

hydrochloride may also be precipitated by passing in gaseous hydrogen chloride. After recrystallisation from isopropanol, 157 g (78% of theory) of γ-dimethylaminopropyl 3-acetylphenothiazine-10-carboxylate are obtained. The hydrochloride melts at 212°C.

In practice it is usually used as maleate salt.

References

Hoerlein U. et al,; DE Patent No. 1,049,865; Assigned to Farbenfabriken Bayer Aktiengesellschaft, Leverkusen-Bayerwerk
GB Patent No. 808,050; Jan. 28,1959; BAYER AG

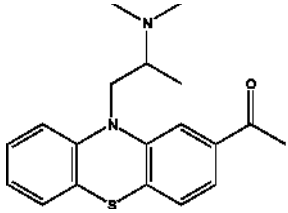
ACEPROMETAZINE

Therapeutic Function: Neuroleptic, Antitussive

Chemical Name: Ethanone, 1-(10-(2-(dimethylamino)propyl)-10H-phenothiazin-2-yl)-

Common Name: Aceprometazine

Structural Formula:



Chemical Abstracts Registry No.: 13461-01-3

Trade Name	Manufacturer	Country	Year Introduced
Aceprometazine	ZYF Pharm Chemical	-	-

Raw Materials

2-Acetylphenothiazine
1-Dimethylamino-2-chloropropane
Sodium hydride

Manufacturing Process

In a 1 liter flask, equipped with stirrer, thermometer and nitrogen inlet, 241.0 g of 2-acetylphenothiazine (1 mole) is dissolved in 300 ml of dry dimethylformamide. When the 2-acetylphenothiazine is almost completely soluble, to this solution is added 275 ml of a 4 N solution of 1-dimethylamino-2-chloropropane in toluene.

The mixture is heated to 50°C and 26.0 g (1.08 moles) of sodium hydride is added portion-wise, maintaining the temperature at 50°-60°C. The addition should take about 1 h. The reaction is allowed to stir for 3 h at 50°-60°C. Any excess hydride is destroyed by the cautious addition of 10 ml methanol, and the reaction mix is poured into 800 ml of 20% acetic acid.

The toluene layer is separated and extracted with 150 ml of 20% acetic acid, and discarded. The acid solutions are combined and washed once with toluene. The toluene is discarded. Fresh toluene (200 ml) is added and caustic solution is added with cooling and stirring until the pH is 9 or above. The toluene layer is separated. The aqueous layer is extracted once more with 75 ml of toluene and discarded. The toluene extracts are combined, given a small water wash, and concentrated. The residue is distilled yielding 10-[2-(dimethylamino)propyl]-2-acetylphenothiazine.

References

Kantor M.L., Tubis S.; US Patent No. 3,100,772; August 13, 1963; Assigned: America Home Products Corporation, New York, N.Y.

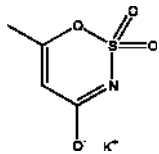
ACESULFAME POTASSIUM

Therapeutic Function: Pharmaceutic aid

Chemical Name: 6-Methyl-1,2,3-oxathiazin-4(3H)-one 2,2-dioxide potassium salt

Common Name: Acetylfame K, Acetylfame potassium

Structural Formula:



Chemical Abstracts Registry No.: 55589-62-3; 33665-90-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Acesulfame Potassium	Hoechst	-	-
Acesulfame K	Wuzhou international Co., Ltd.	-	-
Acesulfame Potassium	Zhang Peng International	-	-
Acesulfame K	AroKor Holdings Inc.	-	-
Acesulphame K	Acroyali Holdings Qingdao Co., Ltd.	-	-

Trade Name	Manufacturer	Country	Year Introduced
Acesulfame K	Zhangjiagang Hope Chemicals Co., Ltd.	-	-
VitaSweet Ace K	VitaSweet	-	-

Raw Materials

Dimethylethylamine
Sulfamic acid
Sulfur trioxide

Manufacturing Process

80 g (1.096 mol) of dimethylethylamine were added drop-wise, with cooling, to 80 g (0.825 mol) of sulfamic acid suspended in 500 ml of glacial acetic acid. When dissolution was complete, 80 ml (1.038 mol) of diketene were added, while cooling at 25°-35°C. After 16 hours, the mixture was evaporated and the residue was stirred with acetone, whereupon crystallization of dimethylethylammonium acetoacetamide-N-sulfonate took place. Yield: 110 g (43%), melting point 73°-75°C.

12.7 g (50 mmol) of dimethylethylammonium acetoacetamide-N-sulfonate in 110 ml of methylene chloride were added drop-wise to 8 ml (200 mmol) of liquid SO3 in 100 ml of CH_2Cl_2 at -30°C, stirring vigorously, within 60 minutes. 30 minutes later, 50 ml of ethyl acetate and 50 g of ice were added to the solution. The organic phase was separated off, and the aqueous phase was extracted twice more with ethyl acetate. The combined organic phases were dried over sodium sulfate, evaporated and the residue was dissolved in methanol. On neutralization of the solution with methanolic KOH, the potassium salt of 6-methyl-3,4-dihydro-1,2,3-oxathiazin-4-one 2,2-dioxide precipitated out. Yield: 7.3 g (73%). The product was detected by thinlayer chromatography; the structure of it was confirmed with IR spectrum.

References

Clauss K. et al.; US Patent No. 5,103,046; April 7, 1992; Assigned to Hoechst Aktiengesellschaft Frankfurt am Main, DE)

ACETAMINOPHEN

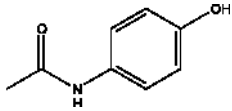
Therapeutic Function: Analgesic, Antipyretic

Chemical Name: N-(4-Hydroxyphenyl)acetamide

Common Name: Paracetamol; Acetyl-p-aminophenol; APAP

Chemical Abstracts Registry No.: 103-90-2

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Trigesic	Squibb	US	1950
Apamide	Ames	US	1952
Nebs	Norwich Eaton	US	1955
Tylenol	McNeil	US	1955
Febrolin	Tilden Yates	US	1957
Tempra	Mead Johnson	US	1957
Fendon	Am. Pharm.	US	1958
Amdil	Breon	US	1958
Lyteca	Westerfield	US	1962
Menalgesia	Clapp	US	1963
Dial-Agesic	Borden	US	1968
Tenlap	Dow	US	1970
SK-APAP	SK and F	US	1971
Valadol Tablets	Squibb	US	1971
Tapar	Parke Davis	US	1974
Cen-Apap	Central	US	1974
Acephen	G and W	US	1978
St. Joseph Aspirin	St. Joseph	US	1982
Panadol	Glenbrook	US	1983
Pain and Fever	Lederle	US	-
Accu-Tap	Accu-Med	US	-
Actamin	Buffington	US	-
Am inofen	Dover	US	-
Anuphen	Comatic	US	-
Dapa	Ferndale	US	-
Datril	Bristol-Myers	US	-
Dirox	Winthrop	US	-
Dolanex	Lannett	US	-
Febrogesic	First Texas	US	-
Halenol	Halsey	US	-
Hedex	Winthrop	US	-
Homoolan	Winthrop	US	-
Injectapap	Johnson and Johnson	US	-
Korum	Geneva	US	-
Metalid	Philips Roxane	US	-
Minotal	Carnrick	US	-

Trade Name	Manufacturer	Country	Year Introduced
Neopap	Webcon	US	-
Neotrend	Bristol-Myers	US	-
Nilprin	AVP	US	-
Panamax	Winthrop	US	-
Panodil	Winthrop	US	-
Parten	Parmed	US	-
Phenaphen	Robins	US	-
Phendex	Mallard	US	-
Phrenilin	Carnrick	US	-
Prompt	Delree	US	-
Proval	Reid-Provident	US	-
Robigesic	Robins	US	-
Valorin	Otis Clapp	US	-
Abrol	Rekah	Israel	-
Abrolet	Rekah	Israel	-
Acamol	Ikapharm	Israel	-
Acetalgin	Streuli	Switz.	-
Aldolor	Novis	Israel	-
Alpiny	SS Pharmaceutical	Japan	-
Alvedon	Draco	Sweden	-
Anaflon	Duphar	UK	-
Anhiba	Hokuriku	Japan	-
APA/Aparacet	Arcana	Austria	-
Apiretal	Ern	Spain	-
Arasol	Horner	Canada	-
Benmyo	Heilmittelwerke Wien	Austria	-
Ben-U-Ron	Benechemie	W. Germany	-
Calpol	Calmic	UK	-
Campain	Winthrop	Canada	-
Ceetamol	Protea	Australia	-
Cetadol	Rybar	UK	-
Chemcetaphen	Chemo-Drug	Canada	-
Dipramat Infantil	Byk Gulden	W. Germany	-
Dolamin	Nyal	Australia	-
Doliprane	Bottu	France	-
Dolprone	Siegfried	W. Germany	-
Dymadon	Calmic	UK	-
Efferalgan	UPSA	France	-
Enelfa	Dolorgiet	W. Germany	-
Exdol	Merck-Frosst	Canada	-
Febrilix	Boots	UK	-

Trade Name	Manufacturer	Country	Year Introduced
Finimal	Mepros	Netherlands	-
Finimal	Pharmaton	Switz.	-
Gelocatil	Gelos	Spain	-
Ildamol	Rekah	Israel	-
Kinder-Finiweh	Cesmopharma	Netherlands	-
Kratofin	Kwizda	Austria	-
Labamol	Vitamed	Israel	-
Langesic	Boots	UK	-
Letamol	Letap	Switz.	-
Momentum	Much	W. Germany	-
Myalgin	Allied Labs	UK	-
Napional	Pharma Import	Austria	-
Nealgyl	Bottu	France	-
Nevral	Lepetit	Italy	-
Pacemo	Alpinapharm	Switz.	-
Pacet	Rekah	Israel	-
Painex	A.L.	Norway	-
Pamol	Marshalls Pharm.	UK	-
Panacete	Prosana	Australia	-
Panadol	Sterwin Espanola	Spain	-
Panadon	Isis	Yugoslavia	-
Panasorb	Winthrop	UK	-
Panasorb	Bayer	W. Germany	-
Panok	B.M. Labs	UK	-
Pantalgin	UCB	Belgium	-
Paracet	Zdravlje	Yugoslavia	-
Paracet	Weifa	Norway	-
Paralgin	ICN	Canada	-
Paramol	Duncan Flockhart	UK	-
Paramolan	Trima	Israel	-
Parasin	Adams	Australia	-
Paraspen	Fisons	UK	-
Para-Suppo	Orion	Finland	-
Parmol	Knoll	Australia	-
Parol	Atabay	Turkey	-
Pasolind	Stada	W. Germany	-
PCM	Napp	UK	-
Pediaphen	Ross	Canada	-
Phenipirin	Aksu	Turkey	-
Pinex	A.L.	Norway	-

Trade Name	Manufacturer	Country	Year Introduced
Puernol	Formenti	Italy	-
Pyrinazin	Yamanouchi	Japan	-
Pyrital	Medica	Finland	-
Reliv	ACO	Sweden	-
Rivalgyl	Rivopharm	Switz.	-
Rounox	Rougier	Canada	-
Servigesic	Servipharm	Switz.	-
Setamol	Pharmacia	Sweden	-
Setol	Dif-Dogu	Turkey	-
Supramol	Sam-On	Israel	-
Tabalgin	Bayer	W. Germany	-
Tachipirina	Angelini	Italy	-
Temperal	Prodes	Spain	-
Trenodin	Fresenius	W. Germany	-
Tymol	Reckitt and Colman	W. Germany	-
Veralydon	Lelong	France	

Raw Materials

Nitrobenzene
Acetic anhydride

Manufacturing Process

About 250 ml of a reaction mixture obtained by the electrolytic reduction of nitrobenzene in sulfuric acid solution and containing about 23 grams of p-aminophenol by assay is neutralized while at a temperature of 60°C to 65°C, to a pH of 4.5 with calcium carbonate. The calcium sulfate precipitate which forms is filtered off, the precipitate washed with hot water at about 65°C and the filtrate and wash water then combined. The solution is then extracted twice with 25 ml portions of benzene and the aqueous phase is treated with 0.5 part by weight, for each part of p-aminophenol present, of activated carbon and the latter filtered off. The activated carbon is regenerated by treatment with hot dilute caustic followed by a hot dilute acid wash, and reused a minimum of three times.

To the filtrate obtained, there are then added about 0.2 gram of sodium hydrosulfite or sodium sulfite and 15.0 grams of anhydrous sodium acetate in about 27 grams of acetic anhydride at 40°C. The reaction mixture formed is cooled to 8°C to 10°C with stirring and held at this temperature for 60 minutes. A crystalline precipitate of about 27 grams of N-acetyl-p-aminophenol is obtained melting at 169-171°C. This is equivalent to a yield of 85%.

In lieu of utilizing calcium carbonate as the neutralizing agent, calcium hydroxide, barium hydroxide, barium chloride or other alkaline earth metal salt or hydroxide forming an insoluble sulfate may be employed.

References

Merck Index 39
Kleeman and Engel p. 684
PDR p. Many References
OCDS Vol. 1 p. 111 (1977)
DOT 16 (2) p. 59 (1980)
I.N. p. 728
REM p. 1111
Wilbert,G. and De Angelis, J.; US Patent 2,998,450; August 29, 1961; Assigned to Warner-Lambert Pharmaceutical Company

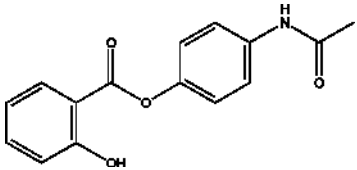
ACETAMINOSALOL

Therapeutic Function: Analgesic, Antineuralgic, Antirheumatic, Antipyretic

Chemical Name: 2-Hydroxybenzoic acid 4-(acetylamino)phenyl ester

Common Name: Acetamidosalol; Acetaminosal; Acetylparaminosalol; Acetaminosalol; Phenetsal

Structural Formula:



Chemical Abstracts Registry No.: 118-57-0

Trade Name	Manufacturer	Country	Year Introduced
Acetaminosal	ZYF Pharm Chemical	-	-

Raw Materials

N-Acetyl-p-aminophenol
Acetyl salicylic chloride
Sodium hydroxide
Acid chloride

Manufacturing Process

2 Methods of producing of acetyl salicylic acid ester of N-acetyl-p-aminophenol:

1. 65.0 g of N-acetyl-p-aminophenol were slurried with 400 ml of water and cooled to 10°C. 125 ml of 20% sodium hydroxide were slowly added to the mixture with stirring, the temperature being maintained 10°-15°C. To the solution obtained, 75.0 g of acetyl salicylic chloride were added with vigorous stirring over a period of 0.5 h, the solution being maintained at a temperature

of about 10°C. Towards the end of the reaction the pH was checked and adjusted to greater than 10 by the addition of a small amount of 20% sodium hydroxide. After all the acid chloride had been added, vigorous stirring was continued for 0.5 h during which time the crude product separated out. The acetyl salicylic acid ester of N-acetyl-p-aminophenol was filtered off, washed thoroughly with water and recrystallised from ethanol.

2. 65.0 g of sodium N-acetyl-p-aminophenol were slurried with 500.0 g of dry benzene and 80.0 g of acetyl salicylic chloride added. The mixture was heated under reflux for 4 h and filtered hot. The excess benzene was removed under vacuum and the crude acetyl salicylic acid ester of N-acetyl-p-aminophenol crystallized from ethanol.

References

Robertson A.; US Patent No. 3,431,293; March 4, 1969; Assigned: Sterling Drug Inc., New York, N.Y.

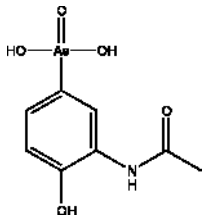
ACETARSOL

Therapeutic Function: Antiprotozoal, Tonic

Chemical Name: Arsonic acid, (3-(acetylamino)-4-hydroxyphenyl)-

Common Name: Acetarsol; Acetarsone; Osarsol(um)

Structural Formula:



Chemical Abstracts Registry No.: 97-44-9

Trade Name	Manufacturer	Country	Year Introduced
Acetarsol	Cyklo Pharma Chem Pvt. Ltd.	-	-
Acetarsol	Nizhpharm	-	-
Fluoryl	AFI	-	-
Gynoplix	Theraplix	-	-
Laryngarsol	Sanofi-Synthelabo	-	-
Nilacid	Sanofi-Synthelabo	-	-
Orarsan	Boots	-	-
Osarbon	Nizhpharm	-	-

Trade Name	Manufacturer	Country	Year Introduced
Pallicid	Wander	-	-
Spirocid	Hoechst	-	-
Stovarsol	Abbott	-	-

Raw Materials

4-Chloroaniline	Sodium nitrite
Hydrogen chloride	Sodium arsenite
Sodium hydroxide	Nitric acid/Sulfuric acid
Sodium thiosulfate	Acetic anhydride

Manufacturing Process

1 part of 4-chloroaniline is dissolved with 2 parts of concentrated hydrochloric acid (specific gravity 1.16) and 10 parts of water, and diazotised in the usual manner. 3 parts of sodium arsenite are introduced into the diazo solution thus obtained, the sodium arsenite being dissolved in 5 parts of water and 1 part of 96% ethanol. The solution is heated slowly to 70°C. When evolution of nitrogene ceased, it is filtered from separated oil and the addition of hydrochloric acid precipitates the 4-chlorophenylarsonic acid, which crystallizes out in the form of white needles.

By action HNO_3/H_2SO_4 on 4-chlorophenylarsonic acid is obtained 4-chloro-3-nitrophenylarsonic acid which is converted at 100°C with 33% aqueous solution of sodium hydroxide to 4-hydroxy-3-nitrophenylarsonic acid. After reduction of NO_2 group of 4-hydroxy-3-nitrophenylarsonic acid by the action of $Na_2S_2O_3$ or Fe/NaOH is obtained 3-amino-4-hydroxyphenylarsonic acid. From 3-amino-4-hydroxyphenylarsonic acid and acetic anhydride is prepared N-acetyl-4-hydroxy-m-arsanilic acid.

References

Bart H.; GB Patent No. 568; Jan. 9, 1911
GB Patent No. 5595; 06.03.1911; Assigned to Farbwerke vorm. Meister, Lucius, and Bruning, Hoechst, Germany

ACETAZOLAMIDE

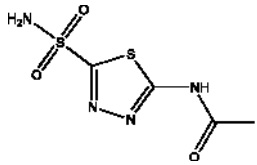
Therapeutic Function: Carbonic anhydrase inhibitor, Diuretic, Antiglaucoma

Chemical Name: N-[5-(Aminosulfonyl)-1,3,4-thiadiazol-2-yl]acetamide

Common Name: -

Chemical Abstracts Registry No.: 59-66-5

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Diamox	Lederle	US	1953
Hydrazole	Softcon Products	US	1975
Acetamide	Nessa	Spain	-
Acetamox	Santen	Japan	-
Acetazolam	ICN	Canada	-
Acetazolamide Chibret	Chibret	France	-
Albox	Kwizda	Austria	-
Atenezol	Tsuruhara	Japan	-
Defiltran	Jouveinal	France	-
Diazomid	Dif-Dogu	Turkey	-
Diamox	Theraplix	France	-
Didoc	Sawai	Japan	-
Diluran	Spofa	Czechoslovakia	-
Diuramid	Polfa	Poland	-
Dirureticum-Holzinger	Holzinger	Austria	-
Diuriwas	Wassermann	Italy	-
Donmox	Hona	Japan	-
Edemox	Wassermann	Spain	-
Glauconox	Llorens	Spain	-
Glaupax	Erco	Denmark	-
Glaupax	Baeschlin	W. Germany	-
Gleupax	Dispersa	Switz.	-
Inidrase	Omikron-Gagliardi	Italy	-
Nephramid	Chemiek	E. Germany	-
Oedemin	Astra	Sweden	-
Renamid	Pliva	Yugoslavia	-
Uramox	Taro	Israel	-
Zohnox	Konto	Japan	-

Raw Materials

Hydrazine hydrate
Ammonium thiocyanate
Acetic anhydride
Chlorine
Ammonia
Bromine

Manufacturing Process

According to REM, hydrazine hydrate is reacted with 2 mols of ammonium thiocyanate to produce 1,2-bis(thiocarbamoyl)hydrazine which by loss of ammonia and rearrangement produces 5-amino-2-mercapto-1,3,4-thiadiazole. That compound is acetyled with acetic anhydride.

Then, as described in US Patent 2,554,816, the 2-acetylamido-5-mercapto-1,3,4-thiadiazole is converted to the sulfonyl chloride by passing chlorine gas into a cooled (5-10°C) solution in 33% acetic acid (66 parts to 4 parts of mercapto compound) used as a reaction medium. Chlorine treatment is continued for two hours. The crude product can be dried and purified by recrystallization from ethylene chloride. The pure compound is a white crystalline solid, MP 194°C, with decomposition, when heated rapidly. The crude damp sulfonyl chloride is converted to the sulfonamide by addition to a large excess of liquid ammonia. The product is purified by recrystallization from water. The pure compound is a white, crystalline solid, MP 259°C, with decomposition. The yield of sulfonamide was 85% of theory based on mercapto compound.

An alternative process is described in US Patent 2,980,679 as follows. 15 grams of finely powdered 2-acetylamino-1,3,4-thiadiazole-5-mercaptain are suspended in 200 ml of water containing 4 grams of potassium bromide. From 0.5 to 1 gram of ferric chloride are subsequently added. The mass is energetically stirred and 52 grams of liquid bromide are added by increments for about 45 minutes, while keeping the reaction temperature below 10°C, and, preferably, at 4-8°C by employing a cooling bath. Stirring is continued for a further 10 minutes, then the 2-acetylamino-1,3,4-thiadiazole-5-sulfobromide is collected on a funnel equipped with a porous diaphragm, thoroughly washed with cold water and finally subjected to amidation with liquid ammonia. The reaction mixture is allowed to stand for a certain period, then the ammonia is evaporated, after which the residue is taken up with diluted ammonia and, after decolorizing with carbon, the sulfonamide is precipitated with hydrochloric acid. The yield of crude sulfonamide obtained with this process, with respect to the starting mercapto compound is abut 84%. If the amidation is carried out with 33% aqueous ammonia, the yield is slightly lower.

References

Merck Index 45
Kleeman and Engel p. 6
PDR pp. 830, 1008, 1606
OCDS Vol. 1 p. 249 (1977)
I.N. p. 5
REM p.936
Clapp, J.W. and Roblin, R.O., Jr.; US Patent 2,554,816; May 29, 1951; Assigned to Americar Cyanamid Company
Gianfranco, P.; US Patent 2,980,679; April 18, 1961; Assigned to Omikron-Gagliardi Societa di Fatto, Italy

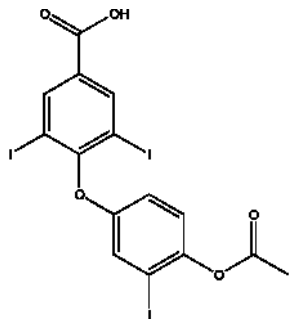
ACETIROMATE

Therapeutic Function: Antihyperlipidemic

Chemical Name: Benzoic acid, 4-(4-hydroxy-3-iodophenoxy)-3,5-diiodo-, acetate

Common Name: Acetiromate; Adecol

Structural Formula:



Chemical Abstracts Registry No.: 2260-08-4

Trade Name	Manufacturer	Country	Year Introduced
Acetiromate	ZYF Pharm Chemical	-	-

Raw Materials

3,5-Diiodo-4-(3-iodo-4-hydroxyphenoxy)benzoic acid
Acetic anhydride

Manufacturing Process

To 3 parts of 3,5-diiodo-4-(3-iodo-4-hydroxyphenoxy)benzoic acid 10 parts of acetic acid anhydride was added and mixture was heated on oil bath for some hours. In the result of this reaction amorphous precipitate was obtained. After recrystallization from glacial acetic acid 2.4 parts of 3,5-diiodo-4-(3-iodo-4-acetoxyphenoxy)benzoic acid were obtained.

References

Fr. Patent No. M1610; Dec. 10, 1962; Assigned: Takeda Chemical Industries, LTD

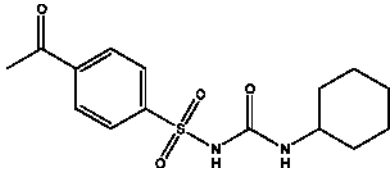
ACETOHEXAMIDE

Therapeutic Function: Hypoglycemic

Chemical Name: 1-[(p-Acetylphenyl)sulfonyl]-3-cyclohexylurea

Common Name: Cyclamide

Structural Formula:



Chemical Abstracts Registry No.: 968-81-0

Trade Name	Manufacturer	Country	Year Introduced
Dymelor	Lilly	US	1964
Dimelin	Shionogi	Japan	-
Dimelor	Lilly	UK	-
Gamadiabet	Salvat	Spain	-
Metaglucina	Perga	Spain	-
Ordimel	Lilly	Spain	-

Raw Materials

Sodium nitrite
Hydrogen chloride
Ammonia
p-Aminoacetophenone
Sulfur dioxide
Cyclohexyl isocyanate

Manufacturing Process

Preparation of p-Acetylbenzenesulfonamide: 100 grams of p-aminoacetophenone were dissolved in a solvent mixture containing 165 ml of 12 N hydrochloric acid and 165 ml of glacial acetic acid. The mixture was cooled with stirring to about 0°C. A solution containing 56.2 grams of sodium nitrite and 175 ml of water was added dropwise with stirring to the acidic solution while maintaining the temperature below 5°C.

After the addition had been completed, the acidic solution containing p-acetylphenyldiazonium chloride formed in the above reaction was added dropwise with stirring to a mixture of 530 ml of glacial acetic acid and 530 ml of benzene which had been previously cooled, and the cooled solution saturated with sulfur dioxide and to which had been added 34 g of cupric chloride dihydrate. After the addition had been completed, the reaction mixture was stirred at about 40°C for three hours, and was then poured into 3,000 ml of an ice-water mixture.

The benzene layer containing p-acetylbenzenesulfonyl chloride formed in the above reaction was separated, and the acidic aqueous phase was extracted twice with 250 ml portions of benzene. The benzene layers were combined, the combined extracts were filtered, and the benzene was evaporated from the resulting filtrate in vacuum.

The solid residue comprising p-acetylbenzenesulfonyl chloride was dissolved in 100 ml of dioxane, and the solution was added to 200 ml of 14% aqueous ammonium hydroxide. The resulting solution was stirred overnight at ambient room temperature. The p-acetylbenzenesulfonamide thus prepared was collected by filtration. Recrystallization of the filter cake from aqueous ethanol yielded purified p-acetylbenzenesulfonamide melting at about 176°C to 179°C.

Preparation of N-p-Acetylphenylsulfonyl-N'-Cyclohexylurea: A reaction mixture consisting of 32.7 grams of p-acetylbenzenesulfonamide and 64 grams of anhydrous potassium carbonate in 350 ml of anhydrous acetone was stirred at refluxing temperature for about 1% hours, thus forming the potassium salt of p-acetylbenzenesulfonamide. 30.9 grams of cyclohexylisocyanate were added dropwise to the reaction mixture. Refluxing and stirring were continued during the course of the addition and for an additional 16 hours.

The acetone was removed by evaporation in vacuum, and about 750 ml of water were added to dissolve the resulting residue. The solution was filtered. The potassium salt of N-p-acetylphenylsulfonyl-N'-cyclohexylurea formed in the above reaction, being water-soluble, passed into the filtrate. Acidification of the filtrate with 6 N aqueous hydrochloric acid caused the precipitation of N-p-acetylphenylsulfonyl-N'-cyclohexylurea which was collected by filtration. Recrystallization of the filter cake from 90% aqueous ethanol yielded purified N-p-acetylphenylsulfonyl-N'-cyclohexylurea melting at about 188-190°C.

References

Merck Index 53
Kleeman and Engel p. 7
PDR p. 1049
OCDS Vol. 1 p. 138 (1977)
I.N. p. 6
REM p.976
Sigal, M.V., Jr. and Van Arendonk, A.M.; US Patent 3,320,312; May 16, 1967; Assigned to Eli Lilly and Company.

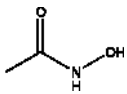
ACETOHYDROXAMIC ACID

Therapeutic Function: Urease inhibitor

Chemical Name: Acetamide, N-hydroxy-

Common Name: Acetohydroxamic acid; Uronefrex

Structural Formula:



Chemical Abstracts Registry No.: 546-88-3

Trade Name	Manufacturer	Country	Year Introduced
Lithostat	Mission Pharmacal Co.	-	-
Uronefrex	Robert	-	-

Raw Materials

Hydroxylamine
Acetamide
Nitrohydroxylamine
Ethyl acetic acid ether
Acetaldehyde

Manufacturing Process

3 Methods of producing of acetohydroxamic acid:

1. Ethyl acetic acid ether was treated with hydroxylamine and acetohydroxamic acid was obtained.

2. Acetohydroxamic acid was obtained in the result of reaction of acetamide with hydroxylamine.

3. Acetohydroxamic acid was obtained by treatment of acetaldehyde with nitrohydroxylamine.

References

Karrer P.; Lehrbuch der organischen chemie; Stuttgart; 1959; 1216 s.

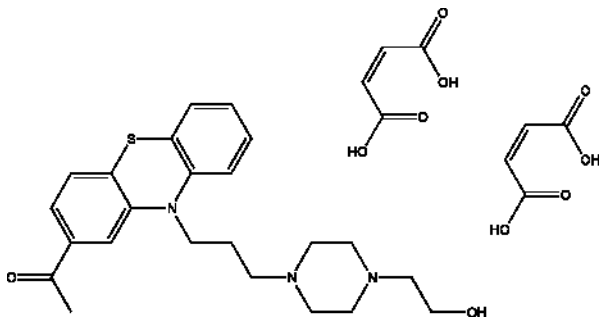
ACETOPHENAZINE DIMALEATE

Therapeutic Function: Tranquilizer

Chemical Name: 10-[3-[4-(2-Hydroxyethyl)-1-piperazinyl]propyl] phenothiazin-2-yl methyl ketone maleate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 5714-00-1; 2751-68-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Tindal	Schering	US	1961

Raw Materials

2-Acetylphenothiazine
Sodium amide
1-Bromo-3-chloropropane
Maleic acid
1-(2-Hydroxyethyl)piperazine

Manufacturing Process

The requisite intermediate, 10-(3-chloropropyl)-2-acetylphenothiazineis prepared as follows: To a suspension of sodium amide (from 3 grams of sodium) in 300 ml of liquid ammonia is added 30 grams of 2-acetylphenothiazine. After stirring for one hour, there is added 19 grams of 1-bromo-3-chloropropane. The ammonia is allowed to evaporate and the residue is diluted with 200 ml of water. The mixture is extracted with ether and the ether solution is dried over anhydrous sodium sulfate, filtered and concentrated.

The residue consists of crude 10-(3-chloropropy1)-2-acetylphenothiazine as a viscous oil and is used in the next step without further purification. The crude base obtained from the reaction of 10-(3-chloropropyl)-2-acetylphenothiazine with 1-(2-hydroxyethyl)piperazine is purified by conversion to its dimaleate salt, MP 167-168.5°C from ethanol.

References

Merck Index 64
Kleeman and Engel p. 7
OCDS Vol. 1 p. 383 (1977)
I.N. p. 6
REM p. 1086
Sherlock, M.H. and Sperber, N.; US Patent 2,985,654; May 23, 1961; Assigned to Schering Corporation, Bloomfield, N.J.., a corporation of a New Jersey

ACETOXOLONE ALUMINUM SALT

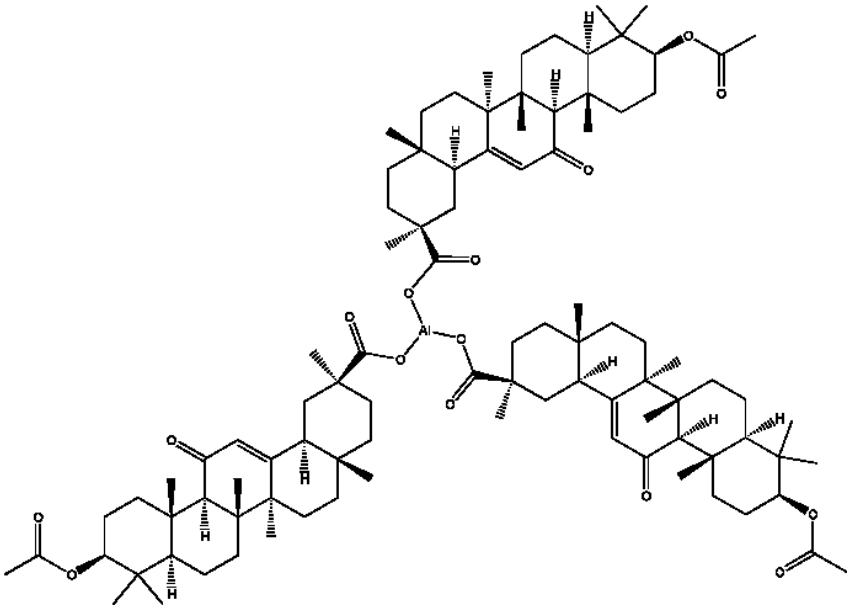
Therapeutic Function: Antiulcer

Chemical Name: 3-(Acetyloxy)-11-oxoolean-12-en-29-oic acid aluminum salt

Common Name: -

Chemical Abstracts Registry No.: 6277-14-1 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Oriens	Inverni Beffa	Italy	1981

Raw Materials

3-Acetyl-18β-glycyrrhetinic acid
Aluminum alcoholate

Manufacturing Process

The salts of 3-acetyl-18β-glycyrrhetinic acid can be prepared by reaction between 3-acetyl-18β-glycyrrhetinic acid and an aluminum alcoholate. Preferably lower alcoholates are used, i.e., alcoholates in which the alkoxy group or groups have from one to four carbon atoms. The salification reaction may be carried out at room temperature or at an elevated temperature in conventional fashion, preferably in the presence of organic solvents. As organic solvents may be used alcohols, ethers, ketones, chlorinated solvents (methylene chloride, chloroform) ethyl acetate, etc.

References

Merck Index 70
Bonati, A.; US Patent 3,764,618; October 9,1973; Assigned to Dott. Inverni and Della Befia S.P.A.

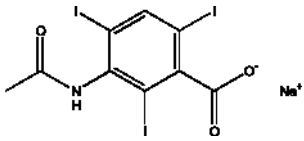
ACETRIZOATE SODIUM

Therapeutic Function: Diagnostic aid (radiopaque medium)

Chemical Name: 3-(Acetylamino)-2,4,6-triiodobenzoic acid sodium salt

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 129-63-5

Trade Name	Manufacturer	Country	Year Introduced
Urokon Sodium	Mallinckrodt Inc.	US	1950
Thixokon	Mallinckrodt Inc.	US	1957
Cystokon	Mallinckrodt Inc.	US	1964
Pyelokon-R	Mallinckrodt Inc.	US	-
Salpix	Ortho	US	-
Diaginol	May and Baker	UK	-
Diaginol	Banyu	Japan	-
Vasurix	Guerbet	France	-
Fortombrin	Dagra	Netherlands	-
Iodopaque	Labaz	Switz.	-
Triurol	Lundbeck	Denmark	-

Raw Materials

3-Amino-2,4,6-triiodobenzoic acid
Acetic anhydride
Sodium hydroxide

Manufacturing Process

3-Amino-2,4,6-triiodobenzoic acid (51.5 g) was mixed with 125 ml of acetic anhydride containing 2 drops of concentrated sulfuric acid and refluxed for thirty minutes. The mixture was allowed to cool slightly, and then was poured into 600 ml of water at room temperature and stirred until crystallization was complete. The mixed anhydride of 3-acetylamino-2,4,6-triiodobenzoic acid with acetic acid thus prepared was then separated by filtration and washed with water. Without drying, the solid was suspended in 600 ml of water and hydrolyzed with a slight excess of ammonium hydroxide. It was necessary to warm the mixture slightly and stir it for about one-half hour in order to dissolve all the solid. The solution was then treated with activated carbon, filtered and precipitated with an excess of hydrochloric acid, filtered, washed and dried at 70°C. The yield was 51.5 g of 3-acetylamino-2,4,6-triiodobenzoic

acid which melted at 276.6-278.2°C with decomposition when placed in the melting block at 260°C and heated at the rate of 3°C per minute. Due to decomposition, the melting point varied from about 269-280°C, depending upon the rate of heating and other conditions.

3-Acetylamino-2,4,6-triiodobenzoic acid (28 g) was dissolved in a little over 50 ml of 1 N sodium hydroxide in a round-bottom flask. The pH was adjusted to slightly over 7 and the solution was evaporated on a steam bath under reduced pressure. After the residue became solid, it was further dried overnight in a vacuum desiccator containing calcium chloride. The salt weighed 31.2 g, theory being 29.0 g, indicating that the product contains about 7% water of crystallization when dried under these conditions. The finished salt was scraped from the flask and ground.

References

Merck Index 73
Kleeman and Engel p. 8
I.N. p.7
Wallingford, V.H.; US Patent 2,611,786; September 23, 1952; Assigned to Mallinckrodt Chemical Works

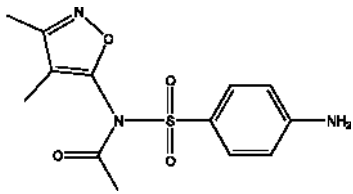
ACETYL SULFISOXAZOLE

Therapeutic Function: Antimicrobial

Chemical Name: N-[(4-Aminophenyl)sulfonyl]-N-(3,4-dimethyl-5-isoxazolyl) sulfanilamide

Common Name: Acetylsulfafurazol

Structural Formula:



Chemical Abstracts Registry No.: 80-74-0

Trade Name	Manufacturer	Country	Year Introduced
Gantrisin Acetyl	Roche	US	1954
Lipo-Gantrisin Acetyl	Roche	US	1954
Pediazole	Ross	US	-

Raw Materials

Sulfisoxazole
Acetic anhydride

Manufacturing Process

267 grams (1 mol) of sulfisoxazole were suspended in 400 ml of acetone and 79 grams (1 mol) of dry pyridine at 20-25°C in a round-bottom flask equipped with a stirrer and thermometer. 132 grams (1 mol) of acetic anhydride were added within 3 minutes with stirring. The sulfisoxazole dissolved in the mixture and a clear solution resulted. The temperature rose to 39-40°C. After stirring for several minutes, the product started to crystallize as a white crystalline mush. The temperature rose to 42-43°C maintained itself at this temperature for 15-30 minutes, and then started to drop. Stirring was continued for 5 hours and the mixture was then allowed to stand for 10 hours. One liter of 2.5-3.0% ice-cold aqueous ammonia and some fresh ice were then added while stirring and the crystals were filtered without delay. The crystals were washed on the filter with 1 liter of ice-cold 1% ammonia and then with 1 liter of water. The material on the filter was well pressed off, washed with 200-300 ml of alcohol and dried at 70°C to constant weight. The N-monoacetyl sulfisoxazole melted at 193-194°C and showed a positive Bratton-Marshall reaction and a positive Hucknall-Turfat reaction.

The product is in the form of colorless crystals which are somewhat water repellent. It is insoluble in alkali but is saponified upon standing in alkaline suspension (3% ammonia). It is soluble in strong acids (20-36% HCl or 10 N H_2SO_4) and is rapidly saponified upon standing.

References

Merck Index 104
Kleeman and Engel p. 13
PDR pp. 1487, 1558
I.N. p. 10
Hoffer, Max; US Patent 2,721,200; October 18, 1955; Assigned to Hoffmann-La Roche Inc.

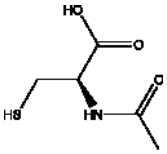
ACETYLCYSTEINE

Therapeutic Function: Expectorant

Chemical Name: N-Acetyl-L-cysteine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 616-91-1

Trade Name	Manufacturer	Country	Year Introduced
Mucomyst	Mead Johnson	US	-
Acetein	Senju	Japan	-
Airbron	BDH	UK	-
Broncholysin	Spofa	Czechoslovakia	-
Brunac	Bruschettini	Italy	-
Fabrol	Ciba	-	-
Fluimucetin	Zambon	Italy	-
Fluimucetin	Inpharzam	Belgium	-
Fluimucil	Zambon	Italy	-
Inspir	Vitrum	Sweden	-
Mucolyticum	Lappe	W. Germany	-
Mucosolvin	VEB Berlin Chemie	E. Germany	-
NAC	Mead Johnson	-	-
Parvolex	Duncan Flockhart	UK	-
Mucomist	Bristol	Italy	-
Mucisol	Deca	Italy	-
Rinofluimucil	Inpharzam	W. Germany	-
A.R.B.	Tokyo Tanabe	Japan	-
Mucofilin	Eisai	Japan	-

Raw Materials

L-Cysteine HCl
Acetic anhydride

Manufacturing Process

To a suspension of 35.2 grams (0.2 mol) of L-cysteine hydrochloride monohydrate stirred in a reaction vessel containing 87 ml of 91% aqueous tetrahydrofuran under a nitrogen atmosphere there is added 54.4 grams (0.4 mol) of sodium acetate trihydrate. The mixture is stirred for 20 minutes at room temperature to insure neutralization of the hydrochloride salt resulting in the formation of a suspension of equimolar amounts of cysteine and sodium acetate.

The mixture is then chilled to 3-6°C by external cooling and 20 ml (20.8 grams, 0.21 mol) of acetic anhydride is added thereto in dropwise fashion with cooling in the above range. The resulting mobile suspension is stirred for 6 hours at room temperature, allowed to stand overnight, and finally heated at reflux (72°C) for 4 hours. The resulting suspension of sodium N-acetyl-L-cysteinate is then neutralized by treatment at 5-10°C with 8 grams of hydrogen chloride. Resulting sodium chloride is removed by filtration and the product is isolated by distilling the solvent from the filtrate in vacuum and crystallizing the residue from 35 ml of water, yield 26.3 grams (80.6%) of N-acetylcysteine as a white solid, MP 109-110°C.

References

Merck Index 82
Kleeman and Engel p. 8

PDR p. 1126
DOT 16 (2) p. 42 (1980)
I.N. p. 8
REM p. 867
Martin, T.A. and Waller, C.W.; US Patent 3,184,505; May 18, 1965; Assigned to Mead Johnson and Company.

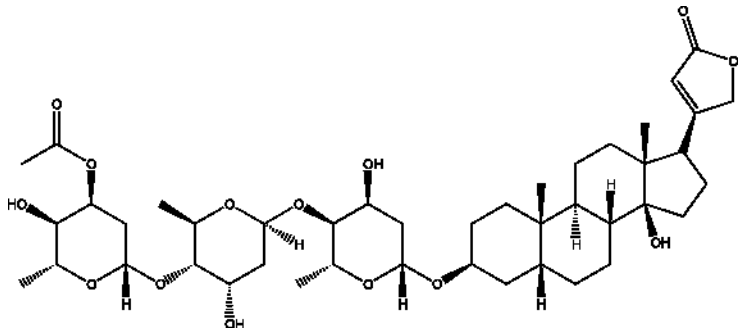
ACETYLDIGITOXIN

Therapeutic Function: Cardiotonic

Chemical Name: Card-20(22)-enolide, 3-((O-2,6-dideoxy-β-D-ribo-hexopyranosyl-(1.4)-O-2,6-dideoxy-beta-D-ribo-hexopyranosyl-(1.4)-2,6-dideoxy-β-D-ribo-hexopyranosyl)oxy)-14-hydroxy-, monoacetate, (3β,5β)-

Common Name: Digitoxin monoacetate

Structural Formula:



Chemical Abstracts Registry No.: 1111-39-3

Trade Name	Manufacturer	Country	Year Introduced
Acylanid	Sandoz	US	1954
Acygoxine	Sandoz	France	1972
Acylanide	Sandoz	France	1954
Acylanid	Sandoz	Italy	1966
Sandolanid	Sandoz	W. Germany	1968

Raw Materials

Digitalis Ferruginea Leaves

Manufacturing Process

Acetyldigitoxin-α can be obtained from acetyldigitoxin-β by heating it in an

anhydrous or aqueous organic solvent at neutral, weakly acid or weakly alkaline pH, i.e., at a pH range from about 3.5 to about 8.

The acetylidigitoxin-β used for this purpose is a cardiac glycoside which can be obtained either by splitting off the glucose residue from lanatoside A, or by extraction of the leaves of *Digitalis ferrugines*. It is composed of the aglycone digitoxigenin and 3 molecules of digitoxose, to one of which an acetyl group is attached. Acetyldigitoxin-α, obtained from acetyldigitoxin-β by rearrangement, differs from the latter in the position of the acetyl group.

The process may be carried out, for example, in the following manner: A solution of acetyldigitoxin-β in a suitable solvent, such as methanol, is boiled under reflux and then diluted with water. The unchanged acetyldigitoxin-β, which crystallizes out first, is filtered off and can again be submitted to the same process. On concentrating the filtrate, acetyldigitoxin-α separates out in crystalline form and after filtering off and recrystallizing is obtained in a pure state. The acetyldigitoxin-α crystallizes from aqueous methanol in platelets melting at 217-221°C.

References

Merck Index 83
Kleeman and Engel p. 9
I.N. p.8
Stoll, A. and Kreis, W.; US Patent 2,776,963; January 8, 1957; Assigned to Sandoz, AG, Switzerland.

β-ACETYLDIGOXIN

Therapeutic Function: Cardiotonic

Chemical Name: Card-20(22)-enolide, 3-((O-4-O-acetyl-2,6-dideoxy-beta-d-ribo-hexopyranosyl-(1.4)-O-2,6-dideoxy-beta-d-ribo-hexopyranosyl-(1.4)-2,6-dideoxy-beta-d-ribo-hexopyranosyl)oxy)-12,14-dihydroxy-, (3β,5β,12β)-

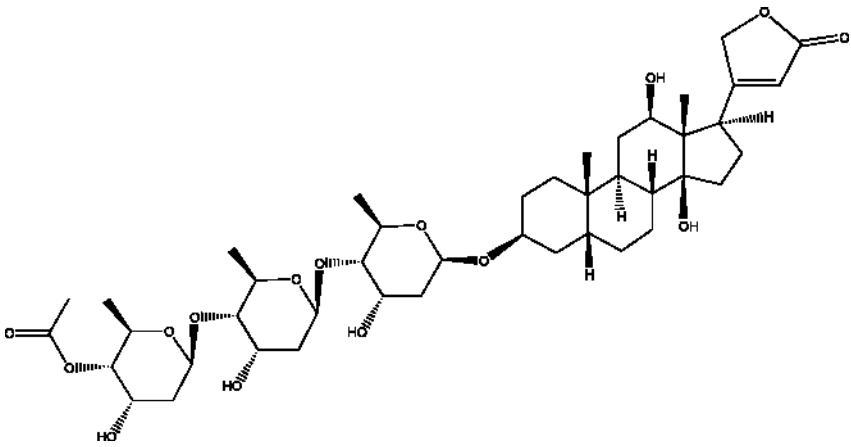
Common Name: beta-Acetyldigoxin; Betagoxinum

Chemical Abstracts Registry No.: 5355-48-6

Trade Name	Manufacturer	Country	Year Introduced
Novodigal	Asta Medica Arzneimittel	-	-
Novodigal	Lilly	-	-
Digoxin	Didier	-	-
Digoxin	Elkins-Sinn	-	-
Digoxin	Roxane	-	-
Digoxin	Wyeth-Ayerst	-	-

Trade Name	Manufacturer	Country	Year Introduced
Lanoxin	GlaxoSmithKline	-	-
Digitek	Bertek	-	-
Digoxin	Novartis	-	-
Corotal	Rosch and Handel	-	-

Structural Formula:



Raw Materials

Crude partial acetylated digoxin	Digoxin
Dicyclohexylcarbodiimide	Acetic acid

Manufacturing Process

Dried crude product of the partial acetylation of digoxin (42 g) prepared from digitalis - is dissolved under reflux in acetone (480 ml) and n-hexane (2400 ml) is added to the solution with stirring. Fine crystals, which begin to separate immediately, are left at room temperature for 5 hours, then they are filtered with suction, washed with n-hexane and dried in vacuum at 40°C, yielding 32 g of crude β-acetyldigoxin (product 1). Product 1 (31 g) is dissolved under reflux in chloroform (500 ml) and toluene (2500 ml) is added thereto with stirring. The crystals, which separate after standing for 6 hours at room temperature, are filtered, washed with toluene and ether and dried in vacuum yielding 29 g of β-acetyldigoxin (product 2). MP: 249°-251°C.

The filtrate, which results from the separation of product 1, is evaparated to dryness in vacuum. The residue, which mainly contains unreacted digoxin, is purified by recrystallization from pyridine/ether/water (3.5:5:40) and repeatedly acetylated. It can then be recycled to produce more β-acetyldigoxin. The filtrate resulting from the separation of product 2 is evaporated to dryness. The resulting residue contains the di- and polyacetyl derivatives of digoxin, which are deacetylated to digoxin in a known manner

and later is returned to a further acetylation process and can then be recycled to produce more β-acetyldigoxin.

Beta-Acetyldigoxin may be prepared from digoxin, acetic acid and dicyclohexylcarbodiimide using the last one as a condensing agent.

References

Pelan B. et al.; G.B. Patent No. 2,000,145 A; June 22, 1977
Haberland G., Arzneim.Forsh. 15, 481 (1965)

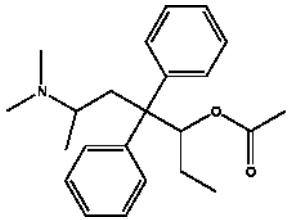
ACETYLMETHADOL

Therapeutic Function: Narcotic analgesic

Chemical Name: Benzeneethanol, β-(2-(dimethylamino)propyl)-α-ethyl-β-phenyl-, acetate (ester)

Common Name: Acemethadone; Acetyldimepheptanol; Acetylmethadol; Amidolacetat; Dimepheptanolacetat; Methadyl acetate; Race-Acetylmethadol

Structural Formula:



Chemical Abstracts Registry No.: 509-74-0

Trade Name	Manufacturer	Country	Year Introduced
Acetylmethadol	National Inst. for Drug Abuse	-	-
ORLAAM	Roxane Laboratories, Inc.	-	-

Raw Materials

Vinyl propionate	1-Dimethylamino-2-propanol
Novozym 435	Thionyl chloride
Sodium hydroxide	Diphenylacetonitrile
Dibenzo-18-crown-6	Hydrogen chloride
Sodium borohydride	Ethyl magnesium bromide

Acetyl chloride
Cerium (III) chloride heptahydrate

Manufacturing Process

Racemic 1-dimethylamino-2-propanol (100.0 g, 0.97 mol) was stirred with vinyl propionate (63.6 ml, 0.58 mol) at 40°C and Novozym 435 (5.0 g) was added. The reaction was stirred slowly for 75 h and after this time TLC (10% methanol/dichloromethane-visualize $KMnO_4$ solution) indicated that the reaction had gone to at least 50% conversion. The enzyme was removed by filtration and the filtrate was distilled at reduced pressure. S-(+)-1-Dimethylamino-2-propanol was obtained as a colourless oil (31.6 g, 64%), boil point 35°C.

A solution of thionyl chloride (37 ml, 0.48 mol) in chloroform (20 ml) was added slowly, with stirring, to a cooled (ice/water) solution of S-(+)-1-dimethylamino-2-propanol (30.6 g, 0.32 mol) in chloroform (85 ml). When the addition was complete a precipitate formed. The mixture was allowed to warm to room temperature over 30 min and then heated to reflux for a further 30 min. The precipitate redissolved on heating but then the product crystallized out from the boiling solvent as it formed. More chloroform (20 ml) was needed to maintain the stirring. The cooled mixture was diluted with ether and filtered. The 45.0 g (96%) of crude product was isolated. This was recrystallised from 2-propanol as in the other series to give 30.9 g (65%) of R-(-)-1-dimethylamino-2-chloropropane, melting point 192°-193°C.

A 50% w/v solution of sodium hydroxide in water (12.5 ml, 0.32 mol) was added to a mechanically stirred suspension of diphenylacetonitrile (15.0 g,0.08 mol) and dibenzo-18-crown-6 (0.5 g, cat.) in dimethylsulphoxide (12.5 ml). The color rapidly deepened to an orange/brown. R-(-)-1-Dimethylamino-2-chloropropane (30.0 g, 0.095 mol) was added in portions over 30 min, this caused the temperature to rise to 30°C. After the addition was complete the mixture was warmed to 45°-50°C (water bath) and stirred for a further hour. The reaction mixture was then allowed to cool to room temperature and was poured into ice/water (250 ml) and extracted with ethyl acetate (3 times 150 ml). The combined extracts were dried ($MgSO_4$) and filtered and evaporated down to -100 ml. The product was extracted into 1N HCl (100 ml+50 ml) and this was back washed with ethyl acetate. The aqueous was basified with 2 M sodium hydroxide and extracted into ethyl acetate (3 times 100 ml). The extracts were washed with brine (70 ml), dried ($MgSO_4$), and evaporated down to a yellow oil. This was chilled and triturated with cold hexane (50 ml) to give a white solid which was collected by filtration and washed thoroughly with a further portion of cold hexane (100 ml). 14.65 g (33%) of S-(+)-2,2-diphenyl-4-dimethylaminopentanenitrile were obtained, melting point 100°-101°C (recrystallised from hexane).

All apparatus was dried and the reaction was carried out under an inert atmosphere of argon. A solution of S-(+)-2,2-diphenyl-4-dimethylaminopentanenitrile (10.0 g, 0.018 mol) in toluene (15 ml) was added to a stirred solution of 3 M ethyl magnesium bromide in ether (10.7 ml, 0.03 mol). The ether was removed under reduced pressure and the remaining solution heated at reflux (135°-140°C) for 3 h. The solution went slightly cloudy but there was no significant precipitation. After cooling to room temperature 2 N HCl (30 ml) was added with care and then stirring was

continued at 135°-140°C for a further 30 min. The two phases were allowed to separate and cool to room temperature. After scratching the sides of the flask a solid started to crystallise from the aqueous phase. The flask was cooled to complete crystallisation and the white solid was collected by filtration. This solid was recrystallised from water to yield 6.6 g (53%) of S-(+)-methadone hydrochloride (6-dimethylamino-4,4-diphenyl-3-heptanone hydrochloride) were obtained, melting point 240°-241°C.

S-(+)-Methadone hydrochloride (600.0 mg,1.74 mmol) was dissolved in ethanol (10 ml) and the solution was stirred whilst sodium borohydride (3.47 mmol) was added portion-wise over a period of 5 min. When the addition was complete a spatula end of cerium (III) chloride heptahydrate was added. The resultant solution was allowed to stir at room temperature for 30 min then the ethanol was removed under reduced pressure. The residue was portioned between diethyl ether (40 ml) and water (40 ml). The aqueous layer was extracted with more diethyl ether (2 times 20 ml) and then the combined organics were washed with brine (40 ml) and dried ($MgSO_4$). The ether was removed under reduced pressure to leave 435.0 mg, (80%) of 6-dimethylamino-4,4-diphenyl-3-heptanol.

6-Dimethylamino-4,4-diphenyl-3-heptanol (435.0 mg, 1.40 mmol) dissolved in ethyl acetate (10 ml) was treated with acetyl chloride (183.0 mg, 2.33 mmol). The mixture was refluxed for 2 h. After allowing the solution to cool to room temperature the solvent was removed under reduced pressure to leave a white foam, this crystallised from ethyl acetate to give 6-dimethylamino-4,4-diphenyl-3-acetoxyheptane hydrochloride (levo-α-acetyl methadol hydrochloride) (420.0 mg, 79%).

The 6-dimethylamino-4,4-diphenyl-3-acetoxyheptane may be produced by treatment of the 6-dimethylamino-4,4-diphenyl-3-acetoxyheptane hydrochloride with sodium hydroxide.

References

Scheinmann F. et al.; US Patent No. 6,143,933; Nov. 7, 2000; Assigned: Salford Ultrafine Chemicals and Research Ltd., United Kingdom

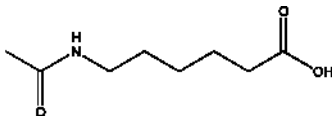
ACEXAMIC ACID

Therapeutic Function: Antifibrinolytic

Chemical Name: Hexanoic acid, 6-(acetylamino)-

Common Name: Acexamic acid; Plastesol

Structural Formula:



Chemical Abstracts Registry No.: 57-08-9

Trade Name	Manufacturer	Country	Year Introduced
Acexamic acid	Flamma	-	-
Acide Acexamicum	ZYF Pharm Chemical	-	-
Plastenan	Sanofi Winthrop	-	-

Raw Materials

Calcium hydroxide
Acetylcaprolactame
Hydrogen chloride

Manufacturing Process

400 L of demineralized water, 5.0 kg of calcium hydroxide, and 155.0 kg (1000 moles) of acetyl-caprolactame are introduced under stirring and at a temperature of about 25°C into a 1000 L stainless double walled reactor.

The temperature is raised to 30°C. 75.0 kg of calcium hydroxide are introduced stepwise in the form of successive amounts of 2.0 kg each in the medium, under stirring and at a temperature adjusted and maintained 25°-30°C through external cooling, in a manner such that the time required to introduce into the reactor the whole amount of calcium hydroxide approximates 1.5 h. When the stirring is stopped, the pH is about 7.5-7.8.

The obtained mixture is stirred continuously at a temperature of 30°C during 14 h. At the end of this operation the pH is again adjusted at a value 7.5-7.8.

The hydrolysate is filtered on a 60 x 60 pressfilter comprising 6 compartments and equipped with fabrics of the polyester known under the designation TERGAL which have been previously coated with a suspension of a cellulose commercialized under the trademark SOLKA FLOX BW20. The duration of filtration is of 1.5 h. 580 L of the filtrate are recovered and subjected to a concentration under reduced pressure in an evaporator the volume of which is of 750 L, at a distillation temperature ranging from 45°-50°C under a reduced pressure of 10-15 Torr.

The operation is ran until concentration of the solution to 280 L, the concentrated solution being then left standing. The crystallisation is already considerable 2 h after the end of the operation of concentration. Crystallisation is ended after 16-24 h.

The crystals are centrifuged at a speed of 700 revolutions/minute. The centrifuged crystals of calcium acexamate are washed twice on the centrifuge with 20 l of acetone. 107.0 kg of crystals are obtained, which are dried under vacuum at 40°C. The 96.0 kg of dry calcium acexamate obtained are ground and sifted.

Acexamic acid may be produced by treatment of the calcium acexamate with HCl.

References

Goulay J.; US Patent No. 3,974,215; Aug. 10, 1976; Assigned: Choay S.A., Paris, France

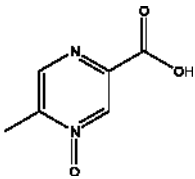
ACIPIMOX

Therapeutic Function: Antihyperlipidemic

Chemical Name: 2-Pyrazinecarboxylic acid, 5-methyl-, 4-oxide

Common Name: Acipimox; Zopinox

Structural Formula:



Chemical Abstracts Registry No.: 51037-30-0

Trade Name	Manufacturer	Country	Year Introduced
Olbetam	Pfizer	-	-
Nedios	Byk Pharmaceuticals	-	-
Olbemox	Pharmacia	-	-
Olbemox	Pfizer	-	-

Raw Materials

Ethyl chloroformate
Ammonia
Hydrogen peroxide
Hydrochloric acid
2-Carboxy-5-methylpyazine
Acetic acid
Sodium hydroxide

Manufacturing Process

2-Carboxy-5-methylpyazine (9.7 g) in dry dioxan (114 ml) and tributylamine (17.7 ml) was treated with ethyl chloroformate (7.5 ml), keeping the temperature at 0-5°C. After 10 min, dioxan (190 ml) saturated with ammonia was added. The mixture was stirred for 3 h at room temperature, then dioxin was distilled off, and the residue was taken up tin saturated aqueous sodium bicarbonate (20 ml). The mixture was filtered and the product washed with water to give 2-carbamoyl-5-methylpyrazine (9.2 g), melting point 204°-206°C.

This 2-carbamoyl-5-methylpyrazine (7.0 g) in glacial acetic acid (30 ml) and 35% (w/v) hydrogen peroxide (20 ml) was heated with stirring at 70°C for 7 h. The reaction mixture was cooled, the product which separated was filtered and washed with water to give 2-carbamoyl-5-methylpyrazine-4-oxide (5.5 g), melting point 206°-208°C.

2-Carbamoyl-5-methylpyrazine 4-oxide (5.0 g) was added to 10% by weight sodium hydroxide (50 ml) and then refluxed for 30 min. The reaction mixture was acidified with dilute hydrochloric acid and extracted in a continuous extractor with ethyl acetate. The ethyl acetate extract was concentrated to small volume and gave, after filtration 2-carboxy-5-methylpyrazine 4-oxide (3.2 g), melting point 178°-180°C.

References

GB Patent No. 1,361,967; July 31, 1974; Assigned: CARLO ERBA SPA an Italian body corporate of Via Carlo Imbonati 24, 20159 Milan, Italy

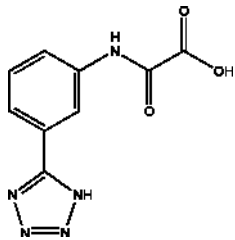
ACITAZANOLAST

Therapeutic Function: Anti-asthmatic, Antiallergic, Bronchodilator

Chemical Name: Acetic acid, oxo-((3-(1H-tetrazol-5-yl)phenyl)amino)-

Common Name: Acitazanolast; Azitanolast; Zepenolast

Structural Formula:



Chemical Abstracts Registry No.: 114607-46-4

Trade Name	Manufacturer	Country	Year Introduced
Zepelin	Kowa	-	-
Zepelin	Wakamoto	-	-

Raw Materials

3-(1H-Tetrazol-5-yl)aniline
Oxalyl chloride
Hydrochloric acid
Triethylamine
Sodium hydroxide

Manufacturing Process

2 Methods of preparation of 3-(1H-tetrazol-5-yl)oxanilic acid:

1. 5.0 g of 3-(1H-tetrazol-5-yl)aniline was dissolved in 25 ml of N,N-dimethylformamide, followed by adding 5.68 g of triethylamine. Then, 5.64 g of ether oxalyl chloride was dropwise added to the solution while cooling in ice water. After completion of the dropwise addition, the reaction temperature was slowly raised up to room temperature and the reaction was continued for 15 h. After the reaction was completed, the reaction mixture was poured into 100 ml of ice water and crystals separated out from the solution was filtered off to obtain 8.3 g of ethyl 3-(1H-tetrazol-5-yl)oxanilate (yield 94.1%), melting point 192°-l93°C (recrystallized from acetone/n-hexane).

The ethyl 3-(1H-tetrazol-5-yl)oxanilate (5.0 g), was dissolved in 35 ml of ethanol and 100 ml of 0.5 N sodium hydroxide was dropwise added thereto under water cooling. After the dropwise addition, the reaction temperature was slowly raised up to room temperature and under such condition, the reaction was carried out for 3 h. This solution was dropwise added to 70 ml of 4 N hydrochloric acid at room temperature. Thereafter, the solution was stirred for 1 h and crystals separated out from the solution was filtered off. The resultant crystals were washed with water and 3.9 g of 3-(1H-tetrazol-5-yl)oxanilic acid was recovered (yield 87.4%), melting point 241°-243°C (dec. recrystallized from isopropyl).

2. Oxalyl chloride (12.0 g) was dissolved in 50 ml of anhydrous dimethoxyethane. To this solution a solution of 3-(1H-tetrazol-5-yl)aniline (5.0 g) in 250 ml of anhydrous dimethoxyethane was dropwise added over 3 h at room temperature while stirring. Insolubles were removed by filtering the solution, then 50 ml of water was gradually added to the reaction mixture under ice cooling and stirring was continued for 1 h at room temperature. Then, 500 ml of ethyl acetate was added thereto to carry out extraction, the extract was washed with water, dried over anhydrous sodium sulfate and then the solvent was distilled off to obtain 5.4 g of the 3-(1H-tetrazol-5- yl)oxanilic acid (yield 74.8%), melting point 241°-243°C (dec. recrystallized from isopropyl).

References

Sawaki S. et al.; US Patent No. 4,795,754; Jan. 3, 1989Assigned: Wakamoto Pharmaceutical Co., Ltd., Tokyo, Japan

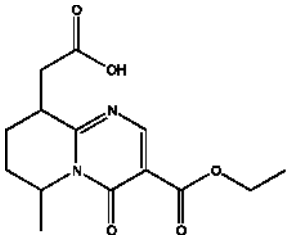
ACITEMATE

Therapeutic Function: Platelet aggregation inhibitor, Antihyperlipidemic

Chemical Name: 3-(Ethoxycarbonyl)-6,7,8,9-tetrahydro-6-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidine-9-acetic acid

Common Name: Acitemate; Vapedrine

Structural Formula:



Chemical Abstracts Registry No.: 64405-40-9

Trade Name	Manufacturer	Country	Year Introduced
Acitemate	Onbio Inc.	-	-

Raw Materials

3-Ethoxycarbonyl-7-methyl-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2a]pyrimidine
Palladium on carbon
Glyoxylic acid monohydrate
Hydrogen

Manufacturing Process

23.6 g of 3-ethoxycarbonyl-7-methyl-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2a]pyrimidine and 10.0 g of glyoxylic acid monohydrate are reacted and the obtained 3-ethoxycarbonyl-7-methyl-9-carboxy(hydroxymethyl)-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2a]pyrimidine is heated in 150 ml ethanol under stirring for 3 h. After cooling the crystals are filtered off and recrystallized from ethanol. Thus 3-ethoxycarbonyl-7-methyl-9-(carboxymethylene)-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2a]pyrimidine melting point 110°-112°C, is obtained (yield: 51%).

55.6 g of 3-ethoxycarbonyl-9-(carboxymethylene)-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2a]pyrimidine are hydrogenated in 500 ml of ethanol in the presence of 20.0 g of 9% by weight Pd/C catalyst containing metal. When 1 mole of hydrogen has been used up, the catalyst is removed from the reaction mixture by filtration and the solution is evaporated under reduced pressure. The 3-ethoxycarbonyl-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-9-acetic acid is obtained (yield: 57%), melting point 156°-157°C (recrystallized from ethanol).

References

Hermecz I. et al.; US Patent No. 4,123,533; Oct. 31, 1978; Assigned: Chinoin Gyogyazer es Vegyeszeti Termekek Gyara R.T., Budapest, Hungary

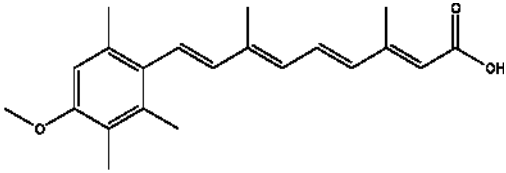
ACITRETIN

Therapeutic Function: Antipsoriatic

Chemical Name: 2,4,6,8-Nonatetraenoic acid, 3,7-dimethyl-9-(4-methoxy-2,3,6-trimethyl-phenyl)-, (all-E)

Common Name: Acitretin; Etretin

Structural Formula:



Chemical Abstracts Registry No.: 56079-83-9

Trade Name	Manufacturer	Country	Year Introduced
Acitretin	Roche	-	-
Neotigason	Roche Pty Limited	Australia	-
Neotigason	Roche	-	-
Soriatane	Roche Pharmaceuticals	-	-

Raw Materials

5-(4-Methoxy-2,3,6-trimethylphenyl)-3-methylpenta-2,4-diene-1-triphenylphosphonium bromide
3-Formylcrotonic acid butyl ester
Sodium hydride

Manufacturing Process

228 g of 5-(4-methoxy-2,3,6-trimethyl-phenyl)-3-methyl-penta-2,4-diene-1-triphenylphosphonium bromide was added under nitrogen to 910 ml of dimethylformamide and treated at 5-10°C within 20 min. with 17.5 g of a suspension of sodium hydride (about 50% by weight) in mineral oil. The mixture was stirred for 1 hour at about 10°C, then 61.8 g of 3-formylcrotonic acid butyl ester was added dropwise at 5-8°C, a mixture was heated for 2 hours at 65°C, subsequently introduced into 8 L of ice-water, then was added 300 g of sodium chloride, and the mixture thoroughly extracted with a total 18 L of hexane. The extract was washed 5 times with 1 L of methanol/water (6:4 parts by volume) each time and 2 times with 1.5 L water each time, dried over sodium sulphate and evaporated under reduced pressure to leave 9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester, m.p. 80-81°C.

125.8 g of this ester was introduced into 2 L of abs. ethanol and treated with a solution of 125.6 g of hydroxide in 195 ml of water. The mixture was heated

to boiling under nitrogen gassing for 30 minutes, then cooled, introduced into 10 L of ice-water and, after the addition of about 240 ml of conc. hydrochloric acid (pH 2-4), thoroughly extracted with total 9 L methylene chloride. Extract is washed with about 6 L water to neutrality, dried over calcium chloride and evaporated under reduced pressure. The residue is taken up in 700 ml of hexane. The precipitated 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid melts at 228-230°C.

References

W. Bollang, R. Ruegg, G. Ryser, US Patent No. 4,105,681, Aug. 8, 1978

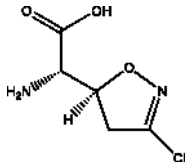
ACIVICIN

Therapeutic Function: Antineoplastic

Chemical Name: 5-Isoxazoleacetic acid, α-amino-3-chloro-4,5-dihydro-, (S-(R*,R*))-

Common Name: Acivicin; NSC-163501

Structural Formula:



Chemical Abstracts Registry No.: 42228-92-2

Trade Name	Manufacturer	Country	Year Introduced
Acivicin	ZYF Pharm Chemical	-	-
LKT-A0934-M010	LKT Laboratories, Inc.	-	-

Raw Materials

cis-2-Buten-1,4-dio
Trichloroacetonitrile
Dibromoformaldoxime
Monotrichloroacetimidate
tert-Butyl benzene
Bromonitrile oxide

Manufacturing Process

Starting from commercial, cis-2-buten-1,4-diol, the monotrichloroacetimidate was obtained as a colorless liquid (60%, b.p. 88°-102°C/0.2 mm Hg) by treatment with trichloroacetonitrile (1 equivalent) in tetrahydrofuran at -23°C in the presence of catalytic amount of sodium. Monotrichloroacetimidate upon refluxing in tert-butyl benzene for about 1 hour underwent, smoothly,

rearrangement to afford the vinylglycine synton (84%, MP: 30°C). The treatment of the last compound with bromonitrile oxide (3 equiv.) generated in situ from dibromoformaldoxime in ethyl acetate containing excess of $KHCO_3$ and trace amounts of water afforded 3:2 mixture of cycloadducts threo- and erythro-N-[1-(3-bromo-4,5-dihydroisoxazol-5-yl)-2-hydroxyethyl]-2,2,2-trichloroacetamide. The undesired threo- isomer (MP: 164°-165°C) was quantitatively removed from the mixture by fractional crystallization from chloroform. The erythro-isomer (oil) was refluxed with methanolic-HCl for 1 hour to give the chloro-alchohol (50%, syrup), which upon Jones oxidation (with $H_2Cr_2O_7$/acetone) followed by deprotection of trichloroacetyl group ($Ba(OH)_2/H_2O$, H_3^+O) afforded racemic acivicin (66 %). The synthetic, racemic antibiotic was spectrally (UV, ^1H NMR) indistinguishable from natural product, prepared from fermentation broth of Stretomyces sviceus.

References

Vyas D.M., Chiang Y. and Doyle T.W.; Tetrahedron Letters, vol. 25, No 5, p.p. 487-490; 1984

Mrtin D.G., Duchamp D.J. and Chidester C.G.; Tetrahedron Letters, No 27, p.p. 2549-2552, 1973

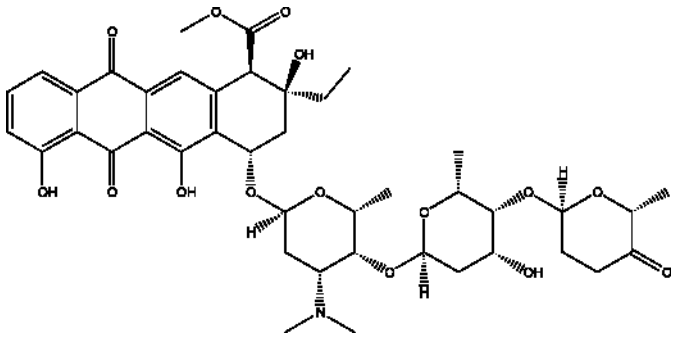
ACLARUBICIN

Therapeutic Function: Antitumor, Antibiotic

Chemical Name: Aclacinomycin A

Common Name: Aclacinomycin A

Structural Formula:



Chemical Abstracts Registry No.: 57576-44-0

Trade Name	Manufacturer	Country	Year Introduced
Aclacinon	Yamanouchi	Japan	1981
Aclacinomycine	Roger Bellon	France	1981

Raw Materials

Carbohydrates

Manufacturing Process

An aqueous medium having the following composition was prepared:

	Percent
Potato starch	1
Glucose	1
Prorich	1.5
KH_2PO_4	0.1

	Percent
K_2HPO_4	0.1
$MgSO_4 \cdot 7H_2O$	0.1
NaCl	0.3
Minerals*	0.125
Silicone (KM75)	0.05
pH	7.0

*2.8 g $CuSO_4 \cdot 5H_2O$, 0.4 g $FeSO_4 \cdot 7H_2O$, 3.2 g $MnCl_2 \cdot 4H_2O$, 0.8 g $ZnSO_4 \cdot 7H_2O$ in 500 ml water

100 ml of this medium was sterilized at 120°C for 15 min in a 500 ml Sakaguchi-shaking flask which was inoculated from an agar slant culture of Streptomyces galilaeus MA144-M1 by platinum loop. Incubation proceeded for 48 hr at 28°C on a reciprocal shaker. 10 L of the previously sterilized medium in a 20 L stainless steel jar fermenter were aseptically inoculated with 200 ml of the above seed cultures. Fermentation was carried out at 28°C for 32 hours with agitation (240 rpm) and aeration (5 L/min). The cultured broth obtained was adjusted to pH 4.5, mixed with an adsorbent siliceous earth material and filtered from the mycelium. The filtrate and cake obtained thereby were extracted separately. The cake was suspended in acetone (3 L/kg wet cake), stirred for 2 hr and filtered, and the cake was further extracted with acetone once again. The extracts thus obtained were evaporated to one-tenth volume in vacuum. The culture filtrate was adjusted to pH 6.8 and extracted twice with one-third volume of ethyl acetate, and the ethyl acetate extracts were concentrated to one-tenth volume in vacuum.

Twenty grams of the resulting oily substances were mixed with 20 grams of silicic acid (Mallinckrodt Chemical Co.), applied to a column 40 cm in length and 4.5 cm in diameter filled with silicic acid, and eluted with a benzene-acetone-methanol mixture. The initial eluate which eluted with a 1:1:0 mixture was discarded and the active fractions eluted with 1:3:0 and 1:3:0.3 mixtures were collected and concentrated to dryness in vacuum. 11.5 g of this crude substance was then dissolved in a small amount of ethyl acetate and applied to the same silicic acid column as above. After discarding the initial eluates by the 1:1 and 2:1 benzene-acetone mixtures, aclacinomycin B fractions were first eluted with the above mixtures of 1:3 and 1:5 ratio, and aclacinomycin A fractions were then eluted with the 1:5:0.5 and 1:5:1

benzene-acetone-methanol mixtures. The eluates were dried over anhydrous sodium sulfate and concentrated to dryness in vacuum. 4.8 g of crude aclacinomycin A and 3.5 g of aclacinomycin B were obtained as yellow powder.

2.0 g of crude aclacinomycin A obtained as above were dissolved in a small amount of chloroform, applied to a column 20 cm in length and 20 cm in diameter filled with 30 g of silicic acid. After eluting off the pigments containing aglycone and aclacinomycin B and other impurities with chloroform and 1.5% methanol-containing chloroform, aclacinomycin A fractions were eluted with 2% methanol-containing chloroform, and concentrated to dryness in vacuum. 53 mg of yellow powder of aclacinomycin A was obtained. Its melting point was 129°C to 135°C.

References

DFU2 (3) 171 (1978) (as Aclacinomycin A)
DOT 18 (10) 517 (1982)
I.N. p.42 (1984)
Umezawa, H., Takeuchi, T., Hamada, M., Takamatsu, A. and Oki, T.; US Patent 3,988,315; October 26, 1976; Assigned to Zaidan Hojin Biseibutsu Kagaku Kenkyu Kai

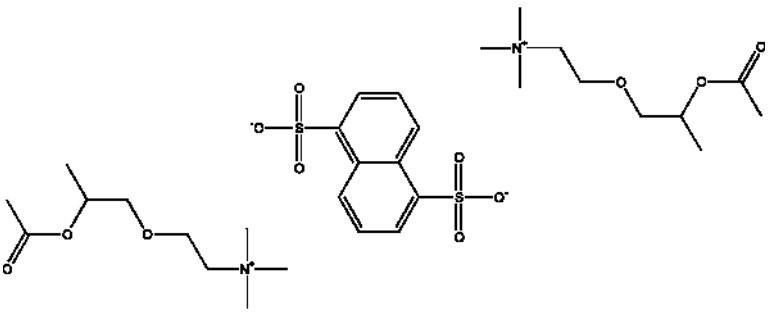
ACLATONIUM NAPADISYLATE

Therapeutic Function: Cholinergic

Chemical Name: 2-[2-(Acetyloxy)-1-oxopropoxy]-N,N,N-trimethylethan-aminium 1,5-naphthalenedisulfonate (2:1)

Common Name: Bis[acetoxy-methyl acetic acid trimethylammoniumethyl ester]-naphthalene-1,5-disulfonate

Structural Formula:



Chemical Abstracts Registry No.: 55077-30-0

Trade Name	Manufacturer	Country	Year Introduced
Abovis	Toyama	Japan	1981

Raw Materials

Bis(choline)-naphthalene-1,5-disulfonate
Lactic acid anhydride diacetate

Manufacturing Process

5.2 g of bis(choline)-naphthalene-1,5-disulfonate was suspended in 30 ml of acetonitrile, and 10 g of lactic acid anhydride diacetate was added thereto. This mixture was refluxed for 3 hours. The resulting reaction mixture was allowed to stand at room temperature while cooling to precipitate the desired product crystals, which were collected by filtration. 5.5 g (76% yield) of the desired product having a melting point of 189°C to 191°C were obtained.

References

Merck Index 110
DFU 7 (4) 227 (1982)
DOT 19 (1) 8 (1983)
I.N.p.42
Miura, K., Takagawa, N., Suzuki, Y. and Matsumoto, Y.; US Patent 3,903,137; September 2, 1975; Assigned to Toyama Chemical Co., Ltd.

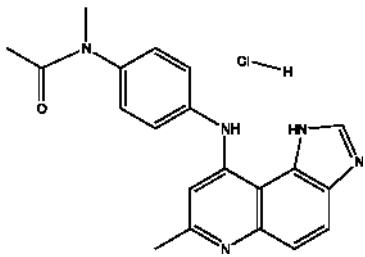
ACODAZOLE HYDROCHLORIDE

Therapeutic Function: Antineoplastic

Chemical Name: Acetamide, N-methyl-N-(4-((7-methyl-1H-imidazo[4,5-f]quinolin-9-yl)amino)phenyl)-, hydrochloride

Common Name: Acodazole hydrochloride; NSC-305884

Structural Formula:



Chemical Abstracts Registry No.: 55435-65-9; 79152-85-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Acodazole Hydrochloride	ZYF Pharm Chemical	-	-

Raw Materials

Acetic anhydride	N-Methyl-p-nitroaniline
Hydrogen	Nickel Raney
5-Nitrobenzimidazole	Palladium on carbon
Ethyl acetoacetate	Calcium sulfate
Acetic acid	$POCl_3$
Sodium hydroxide	Dowtherm®

Manufacturing Process

An 82.0 g (0.5 mole) of 5-nitrobenzimidazole in 900 ml of ethanol was reduced over 4.0 g of 5% Pd/C catalyst containing 50% H_2O. After filtration of the catalyst, 65.0 g (0.5 mole) of ethyl acetoacetate, 20.0 g of anhydrous calcium sulfate, and 0.5 ml of HOAc was added. After filtration, the solution was concentrated in vacuo till a solid remained. The product was filtered and washed with fresh ethanol and air-dried. The yield of ethyl 3-(5-benzimidazolylamino)crotonate was 84.0 g (69%), melting point 160°-162°C.

40.0 g of ethyl 3-(5-benzimidazolylamino)crotonate was added to 80 ml of boiling Dowtherm® and the boiling was continued for 5 min. The product separated upon cooling. The product was filtered, washed with Dowtherm® and then acetone and air-dried. The yield of 7-methyl-9-imidazo[4,5-f]quinolinol was 29.0 g (91%), melting point 345°-347°C.

Into a 22 L, 4-necked flask set in a tub and equipped with a stirrer, an air condenser (drying tube), thermometer, and dropping funnel was placed $POCl_3$ (4590 ml). The 7-methyl-9-imidazo[4,5-f]quinolinol (1062.0 g, 5.33 moles) was added with no heating effect noted. Dimethylformamide (4690 ml) was added dropwise over a 2.5 h period at a rate to control the temperature below 85°C. The resulting viscous solution was allowed to stand overnight at room temperature and then added cautiously to ice to a total volume of ca. 50 L. The resulting solution was then adjusted to a pH of 7 to 8 by the addition of NaOH pellets (9771.0 g). More ice was added as needed to keep the temperature below 45°C. The resulting precipitate was collected by filtration, washed well by stirring in water (3x20 L) and dried at 60°C to yield 1107.0 g (95.5%) of 9-chloro-7-methylimidazo[4,5-f]quinolone.

To 500 ml of acetic anhydride was added portionwise, 100.0 g (0.658) of N-methyl-p-nitroaniline. Following the addition, the solution was heated on a steam bath for 2 h, then stirred overnight at room temperature. The white precipitate of the N-methyl-4-nitroacetanilide was collected by filtration, washed with ether and air-dried to give 53.0 g, melting point 153°-156°C. The filtrate was concentrated in vacuum to give another 61.0 g, melting point 150°-154°C.

A mixture of 114.0 g (0.587 m) of N-methyl-4-nitroacetanilide and 800 ml of ethanol was shaken with hydrogen over one teaspoon of Raney active nickel catalyst in water. A pressure drop of 127 psi was recorded (calc. 118 psi). The catalyst was removed by filtration and the ethanol filtrate refluxed overnight with 127.0 g (0.587 m) of the 9-chloro-7-methylimidazo[4,5-f]quinolone. The mixture was chilled, filtered, washed with ether and air-dried to give 75.5 g of 9-[p-(N-methylacetamido)anilino]-7-methyl-1-H-imidazo[4,5-f]quinoline

hydrochloride sesquihydrate, melting point 315°-318°C (recrystallized from 4,000 ml of MeOH).

By treatment of 9-p-(N-methylacetamido)anilino-7-methyl-1H-imidazo[4,5-f]quinolone hydrochloride sesquihydrate with NaOH may be produced the 9-p-(N-methylacetamido)anilino-7-methyl-1H-imidazo[4,5-f]quinolone.

References

Spencer C.F., Snyder H.R.; US Patent No. 3,878,206; April 15, 1975; Assigned: Morton-Norwich Products, Inc., Norwich, N.Y.

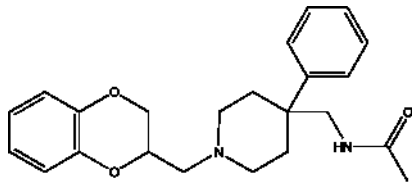
ACOXATRINE

Therapeutic Function: Vasodilator, Antihypertensive

Chemical Name: Acetamide, N-((1-(1,4-benzodioxan-2-ylmethyl)-4-phenyl-4-piperidyl)methyl)-

Common Name: Acetoxatrine; Acoxatrine

Structural Formula:



Chemical Abstracts Registry No.: 748-44-7

Trade Name	Manufacturer	Country	Year Introduced
Acoxatrine	ZYF Pharm Chemical	-	-

Raw Materials

Lithium aluminum hydride
Acetyl chloride
DL-1-Cyano-4-phenyl-piperidine
Sodium hydroxide

Manufacturing Process

To a solution of 11.5 parts lithium aluminum hydride in 100 parts tetrahydrofurane is added dropwise a solution of 94 parts DL-1-cyano-4-phenyl-piperidine in 240 parts tetrahydrofurane, at a temperature of about 45°C. After the addition is complete, the reaction mixture is stirred first at the same temperature for 3 h and 30 min and then refluxed for 1 h. The whole is decomposed by successive addition of 12 parts water, 9 parts sodium

hydroxide 20% and 50 parts water. The mixture is filtered from inorganic matter. The filter-cake is washed with tetrahydrofurane and the combined filtrates are evaporated. The oily residue is dissolved in 240 parts 2-propanol and to this solution are added about 60 parts concentrated hydrochloric acid. After keeping at room temperature, the precipitated salt is filtered off, washed with 2-propanol and dried, yielding DL-4-(amino-methyl)-1-[1,4-benzodioxanyl)methyl]-4-phenylpiperidine dihydrochloride; melting point 272°-278°C as a white amorphous powder.

From 4.1 parts DL-4-(aminomethyl)-1-[2-(1,4-benzodioxanyl)methyl]-4-phenylpiperidine dihydrochloride, the free base is liberated in the usual manner and extracted with chloroform. The organic layer is separated, dried and evaporated. The DL-4-(aminomethyl)-1-[2-(1,4-benzodioxanyl)methyl]-4-phenylpiperidine obtained is dissolved in 128 parts anhydrous chloroform. This solution is cooled to 5°C and there is added dropwise a solution of 1.6 parts acetylchloride in 7 parts anhydrous chloroform (exothermic reaction). The reaction mixture is stirred over night at room temperature and then alkalized with about 25 parts sodium hydroxide 20% at a temperature of 20°C. The aqueous layer is separated and extracted twice with chloroform. The combined organic layers are washed with water, dried over magnesium sulfate, filtered and evaporated. The oily residue is dissolved in a mixture of 40 parts acetone and 20 parts diisopropyl ether and evaporated again. The solid residue is triturated in diisopropylether, yielding DL-4-(N-acetylaminomethyl)-1-[2-(1,4-benzodioxanyl)-methyl]-4-phenylpiperidine; melting point 140°-141.1°C, as a white microcrystalline powder.

References

Janssen P.A.J.; US Patent No. 3,166,561; January 19, 1965; Assigned: Research Laboratorium Dr. C. Janssen N.V., a corporation of Belgium

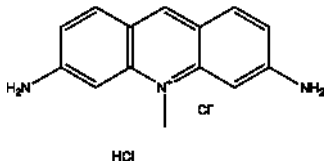
ACRIFLAVINE HYDROCHLORIDE

Therapeutic Function: Antiseptic, Topical antibacterial

Chemical Name: Acridinium, 3,6-diamino-10-methyl-, chloride, monohydrochloride, mixture with 3,6-acridinediamine hydrochloride

Common Name: Acid acriflavine; Acriflavin; Acriflavinium chloride; Euflavin; Flavacridinum; Xanthacridinum

Structural Formula:



Chemical Abstracts Registry No.: 6034-59-9; 837-73-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Acriflavine hydrochloride	ABCR GmbH and Co. KG	-	-
Acriflavine hydrochloride	Advance Scientific and Chemical, Inc.	-	-
Acriflavine hydrochloride	Spectrum Chemicals and Laboratory Products, Inc.	-	-
Acriflavine hydrochloride	Ruger Chemical Co., Inc.	-	-
Acriflavine hydrochloride	AppliChem	-	-
Acriflavine hydrochloride	Amend Drug and Chemical Company	-	-
Acriflavine hydrochloride	CCA (Changzhou) Biochemical Co., Ltd.	-	-
Acridina	Fatro	-	-
Acriflavin	Koi	-	-
Acriflavin	Vipor Chemicals Pvt.Ltd.	-	-
Acriflavin	Advance Scientific and Chemical, Inc.	-	-
Acriflavin	C. Krieger + Co. Nachf. GmbH + Co.	-	-
Acriflavin	Exim-Pharm International	-	-
Acriflavin	Hasco-Lek	-	-
Acriflavin	Dr Zdrowie SA	-	-
Acriflavin	Rasfer Internacional, S.A.	-	-
Acriflavin	Trannspharma, Sas	-	-
Acriflavin	Mediplus International	-	-
Acriflavin	Unical (Ceylon) Limited	-	-
Acriflavin	Olita Scientific Works	-	-
Acriflavin	Hygea SA; Polska Grupa Aptekarska	-	-
Acriflavin	Internatio NV	-	-
Acrinol	Pasteur	-	-
Burnol	Boots Company PLC	-	-
Diacrid	Sidroga AG	-	-
Euflavin	Macsen Laboratories	-	-
Gonacrine	May and Baker	-	-
Panflavin	Chinosolfabrik	-	-
Trypaflavin	Zoolek	-	-

Raw Materials

4,4-Diaminodiphenylmethane
Nitric acid
Hydrochloric acid
Tin
Ferric chloride
Acetanhydride
4-Toluolsulfomethyl ether

Manufacturing Process

4,4-Diaminodiphenylmethane reacted with HNO_3 and as a result of this reaction 4,4-diamino-2,2-dinitro-diphenylmethane was obtained.

By reducing of 4,4-diamino-2,2-dinitro-diphenylmethane with HCl and Sn, 2,2,4,4-tetraaminodiphenylmethane was produced, which at heating to 150°C gave 3,6-diamino-9,10-dihydroacridine.

The 3,6-diamino-9,10-dihydroacridine by oxidation with $FeCl_3$ was converted to 3,6-diaminoacridine.

3,6-Diaminoacridine was reacted with acetanhydride and 3,6-bis-(acetylamino)-acridine was produced.

3,6-Bis-(acetylamino)-acridine was methylated by p-toluolsulfomethyl ether and 3,6-bis-(acetylamino)-10-methylacridinumtosylate was produced.

Then the 3,6-bis-(acetylamino)-10-methylacridinumtosylate was converted to 3,6-diamino-10-methylacridinum chloride (acriflavinum chloride) by reaction with hydrochloric acid.

References

Kleemann A., Engel J.; Pharmazeutische Wirkstoffe, GeorgThieme Verlag Stuttgart, New York, 1982

ACRISORCIN

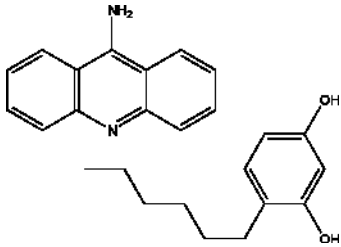
Therapeutic Function: Antifungal, Anthelmintic

Chemical Name: 1,3-Benzenediol, 4-hexyl-, compd. with 9-acridinamine (1:1)

Common Name: Acrisorcin; Akrinol; Aminacrine hexylresorcinate

Chemical Abstracts Registry No.: 7527-91-5

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Aminacrine hexylresorcinate	ZYF Pharm Chemical	-	-

Raw Materials

4-Hexylresorcinol	Potassium hydroxide
Hydrochloric acid	9-Aminoacridine

Manufacturing Process

4-Hexylresorcinol 194.0 g is added to a solution composed of 56.1 g potassium hydroxide in 1.5 L of water with stirring, and the mixture heated to about 40°C to effect complete solution. The pH of this solution is 12. A second solution of 9-aminoacridine hydrochloride is prepared as follows: 2 L of water containing 83 ml of concentrated hydrochloric acid are heated with stirring to about 80°C. Slowly 194.0 g of 9-aminoacridine are added. Heating is continued until a clear solution is obtained. About 2 ml of additional concentrated hydrochloric acid are added in small increments until the solution is slightly acid (pH of about 6). The 4-hexyl resorcinol solution is now slowly added under rapid agitation to the 9-aminoacridine hydrochloride solution. A copious precipitate is formed which, upon :stirring and continued addition of the 4-hexylresorcinol solution, becomes a creamy yellow slurry. At the end of the addition, the pH is 7-8 (indicator paper). The slurry is stirred while heated for an additional 15 min and then rapidly filtered on a 15 cm Buchner funnel. The product thus obtained is washed thoroughly, using about 1 L of cold water, to give a very pale yellow color in the last wash. The compound is then pressed dry and then oven-dried for 2-3 h at 50°C. The resultant product, 9-aminoacridine 4-hexyl resorcinolate, has a melting point of 189°-190°C.

References

Seneca H.; US Patent No. 3,122,553; Feb. 25, 1964; Assigned: Bansen, Inc., New York, N.Y., a corporation of New York

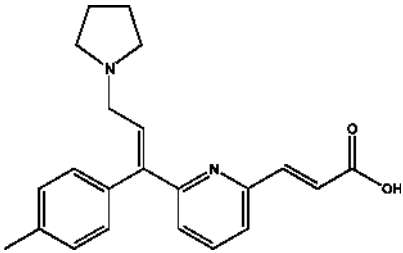
ACRIVASTINE

Therapeutic Function: Antihistaminic

Chemical Name: 2-Propenoic acid, 3-(6-(1-(4-methylphenyl)-3-(1-pyrrolidinyl)-1-propenyl)-2-pyridinyl)-, (E,E)-

Common Name: Acrivastine; Semprex

Structural Formula:



Chemical Abstracts Registry No.: 87848-99-5

Trade Name	Manufacturer	Country	Year Introduced
Acrivastine	ZYF Pharm Chemical	-	-
Semprex Cap.	Glaxo Wellcom-Misr Co.	-	-
Benadryl	Warner-Lambert	-	-
Benadryl	Pfizer	-	-

Raw Materials

Sulfuric acid	Triphenyl-2-pyrrolidinoethylphosphonium bromide
Butyl lithium	2,6-Dibromopyridine
4-Tolunitrile	Hydrochloric acid
Sodium carbonate	4-Toluenesulfonic acid
Ammonia	Sodium hydride
Sodium hydroxide	Triethyl phosphonoacetate

Manufacturing Process

Butyl lithium (50 ml, 1.65 mol in hexane) was added under nitrogen to a stirred suspension of 2,6-dibromopyridine (19.5 g) in dry ether (200 ml) at -50°C. After 0.75 h a solution of 4-tolunitrile (10.0 g) in ether (50 ml) was added; stirring was continued at -50°C for 3 h. The mixture was allowed to warm to -30°C and treated with hydrochloric acid (200 ml, 2 mol). The precipitated solid was collected, washed with water to give the 2-bromo-6-(4-toluoyl)pyridine as colourless needles (12.2 g), melting point 97°-98°C (recrystallized from aqueous ethanol).

A mixture of 2-bromo-6-(4-toluoyl)pyridine (200.0 g), ethylene glycol (85 ml), p-toluenesulphonic acid (32.0 g) and benzene (11 ml) was boiled under a Dean/Stark trap until water collection had become very slow (about 20 ml collected in 16 h).

The cooled solution was poured into ice/water containing sodium carbonate (100.0 g) with stirring. The benzene layer was separated, washed with water, dried with sodium sulfate and evaporated to about 500 ml. Cooling gave a

first crop of 2-(6-bromo-2-pyridyl)-2-(4-tolyl)-1,3-dioxolan, melting point 113°-114°C (170.0 g). Dilution with petroleum ether gave a second crop, melting point 109°-112°C (34.0 g). The residue after evaporation (31.0 g) was recycled.

A solution of 2-(6-bromo-2-pyridyl)-2-(4-tolyl)-1,3-dioxolan, vide supra, (70.0 g) in dry toluene (800 ml) was added dropwise during 5 h to a stirred solution of butyl lithium (1.6 mol in hexane, 200 ml) and toluene (200 ml) at -65° to -72°C under nitrogen. After a further 30 min at -70°C, dry dimethylformamide (40 ml) was added during 35 min. Stirring continued overnight at -70° to -60°C. Hydrochloric acid (2 N, 400 ml) was added, allowing the temperature to rise to about -10°C. After 30 min, 2 N ammonia (ca. 90 ml) was added to pH 7-8. The toluene layer was separated and the aqueous phase was extracted with ether. The combined organic liquids were washed with ice/water, dried ($MgSO_4$) and evaporated in vacuum below 50°C. The aldehyde, 2-(6-formyl-2-pyridyl)-2-(4-tolyl)-1,3-dioxolan, (63.9 g) crystallized on keeping at 3°C, melting point 52-63°C.

The 2-(6-formyl-2-pyridyl)-2-(4-tolyl)-1,3-dioxolan (2.5 g) was dissolved in 1,2-dimethoxyethane (10 ml) and added to a solution of the phosphonate carbanion produced from triethyl phosphonoacetate (2.0 g) and sodium hydride (0.22 g) in the same solvent. The mixture was stirred for 2 h, diluted with ether (25 ml) and treated with hydrochloric acid (5 ml, 2 mol). The organic phase was separated, washed with water, dried, and evaporated. The resulting oil was dissolved in ethanol (20 ml) containing concentrated hydrochloric acid (3 ml) and water (3 ml). After heating on the steam bath for 10 min, the solution was diluted with ice water, rendered alkaline with sodium bicarbonate solution, and extracted with ether. Evaporation gave 1.0 g ((E)-3-(6-(4-toluoyl)-2-pyridyl)acrylate as colourless platelets, melting point 108°-111°C (crystallized from cyclohexane).

Butyl lithium (10 ml, 1.64 mol in hexane) was added under nitrogen to a stirred suspension of triphenyl-2-pyrrolidinoethylphosphonium bromide (7.2 g) in dry toluene (75 ml). After 0.5 h, ((E)-3-(6-(4-toluoyl)-2-pyridyl)acrylate, vide supra, (4.8 g) in toluene (50 ml) was added. The suspension, initially orange, became deep purple, then slowly faded to yellow during 2 h heating at 75°C. The cooled solution was diluted with ether (150 ml) and treated with hydrochloric acid (50 ml, 2 mol). The aqueous phase was separated, washed with ether, and basified with potassium carbonate (ice) and extracted with ether. The mixture of isomeric esters obtained by evaporation was dissolved in ethanol (100 ml) containing sodium hydroxide solution (20 ml, 1 mol) and partially evaporated on the steam bath under reduced pressure for 5 min. The residual aqueous solution was neutralized with sulfuric acid (20 ml, 0.5 mol) and evaporated to dryness. The solid residue was extracted with hot isopropanol (3x50 ml) and the extracts were concentrated until crystallization commenced. The (E)-3-(6-(3-pyrrolidino-1-(4-tolyl)prop-1-(E)-enyl)-2-pyridyl)acrylic acid, melting point 222°C (dec. recrystallization from isopropanol) was obtained.

References

Coker G.G., Findlay J.W.A.; EU Patent No. 0,085,959; Feb. 3, 1983; Assigned: The Wellcome Foundation Limited 183-193 Euston Road, London NW1 2BP(GB)

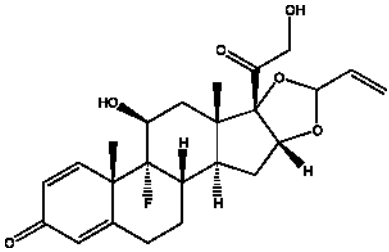
ACROCINONIDE

Therapeutic Function: Antiinflammatory, Antiallergic

Chemical Name: (11β,16α)-9-Fluoro-11,21-dihydroxy-16,17-[2-propenylidenebis(oxy)]pregna-1,4-diene-3,20-dione

Common Name: Acrocinonide

Structural Formula:



Chemical Abstracts Registry No.: 28971-58-6

Trade Name	Manufacturer	Country	Year Introduced
Acrocinonide	Onbio Inc.	-	-

Raw Materials

9-Fluoro-11β,16α,17,21-tetra-hydroxy-pregna-1,4-diene-3,20-dione
Perchloric acid
Sodium bicarbonate
Acrolein

Manufacturing Process

A suspension of 1.0 g of 9-fluoro-11β,16α,17,21-tetra-hydroxy-pregna-1,4-diene-3,20-dione in a mixture of 35 ml of dioxan, 15 ml of acrolein and 0.1 ml of perchloric acid was stirred for 3 h at room temperature. The clear solution thus obtained was poured into an aqueous saturated solution of sodium bicarbonate. The mixture was extracted twice with benzene, and the benzenic extract was concentrated to a small volume. The resulting crystals were collected and the 9-fluoro-11β,21-dihydroxy-16α,17-(2-propenylidenedioxy)-pregna-1,4-diene-3,20-dione was obtained as white crystals, melting point 200°-205°C.

References

GB Patent No. 1,292,269; Oct. 11, 1972; Assigned: ROUSSEL-UCLAF SOCIETE ANONYME, a body corporate organized under the laws of France, of 35 Boulevard des Invalides, Paris 7e, France

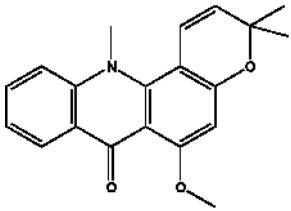
ACRONINE

Therapeutic Function: Antineoplastic

Chemical Name: 7H-Pyrano[2,3-c]acridin-7-one, 3,12-dihydro-6-methoxy-3,3,12-trimethyl-

Common Name: Acronine; Acronycine; NSC-403169

Structural Formula:



Chemical Abstracts Registry No.: 7008-42-6

Trade Name	Manufacturer	Country	Year Introduced
Acronine	ZYF Pharm Chemical	-	-

Raw Materials

2-Nitrobenzoyl chloride	3,5-Dimethoxyphenol
3-Chloro-3-methylbutyne	Zinc
Sodium hydride	Methyl iodide

Manufacturing Process

The acridone alkaloids constitute a small group of natural products found exclusively in the Rutaceae family of higher plants. A sustained interest in this field has been due to the reported activity of acronycine a constituent of Acronnychia baueri and Vepris amphody as an anti-tumor agent.

There are different methods of the synthetic preparation of acronycine (W. M. Bandaranayake et al., J. Chem. Soc. Perkin 1, 998 (1968); J. Hlubucek et al.; Aust. J. Chem. 23, 1881 (1970). One of them is described below. Friedel-Crafts condensation between 2-nitrobenzoyl chloride and 3,5-dimethoxyphenol.

2-Nitrobenzoyl chloride (12 g) and $AlCl_3$, (anhyd., 13 g) were dissolved in dry ether (50 ml) and this mixture added to a solution of 3.5-dimethoxyphenol (5 g) in dry ether 150 ml) at 0°C and the final mixture stirred at 0°C for 3 hours, brought to 20°C and stirred for a further 3 h. Diluted HCl and ice were added and the product extracted with EtOAc (3x50 ml), this extract was washed with aq. $NaHCO_3$, water, dried ($MgSO_4$), filtered and evaporated under reduced pressure to yield a dark red oil. This oil was treated with 2 M aq. NaOH. (100 ml) for 1 h., acidified with diluted HCl and re-extracted with

EtOAc which gave, after a similar work up, a paled red oil (5.0 g). Thin layer chromatography (TLC) showed three components one of which was the starting phenol. Column chromatography (150 g silica gel) and elution with benzene:petrol ether 40°-60°C (1:1) followed by increasing polarity of solvents (benzene through chloroform to chloroform:ether (4:1) gave 59 fractions. Fractions 1-12 were combined to gave a solid, which crystallized from benzene to give 4,6-dimethoxy-2-hydroxy-2-nitrobenzophenone, MP: 198°-199°C. Fractions 13-21 were discarded. Fractions 22-42 were combined (0.3 g), crystallized from benzene and the product added to that obtained from fractions 43-59 which crystallized from benzene to give 2,6-dimethoxy-7-hydroxy-2-nitrobenzophenone (0.5 g) MP: 175°-177°C.

Condensation of 3-chloro-3-methylbutyne with 2,6-dimethoxy-7-hydroxy-2-nitrobenzophenone:

A solution of the above benzophenone (2 g) and excess 3-chloro-3-methylbutyne (4.5 g) in dry DMF (60 ml) containing anhydrous K_2CO_3 (4 g) and dry KI (2 g) was stirred and heated at 65°C for 14 hours (under N_2). The mixture was cooled, diluted with water, acidified, extracted with chloroform (3x50 ml) and the extract was worked up in the usual way (including a NaOH wash) to give an oil, which was redissolved in DMF (20 ml) and heated at 130°C, under N_2, for 7 h whence most of the starting material had disappeared. The solvent was removed under reduced pressure to give a product (0.62 g) which was purified by preparative layer chromatography on silica gel to give 6-(2-nitrobehzoyl)-5,7-dimethoxy-2,2-dimethylchromene (0.22 g) which crystallized from EtOH, MP: 92°-93°C.

6-(2-Aminobenzoyl)-5,7-dimethoxy-2,2-dimethylchromene (0.2 g) was dissolved in EtOH (30 ml) containing water (5 ml) and ammonium chloride (1 g) and Zn mossy (1.5 g) was added in portions and the mixture stirred at room temperature for 5 days. The solution was filtered, evaporated to dryness under reduced pressure and the residue dissolved in EtOAc (25 ml) and worked up in the usual way to give a solid (0.19 g). It crystallised from EtOH with MP: 123°-126°C.

Cyclization of aminodimethylchromenylbenzophenone: 6-(2-aminobenzoyl)-5,7-dimethoxy-2,2-dimethylchromene (0.12 g) was dissolved in DMSO (8 ml) and NaH (0.06 g) added, the mixture was stirred for 6 days at room temperature. A further addition of NaH (0.06 g) was made and the solution heated to 50°C for 0.5 h whence it was poured into water, extracted with EtOAc and worked up in the usual way to give a crude mixture (0.11 g; components). Separation of this mixture on plate (silica gel:benzene:EtOAc, 10:4) gave band 1 (R_f 0.45: 38 mg) identified as starting material. Band 2 (R_f 0.32: 42 mg; 43%) which crystallized from ethylacetate as des-N-methylisoacronycine, MP: 293°-295°C. Band 3 (R_f 0.10; 29 mg, 29%) crystallized from ethyl acetate as des-N-methylacronycine. MP: 237°-240°C.

Des-N-methylacronycine (14 mg) was dissolved in dry acetone (10 ml), anhydrous K_2CO_3 (1 g), and MeI (2 ml) added and the mixture refluxed for 11 hours. The solution was filtered and the solvents evaporated to give a solid (12 mg) which after purification on TLC, gave acronycine which crystallized from aqueous MeOH, MP: 171°-173°C. This product showed identical U.V. and R_f characterization when compared with acronycine and had an accurate mass

measurement of 321.1368. $C_{20}H_{19}NO_3$, required: 321.1364. UV and ^1H NMR spectrum confirmed the structures of all described compounds.

References

Adams Joyce H. et al.; Tetrahedro,n v.37, pp 209-217, 1981
Coker G.G., Findlay J.W.A.; EU Patent No. 0,085,959; Feb. 3, 1983; Assigned: The Wellcome Foundation Limited 183-193 Euston Road, London NW1 2BP(GB)

ACTAPLANIN

Therapeutic Function: Growth stimulant

Chemical Name: See structure

Common Name: -

Structural Formula: Complex of glycopeptide antibiotics produced by Actinoplanes missourinesis

Chemical Abstracts Registry No.: 37305-75-2

Trade Name	Manufacturer	Country	Year Introduced
Actaplanin	Onbio Inc.	-	-

Raw Materials

Potassium chloride
Ferric sulfate
Agar
Hydrochloric acid
Dextrin
Yeast extract
Dextrose
Peptone
Corn steep liquor
Sulfuric acid
Actinoplanes sp
Magnesium sulfate heptahydrate
Yeast
Pre-cooked oatmeal
Glucose
Soybean meal
Calcium carbonate
Dextrin
Molasses, beet sugar
Betaine
Potassium phosphate dibasic

Manufacturing Process

The microorganism used for the production of antibiotic Actaplanin (A-4696) has been identified as a strain of a species of Actinoplanes of the family Actinoplanaceae. The Actinoplanaceae are a new family of microorganisms of the order Actinomycetales, having been first described by Dr. John N. Couch, Jour. Elisha Mitchell Sci. Soc., 65, 315-318 (1949).

The Actinoplanes sp. useful for the production of A-4696 was isolated from a sample of soil obtained from the Cascade mountain area in the state of

Washington.

Mycelial fragments of Actinoplanes sp., strain ATCC 23342 were inoculated on a nutrient agar slant having the following composition (g): pre-cooked oatmeal 60.0; yeast 2.5; K_2HPO_4 1.0; dried distiller's solubles 5.0; Czapek's mineral stock 5.0 ml; agar 25.0; water, deionized 1 L; Czapek's mineral stock has the following composition (g): KCl 100.0; $MgSO_4 \cdot 7H_2O$ 100.0; $FeSO_4 \cdot 7H_2O$ 2.0; (dissolve in 2 ml conc. HCl); deionized water 1 L.

The slant was inoculated with ATCC 23342 and incubated for 6 days at 30°C. The culture does not normally sporulate on this medium, and it is necessary to macerate the mycelial mat with a flattened, sharpened, inoculating needle in order to increase the number of potential growth centers. The macerated mature culture was covered with sterile distilled water and scraped carefully with a sterile rod to obtain a mycelial suspension.

The suspension thus obtained was used to inoculate 100 ml of a sterile vegetative medium having the following composition (g): glucose 5.0; dextrin 20.0; soybean meal 5.0; yeast extract 2.5; calcium carbonate 1.0; tap water 1 L.

The inoculated vegetative medium was grown for 48 h at 30° on a rotary shaker operating at 250 rpm. 10 ml of the incubated vegetative medium was inoculated into 100 ml of a sterile "bump" medium of the same composition as given next above. The thus inoculated "bump" medium was incubated for 24 h at 30°C with constant shaking on a rotary shaker operating at 250 rpm.

0.4 ml of the incubated "bump" medium was inoculated into 100 ml portions of a production medium of the composition shown below contained in 500 ml. Erlenmeyer flasks, and sterilized at 120°C for 30 min (g): dextrose 1.0; dextrin 3.0; peptone 1.5; soybean meal 0.5; $MgSO_4 \cdot 7H_2O$ 0.2; molasses, beet sugar 1.5; corn steep liquor 0.5; betaine 0.1; K_2HPO_4 0.05; deionized water q.s. 25 L.

The pH of the medium was adjusted to 7.5 with 5 N sodium hydroxide solution before sterilization. After sterilization the pH was approximately 6.9. The production fermentation was shaken for about 96 h at a temperature of 30°C on a rotary shaker operating at 250 rpm. The pH at the end of the fermentation cycle was about 7.2.

The preparation of the inoculum proceeded through the incubation of the "bump" medium detailed above 25 L of a production medium as outlined above, with 0.02% Dow Corning antifoam added, was sterilized by autoclaving at 120°C for 30 min and charged into a 40 L fermentation tank. 100 ml of incubated "bump" medium was inoculated into the sterile production medium. The inoculated production medium contained in the 40 L tank was allowed to ferment for 4 days at 30°C. The fermentation was aerated with sterile air in an amount of about 0.5 volume of air per volume of culture medium per minute. The fermenting production medium was agitated with a mixer utilizing an impeller of a proper size and turning at an appropriate rpm to insure adequate mixing of air with the medium. The pH of the culture medium gradually increased from an initial level of about 6.9-7.2 as the fermentation proceeded.

The whole broth obtained from an A-4696 fermentation, was filtered with the aid of a commercial filter aid. The filtrate was set aside. The mycelial cake was washed with 32 L of water and the wash water set aside. The mycelial cake was then suspended in an additional 32 L of water and the pH of the mixture adjusted to pH 10.5 with 5 N sodium hydroxide solution. The mycelial cake water suspension was stirred for 45 min and the mixture was filtered. This filtrate and the water wash were combined with the original filtrate from the fermentation broth and the pH of combined filtrates was adjusted to pH 4.0 with H_2SO_4. The acidified combined filtrates was passed through a carbon column utilizing 1.0 kg of activated carbon, (Pittsburgh, 12x40). The activated carbon column was washed until the effluent was colorless. The A-4696 activity was adsorbed on the carbon column. The A-4696 activity was eluted from the carbon column utilizing a 1% H_2SO_4 solution in acetone: H_2O (1:1). 2 L of the acidified acetone-water solution was sufficient to elute the A-4696 activity from the carbon column. The eluate containing the A-4696 activity as treated with a saturated barium hydroxide solution, in order to form a precipitate of barium sulfate, thus removing the sulfate ions from the solution. The mixture was filtered and the barium sulfate precipitate was discarded. The filtrate containing the A-4696 activity was concentrated under vacuum to dryness. The resulting residue comprising the A-4696 activity amounted to approximately 80.0 g.

References

Hamill R.L. et al.; US Patent No. 3,952,092; April 20, 1976; Assigned: Eli Lilly and Company, Indianapolis, Ind.

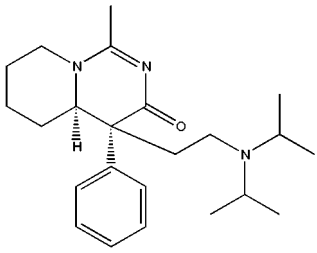
ACTISOMIDE

Therapeutic Function: Cardiac depressant

Chemical Name: 3H-Pyrido[1,2-c]pyrimidin-3-one, 4-(2-(bis(1-methylethyl) amino)ethyl)-4,4a,5,6,7,8-hexahydro-1-methyl-4-phenyl-, cis-(+-)-

Common Name: Actisomide; Dizactamide

Structural Formula:



Chemical Abstracts Registry No.: 96914-39-5

Trade Name	Manufacturer	Country	Year Introduced
Dizactamide	ZYF Pharm Chemical	-	-

Raw Materials

Platinum oxide
N,N-Dimethylacetamide dimethylacetal
4-Diisopropylamino-2-phenyl-2-pyridin-2-yl-butyramide
Lithium aluminum hydride

Manufacturing Process

Hydrogenation of 4-diisopropylamino-2-phenyl-2-pyridin-2-yl-butyramide over platinum oxide catalyst reduced the pyridine ring to a piperidine to give 4-diisopropylamino-2-phenyl-2-piperidin-2-yl-butyramide as a white solid, MP: 107°-108°C. Structure was confirmed by proton, carbon-13-NMR spectra and by elemental analysis.

2-(1-Acetylpiperidin-2-yl)-4-diisopropylamino-2-phenylbutyramide was prepared by acetylation of above product with N,N-dimethylacetamide dimethylacetal by heating at 80°C for about 14 hours. The acetamide melted at 191°-192°C. The treatment of that intermediate with lithium aluminum hydride led the newly introduced acetyl group to condense with the adjacent amide nitrogen. There was thus obtained 4-(2-diisopropylaminoethyl)-1-methyl-4-phenyl-4,4a,5,6,7,8-hexahydropyrido[1,2-c]pyrimidin-3-one, the new anti-arrhythmic agent actisomide, MP: 70°-75°C. Its structure was confirmed by proton NMR and infrared spectra and by elemental analysis.

References

Adelstein G.W., Chorvat R.J.; EP Patent No. 0,104,647; Sept. 27, 1983
Lednicer D., The Organic Chemistry of Drug Synthesis; v. 5; pp. 149-150; 1995; Wiley and Sons Inc.

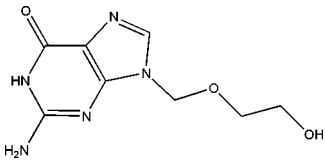
ACYCLOVIR

Therapeutic Function: Antiviral

Chemical Name: 2-Amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6H-purin-6-one

Common Name: Acycloguanosine; 9-(2-Hydroxyethoxymethyl)guanine

Structural Formula:



Chemical Abstracts Registry No.: 59277-89-3

Trade Name	Manufacturer	Country	Year Introduced
Zovirax	Burroughs-Wellcome	UK	1981
Zovirax	Burroughs-Wellcome	US	1982
Zovirax	Burroughs-Wellcome	Switz.	1982
Zovirax	Burroughs-Wellcome	W. Germany	1983
Zovirax	Burroughs-Wellcome	Sweden	1983
Zovirax	Burroughs-Wellcome	France	1983

Raw Materials

Sodium nitrite
2-Chloro-9-(2-hydroxyethoxymethyl)adenine
Ammonia

Manufacturing Process

Solid sodium nitrite (0.97 g) was added at room temperature with stirring over a period of one hour to a solution of 2-chloro-9-(2-hydroxyethoxymethyl)adenine (0.5 g) in glacial acetic acid (10 ml). The reaction mixture was stirred for an additional 4½ hours. The white solid was removed by filtration, washed with cold acetic acid and then well triturated with cold water to remove the sodium acetate present. The solid product was retained. The combined acetic acid filtrate and wash was evaporated at reduced pressure and 40°C bath temperature and the residual oil triturated with cold water. The resulting solid material was combined with the previously isolated solid and the combined solids dried and recrystallized from ethanol to give 2-chloro-9-(2-hydroxyethoxymethyl)-hypoxanthine (0.25 g), MP>310°C. Elemental analysis and NMR spectrum were consistent with this structure.

A mixture of 2-chloro-9-(2-hydroxyethoxymethyl)-hypoxanthine (0.375 g) and methanol (80 ml) saturated with anhydrous ammonia was heated in a bomb at 125°C for 5 hours. The bomb was cooled in an ice bath and the reaction mixture removed. Solvent and excess ammonia were removed under reduced pressure at 50°C. After the residue was triturated with cold water to remove the ammonium chloride formed, the remaining solid was dried and then recrystallized from methanol to give pure 9-(2-hydroxyethoxymethyl) guanine (0.24 g), MP 256.5-257°C.

References

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DFU 4 (11) 842 (1979)
Kleeman and Engel p. 14
PDR p. 773
OCDS Vol. 3 p. 229
DOT 18 (2) 52 (1982)
REM p. 1231
Schaeffer, H.J.; US Patent 4,199,574; April 22, 1980; Assigned to Burroughs-Wellcome Co.

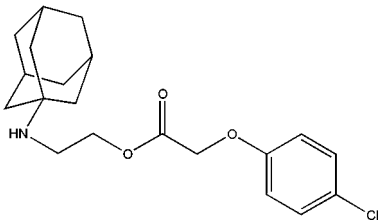
ADAFENOXATE

Therapeutic Function: Nootropic, Psychostimulant

Chemical Name: 2-(1-Adamantylamino)ethyl (p-chlorophenoxy)acetate

Common Name: Adafenoxate

Structural Formula:



Chemical Abstracts Registry No.: 82168-26-1

Trade Name	Manufacturer	Country	Year Introduced
Adafenoxate	Laboratorios Wassermann	-	-

Raw Materials

1-Aminoadamantine-2-ethanol
p-Chlorophenoxyacetyl chloride
p-Chlorophenoxyacetic acid

Manufacturing Process

Preparation of the p-chlorophenoxyacetate of 1-aminoadamantine-2-ethanol, starting from a p-chlorophenoxyacetic acid halide:

22 g (0.11 mol) of 1-aminoadamantine-2-ethanol dissolved in 250 ml of benzene are poured into a 500 ml flask fitted with a mechanical stirrer, using a decanting funnel. 23 g (0.11 m) of p-chlorophenoxyacetyl chloride are added in drops while stirring, the mixture then being stirred for 30 minutes. 120 ml of a 10% solution of sodium carbonate is then added, and the resulting mixture is stirred for 10 minutes. The organic phase is decanted, and the benzene is then removed by distillation. The residue is crystallized with petroleum ether. This yields 37 g (93%) of a white solid.

Preparation of the p-chlorophenoxyacetate of 1-aminoadamantine-2-ethanol, starting from p-chlorophenoxyacetic acid:

In a 1 liter flask, provided with a Dean-Stark separator tube and reflux refrigerant, a mixture of 20.5 g (0.011 m) of p-chlorophenoxyacetic acid, 22 g (0.11 m) of 1-aminoadamantine-2-ethanol, 98 g of conc. sulfuric acid and 700 ml of toluene is heated to boiling point over a period of 24 hours. At the end

of this period, the mixture is treated with an aqueous solution of 5% sodium carbonate to an alkali pH, and is then washed with water. The mixture is then dried on anhydrous sodium sulphate, and the toluene is removed by distillation at reduced pressure. The crude product so obtained is crystallized with petroleum ether. The yield is 35.2 g (88%) of a white solid.

Preparation of the chlorhydrate of p-chlorophenoxyacetate of 1-aminoadamantine-2-ethanol:

A solution of 60 g (0.16 m) of p-chlorophenoxyacetate of 1-aminoadamantine-2-ethanol in 300 ml of ether is subjected to the passage of HCl gas until the precipitation of a solid product is completed. It is left to cool in a refrigerator over a period of 6 hours and it is then filtered. The resulting solid is recrystallized with a mixture of ether and methanol. 61 g (92%) of the product are obtained.

References

Andreoli R.R. et al; US Patent No. 4,476,319; Oct. 9, 1984; Assigned to Sociedad Espanola de Espacialides Formaco-Terapeuticas S.A., Barselona, Spain

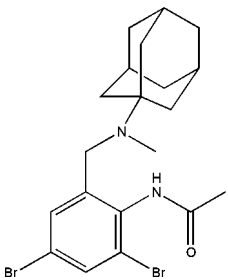
ADAMEXINE

Therapeutic Function: Mucolytic

Chemical Name: Acetamide, N-(2,4-dibromo-6-((methyltricyclo [3.3.1.13,7]dec-1-ylamino)methyl)phenyl)-

Common Name: Adamexine; Broncostyl

Structural Formula:



Chemical Abstracts Registry No.: 54785-02-3

Trade Name	Manufacturer	Country	Year Introduced
Adamexine	ZYF Pharm Chemical	-	-
Broncostyl	Robert	-	-

Raw Materials

2-Bromomemtyl-4,6-dibromo-N,N,diacetylaniline
N-Methyladamantyl

Manufacturing Process

4.3 g 2-brommemtyl-4,6-dibromo-N,N-diacetylaniline and 1.65 g N-methyladamantyl amine in 100 ml of absolute ethanol were heated to reflux for 8 hours. The ethanol was removed and a residue was washed with some times with ether. The resulting hard mass was refluxed with 150 ml 2 N HCl for 2 hours. The obtained product was cooled and stood for 10-12 hours at 4°C in a refrigerator. The crystalline 2-(N-(1-adamantyl)-N-methylaminomethyl-4',6'-dibromacetanilid hydrochloride (adamexine) was filtered off and thoroughly washed with distilled water. It was recrystallized from a mixture glacial acetic acid/water 2:1 (v/v) to give a white crystalline powder, melting at 250°-254°C. The hydrochloride is better for a pharmaceutical composition because of solubility in water. The free base may be prepared by adding of an equivalent of any basic compound (NaOH, $NaHCO_3$ and so on).

References

B.D. Patent No. 2,436,909; July 31, 1974; Ferrer Internacional, S. A. Barcelona (Spain)

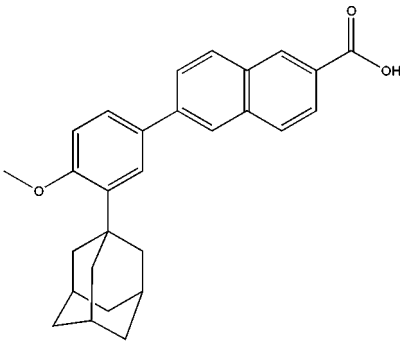
ADAPALENE

Therapeutic Function: Antiacne

Chemical Name: 2-Naphthalenecarboxylic acid, 6-(4-methoxy-3-tricyclo (3.3.1.13,7))dec-1-ylphenyl)-

Common Name: Adapalene

Structural Formula:



Chemical Abstracts Registry No.: 106685-40-9

Trade Name	Manufacturer	Country	Year Introduced
Adaferin	Laboratoires Galderma	France	-
Adapalene	Laboratoires Galderma	France	-
Differin	Laboratoires Galderma	France	-

Raw Materials

4-Bromophenol
Sodium hydride
Dibromoethane
1-Adamantanol
Methyl iodide
Zinc chloride
Nickel chloride/1,2-(diphenylphosphino)ethane-complex

Manufacturing Process

Preparation of 6-(3-(1-adamantyl)-4-methoxyphenyl)-2-naphthoic acid consist of 4 steps.

1. 2-(1-Adamantyl)-4-bromophenol.

34.6 g (200 mmol) of p-bromophenol and 30.4 g (200 mmol) of 1-adamantanol are dissolved in 100 ml of dichloromethane. To the resulting solution there are slowly added 10 ml of concentrated sulfuric acid. The mixture is stirred for 8 hours at ambient temperature, poured into water, neutralized with sodium bicarbonate, extracted with methylehe chloride, dried and evaporated. After recrystallization in isooctane 52.8 g of the expected product are obtained. Yield - 86%. MP: 140°-141°C.

2. 2-(1-Adamantyl)-4-bromoanisole.

To suspension of sodium hydride (80% in oil, 4.32 g, 144 mmol) in 50 ml of THF, there are slowly added while maintaining the temperature at 20°C, 36.8 g (120 mmol) of 2-(1-adamantyl)-4-bromophenol. The mixture is stirred for 1 hour at ambient temperature at which point 9 ml of methyl iodide are added. The mixture is then stirred for 2 hours at 20°C, poured into water, extracted with ether, dried and evaporated. The product is purified by passage through a silica column (10x30), eluting with a mixture of hexane (90%) and dichloromethane (10%). On evaporation, 26.2 g of a white solid are obtained. Yield - 68%. MP: 138°-139°C.

3. Methyl ester of 6-(3-(1-adamantyl)-4-methoxyphenyl)-2-naphthoic acid.

To a suspension of magnesium (1.64 g, 67.5 mmol in 30 ml of THF, there is added a solution of 1.4 g (4.5 mmol) of 2-(1-adamantyl)-4-bromoanisole and 0.39 ml of dibromoethane in 10 ml of THF. The mixture is stirred until the reaction is initiated and then there is slowly added a solution of (40.8 mmol) of 2-(1-adamantyl)-4-bromoanisole in 90 ml of THF. The mixture is refluxed for 2 hours, and then cooled to 20°C. After that 6.2 g (45 mmol) of anhydrous $ZnCl_2$ are added. The mixture is stirred for 1 hour at 20°C at which point 7.95 g (30 mmol) of methyl 6-bromo-2-naphthoate are added followed by addition of 300 g of $NiCl_2$/1,2-(diphenylphosphino)ethane-complex as the catalyst. The mixture is stirred again for 2 hours at 20°C, poured into water, extracted with CH_2Cl_2 dried and evaporated. The product is isolated by column

chromatography, eluting with a mixture of heptane (70%) and dichloromethane (30%) and then recrystallized in ethyl acetate. 12.2 g of the expected product are obtained. Yield - 78%. MP: 222°-223°C.

4. 6-(3-(1-Adamantyl)-4-methoxyphenyl)-2-naphthoic acid.

10.5 g of the ester obtained above (step 3) are treated with a solution of soda in methanol (200 ml, 4.2 N). The mixture is heated at reflux for 48 hours. The solvents are evaporated and the resulting residue is taken up in water and acidified with concentrated HCl. The solid is filtered and dried under vacuum over phosphoric anhydride. The resulting white solid is recrystallized in a mixture of THF and ethyl acetate. 8.2 g of expected product are obtained. Yield - 81%. MP: 325°-327°C.

References

Shroot B. et al.; US Patent No. 4,940,696; July 10, 1990; Assigned to Centre International de Recherches Dermatologioues (CIRD), Valbonne, France

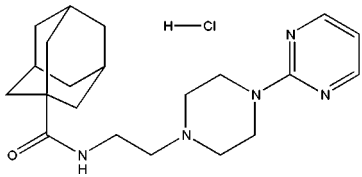
ADATANSERIN HYDROCHLORIDE

Therapeutic Function: Anxiolyticá Antidepressant

Chemical Name: Tricyclo[3.3.1.13,7]decane-1-carboxamide, N-(2-(4-(2-pyrimidinyl)-1-piperazinyl)ethyl)-, hydrochloride

Common Name: Adatanserin hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 144966-96-1; 127266-56-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
WY-50324	Centre de Recherche Pierre Fabre	-	-
Adatanserin hydrochloride	ESTEVE QUIMICA SA	-	-

Raw Materials

[4-(2-Pyrimidinyl)piperazino]ethylamine
Triethylamine
Adamantane-1-carboxylic acid chloride

Manufacturing Process

To a stirred solution of [4-(2-pyrimidinyl)piperazino]ethylamine (2.0 g, 0.01 mol) in 50 ml of methylene chloride, adamantane-1-carboxylic acid chloride (3.6 g, 0.018 mol) and triethylamine (2.9 g, 0.015 mol) were added. Stirring was continued at room temperature overnight. The methylene chloride solution was washed with water, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The remaining residue was subjected to preparative HPLC. The residue was dissolved in ethyl acetate (10 ml) and subjected to flash chromatography using a 9 inch column of silica gel and ethyl acetate as the eluent. The N-[2-[4-(2-pyrimidinyl)-1-piperazinyl]ethyl]tricyclo[3.3.1.1(3,7)] decane-1-carboxamide was separated.

In practice it is usually used as hydrochloride.

References

Abou Gharbia M. A.-M. et al.; GB Patent No. 2,218,988A; Oct. 29, 1989

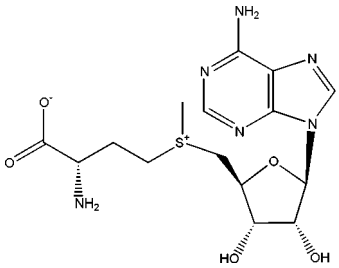
ADEMETIONINE

Therapeutic Function: Metabolic, Antiinflammatory

Chemical Name: S-Adenosyl-DL-methionine

Common Name: Ademethionium; Ademetionine; Adenosylmethionine

Structural Formula:



Chemical Abstracts Registry No.: 29908-03-0

Trade Name	Manufacturer	Country	Year Introduced
Donamet	Ravizza	-	-
Geptral	Knoll	-	-
Gumbaral	AWD.Pharma	-	-
Gumbaral	Asta Pharma AWD	-	-
Legend	Fidia	-	-

Trade Name	Manufacturer	Country	Year Introduced
S-Amet parenteral	Europharma	-	-
Transmetil	Knoll	-	-
Twin	San Carlo	-	-
FO-1501	Sampl-Gibipharma	-	-
Samyr	Knoll	-	-

Raw Materials

- Glucose
- Polypeptone
- Yeast extract
- Sucrose
- Urea
- Methionine, L-
- Boric acid
- Potassium iodide
- Acetic acid
- Sulfuric acid
- Potassium phosphate monobasic
- Magnesium sulfate heptahydrate
- Calcium chloride dihydrate
- Zinc sulfate heptahydrate
- Ferric sulfate heptahydrate
- Copper sulfate pentahydrate
- Cobalt(II) chloride hexahydrate
- Perchloric acid
- Potassium hydrocarbonate

Manufacturing Process

S-Adenosyl methionine (SAM) is produced is prepared by cultivating of Saccharomyces cerevisiae.

One loopful of each of the microorganism strains (IFO 2342, IFO 2343, IFO 2345, IFO 2346, IFO 2347) was inoculated in 10 ml of a heat-sterilized culture medium adjusted to pH 6.0 and composed of 5.0 g/dl of glucose, 0.5 g/dl of polypeptone, 0.4 g/dl of KH_2PO_4, 0.4 g/dl of K_2HPO_4, 0.02 g/dl of $MgSO_4 \cdot 7H_2O$ and 0.2 g/dl of yeast extract, and cultivated with shaking at 28°C for 24 h.

1 L of a culture medium adjusted to pH 6.0 and composed of 10.0 g/dl of sucrose, 1.0 g/dl of yeast extract, 0.4 g/dl of K_2HPO_4, 0.01 g/dl of $MgSO_4 \cdot 7H_2O$, 1.5 g/dl of urea (separately sterilized), 0.75 g/dl of L-methionine, 0.02 g/dl of $CaCl_2 \cdot 2H_2O$, 0.25 mg/dl of $ZnSO_4 \cdot 7H_2O$, 0.25 mg/dl of $FeSO_4 \cdot 7H_2O$, 125.0 mg/dl of $MnSO_4 \cdot 6H_2O$, 2.0 μg/dl of $CuSO_4 \cdot 5H_2O$, 2.0 μg/dl of H_3BO_3, 0.2 μg/dl of $CoCl_2 \cdot 6H_2O$ and 1.0 μg/dl of KI was put in a 2-liter fermentor and sterilized. Then, 5 ml of the seed culture broth prepared as above was inoculated in the culture medium and cultivated at 28°C for 72 h with aeration and agitation.

After the cultivation, the microbial cells were collected by centrifugal separation, washed once with physiological saline, suspended in 100 ml of 1.5 N perchloric acid, and shaken at room temperature for 1 h. The suspension was then centrifuged to remove the microbial cells, and the resulting liquid was adjusted to pH 4.5 by adding potassium hydrogen carbonate. The resulting precipitate of potassium perchlorate was removed by centrifugal separation to give an extract containing SAM. The amount of SAM in the extract was determined, and the amount of SAM based on the dry cells.

The extract in an amount of 0.2 g as SAM was passed through a column filled with 50 ml of Amberlite IRC-50 (H^+ form), a weakly acidic cation exchange resin, to cause adsorption of SAM. 0.005 N acetic acid was passed through the column to wash it until the absorbance at 260 nm of the eluate becames less than 0.1. Thus, impurities were removed. Then, 0.1 N sulfuric acid was passed through the column, and SAM was eluted until the absorbance at 260 nm of the eluate becames less than 0.05. The eluate was treated with Amberlite IRA 900 resin (OH- form) to adjust its pH to 3.0, and then lyophilized to obtain SAM sulfate. The SAM based may be produced from SAM sulfate by treatment with potassium hydrogen carbonate. The purity of SAM was measured by cellulose thin-layer chromatography, paper chromatography and high-performance liquid chromatography. The yield of SAM based on the dry cells: IFO 2343-12.1%; IFO 2346-18.8%; IFO 2347-16.7%.

References

Shiozaki S. et al.; US Patent No. 4,562,149; Dec. 31, 1985; Assigned: Nippon Zeon Co., Ltd., Tokyo, Japan

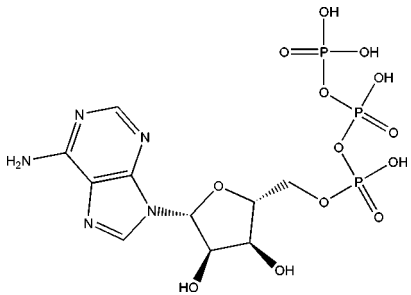
ADENOSINE TRIPHOSPHATE

Therapeutic Function: Coenzyme, Vasodilator

Chemical Name: Adenosine 5'-(tetrahydrogen triphosphate)

Common Name: ATP; Triphosadenine

Structural Formula:



Chemical Abstracts Registry No.: 56-65-5

Trade Name	Manufacturer	Country	Year Introduced
Atepodin	Medix	Spain	-
Atriphos	Biochimica	Switz.	-
Estriadin	Boizot	Spain	-
Striadyne	Auclair	France	-
Triphosphodine	I.C.I.	UK	-

Raw Materials

1,3-Dicyclohexylguanidinium adenosine 5'-phosphoramidate
Bis-Triethylammonium pyrophosphate

Manufacturing Process

With a solution of 0.29 part by weight of well dried 1,3-dicyclohexylguanidinium adenosine 5'-phosphoramidate in 5 parts by volume of ortho-chlorophenol is admixed a solution of 0.95 part by weight of bis-triethylammonium pyrophosphate in a mixed solvent composed of 1 part by volume of ortho-chlorophenol and 2 parts by volume of acetonitrile. The mixture is left standing at 20°C for 2 days. Then 30 parts by volume of water is added to the mixture. After washing with three 15 parts by weight volume-portions of diethyl ether, the aqueous layer is separated, and the remaining diethyl ether in the aqueous layer is removed under reduced pressure. Five parts by weight of activated charcoal is added to the aqueous layer and the mixture is stirred for 30 minutes. The activated charcoal is filtered and further 1 part by weight of activated charcoal is added to the filtrate. After 20 minutes agitation, the activated charcoal is taken out by filtration. The combined activated charcoal is washed with a little water, and eluted twice with respective 300 and 200 parts by volume-portions of 50% (volume) ethanol containing 2% (volume) of concentrated aqueous ammonia. The eluate is concentrated to 40 parts by volume, then is passed through a column packed with 20 parts by volume of a strongly basic anion exchange resin in bead form (chloric type) (polystyrene trimethylbenzyl ammonium type resin sold under the name of Dowex-1 from Dow Chemical Company, Mich. USA). Then, the column is washed with 750 parts by volume of an acid aqueous saline solution containing 0.01 normal hydrochloric acid and 0.02 normal sodium chloride and then eluted with 600 parts by volume of an acid aqueous saline solution composed of 0.01 normal hydrochloric acid and 0.2 normal sodium chloride. After neutralizing with a diluted sodium hydroxide solution, the eluate is treated with activated charcoal to adsorb ATP as its sodium salt. The separated activated charcoal is washed with water and eluted with 60% (volume) ethanol containing 2% (volume) of concentrated aqueous ammonia. The eluate is concentrated to 0.5 part by volume, then 5 parts by volume of ethanol is added. The precipitate thus deposited is centrifuged and dried at low temperature to obtain 0.155 part by weight of tetra-sodium salt of ATP containing 4 mols of water of crystallization as a colorless crystalline powder. The yield is 47% relative to the theoretical.

References

Merck Index 146
I.N.p. 983
Tanaka, K.and Honjo, M.; US Patent 3,079,379; February 26, 1963; Assigned to Takeda Pharmaceutical Industries, Ltd.

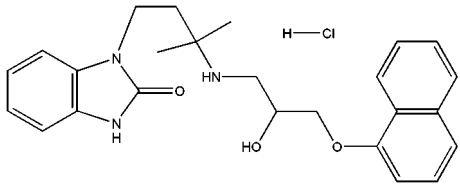
ADIMOLOL HYDROCHLORIDE

Therapeutic Function: Alpa- and Beta-adrenergic blocker

Chemical Name: ()-1-(3-((2-Hydroxy-3-(1-naphthyloxy)propyl)amino)-3-methylbutyl)-2-benzimidazolinone hydrochloride

Common Name: Adimolol hydrochloride; Imidolol hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 75708-29-1; 78459-19-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Adimolol hydrochloride	ZYF Pharm Chemical	-	-

Raw Materials

1-(3-Amino-3,3-dimethyl-n-propyl)benzimidazolidinone-2
1-[Naphthyl-1-oxyl]propylene-(2,3)-epoxide

Manufacturing Process

A mixture consisting of 3 g of 1-(3-amino-3,3-dimethyl-n-propyl) benzimidazolidinone-2, 3.3 g of 1-[naphthyl-(1)-oxyl]propylene-(2,3)-epoxide and 12 ml of 98% ethanol were refluxed for three hours. Thereafter, the ethanol was distilled off, the residue was taken up in some methanol, and the solution was acidified with 1 N hydrochloric acid and then extracted with ethyl acetate. The ethyl acetate was distilled out of the extract solution, and ether and some water were added to the residue, whereupon a crystalline substance separated out. The product was recrystallized from ethanol, yielding 60% of theory of ()-1-(3-((2-hydroxy-3-(1-naphthyloxy)propyl)amino)-3-methylbutyl)-2-benzimidazolinone, which had a melting point of 161°C.

In practice it is usually used as hydrochloride.

References

Koppe H. et al.; US Patent No. 4,255,430; March 10, 1981; Assigned to Boehringer Ingelheim GmbH, Ingelheim am Rhein, Fed. Rep. of Germany

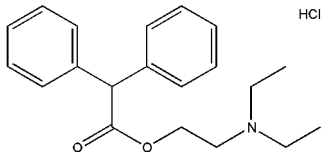
ADIPHENINE HYDROCHLORIDE

Therapeutic Function: Anticholinergic, Spasmolytic, Smooth muscle relaxant

Chemical Name: Benzeneacetic acid, α-phenyl-, 2-(diethylamino)ethyl ester, hydrochloride

Common Name: Adiphenine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 50-42-0; 64-95-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Adiphenine hydrochloride	Spectrum Chemicals and Laboratory Products, Inc.	-	-
Neuro-Trasentin	Aleve	-	-
Paxil	Frosst	-	-
Paxil	SKB	-	-
Paxil	GlaxoSmithKline	-	-
Trasentine	Ciba	-	-

Raw Materials

α,α-Diphenylacetic acid
Thionyl chloride
Diethylaminoethanol

Manufacturing Process

10.6 parts of α,α-diphenylacetic acid are treated with thionyl chloride and the diphenylacetylchloride thus produced is caused to react with 5.9 parts of diethylaminoethanol at 120°C. The α,α-diphenylacetic acid, 2-(diethylamino)ethanol ester hydrochloride thus produced is crystallized from ethyl acetate; it melts at 113-114°C.

References

Merck Index, Monograph number: 160, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Miescher K., Hoffmann K., US Patent No. 2,079,962; May 11, 1937; Assigned to Society of Chemical Industry, Basel, Switzerland

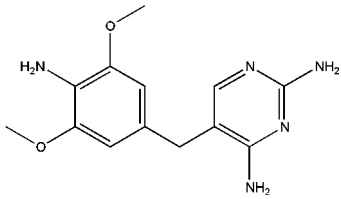
ADITEREN

Therapeutic Function: Diuretic

Chemical Name: 2,4-Diamino-5-(4-amino-3,5-dimethoxybenzyl)pyrimidine

Common Name: Aditeren

Structural Formula:



Chemical Abstracts Registry No.: 56066-19-4

Trade Name	Manufacturer	Country	Year Introduced
Aditeren	Onbio Inc.	-	-

Raw Materials

Aniline
Sodium nitrite
Aluminum oxide
Acetamide
Bromine
Dimethylsulfone
Sodium methylate
p-Anilinepropionitrtile
Guanidine carbonate
4-Toluenesulfonic acid
Bromosuccinimide
Palladium on carbon
Sodium hydride
Sodium borohydride
3-Hydroxy-5-keto-3-cyclohexenecarboxylic acid

Manufacturing Process

A solution of 6.9 g of sodium in 1 liter of absolute ethanol were treated with 54 g of guanidine carbonate and 31.0 g of 4-amino-α-(anilinemethylene)-3,5-dimethoxyhyrocinnamic acid nitrile and boiled under reflux for 20 hours. 500 ml of water were added and the alcohol was removed in vacuum. After standing at room temperature for 2 hours, the crystallized 2,4-diamino-5-(4-amino-3,5-dimethoxybenxyl)pyrimidine was filtered off under suction, washed with water and recrystallised from methanol; melting point 215°-216°C.

The starting material was prepared as follows:

13.8 g of sodium were dissolved in 900 ml of methanol. To this solution were added 46.8 g of 3-hydroxy-5-keto-3-cyclohexenecarboxylic acid. This mixture was stirred, held between -4° and -8°C by means of a cooling bath and treated during 30 minutes with a phenyl-diazonium chloride solution [prepared from 27.9 g of aniline, 450 ml of water, 72 ml of concentrated hydrochloric acid and 21.0 g of sodium nitrite in 90 ml of water]. The resulting mixture was stirred for a further 1 hour at -5°C to -10°C. The deposited, red reaction product was filtered off under vacuum and washed with ca 1000 ml of water. There was obtained 3-hydroxy-5-keto-4-phenyl-azo-3-cyclohexenecarboxylic acid of melting point 218°C.

60 g of 3-hydroxy-5-keto-4-phenyl-azo-3-cyclohexenecarboxylic acid, 200 ml of methanol, 1200 ml of benzene and 5 g of p-toluenesulphonic acid were boiled together under reflux on a water separator for 18 hours. After cooling, the solution was washed with 500 ml of a 5% sodium bicarbonate solution, then washed with water, dried and evaporated. The residue was dissolved in ethyl acetate and purified on an aluminum oxide column [500 g; activity stage I]. After evaporation of the ethyl acetate and recrystallisation of the residue from benzene/petroleum ether, there was obtained 3-hydroxIy-5-keto-4-phenyl-azo-3-cyclohexenecarboxylic acid methyl ester as a solid of melting point 144°C.

54.8 g of 3-hydroxy-5-keto-4-phenyl-axe-3-cyclohexenecarboxylic acid methyl ester, 12.0 g of acetamide and 2.0 g of bromosuccinimide were stirred in 600 ml of chloroform and treated dropwise with 32.0 g of bromine in 400 ml of chloroform [the reaction temperature being held below 35°C]. The separation of acetamide hydrobromide soon began. The mixture was stirred for a further 30 minutes at room temperature, the acetamide hydrobromide filtered off and the filtrate evaporated to dryness. The residue was taken up in a small amount of ethanol, filtered off under vacuum and washed with ethanol. There was obtained 3,5-dihydroxy-4-phenylazobenzoic acid methyl ester of melting point 216°-218°C.

A mixture of 27.2 g of 3,5-dihydroxy-4-phenylazobenzoic acid methyl ester, 150 ml of methanol and 64 g of dimethyl sulfate was treated during 45 minutes with a solution of 23 g of sodium hydroxide in 50 ml of water while stirring. Care was taken that the temperature did not exceed 55°C by means of a cooling bath. The mixture was stirred at room temperature for a further 1 hour, cooled with ice water, filtered off under vacuum and recrystallized from 400 ml of ethanol. Red crystals of 3,5-dimethoxy-4-phenylazobenzoic acid methyl ester were obtained; melting point 130°-132°C.

12 g of 3,5-dimethoxy-4-phenylazobenzoic acid methyl ester were dissolved in 400 ml of ethanol and, after the addition of 0.80 g of palladium on carbon, hydrogenated under atmospheric pressure and at room temperature. With slight warming, 2 moles of hydrogen were taken up during 1.5 hours. The catalyst was filtered off and the filtrate concentrated in vacuum. The resulting aniline was distilled off with steam. After cooling, the 4-amino-3,5-dimethoxybenzoic acid methyl ester which remained as an aqueous suspension, was filtered off under vacuum, dried and recrystallised from cyclohexane; melting point 115°-116°C.

A suspension of 214 g of dimethylsulphone and 78.2 g of sodium hydride (50% dispersion in oil) in 400 ml of absolute dimethyl sulfoxide was stirred at 50°C under nitrogen and with exclusion of moisture for 3 hours. The mixture was cooled to 30°C, whereupon 137 g of 4-amino-3,5-dimethoxybenzoic acid methyl ester were added, the temperature rising to 50°C. After stirring under nitrogen and at room temperature for ca 1 hour, the resulting mixture was left to stand for 3 hours and then dissolved in 2 liters of water under addition of ice. The solution was adjusted to pH 6-7 with glacial acetic acid. After stirring under ice-cooling for 1 hour, the crystallized 4'-amino-3',5'-dimethoxy-2-methylsulfonyl-acetophenone was filtered off under suction, washed with water, dried and recrystallised from ethyl acetate; MP: 166°-167°C.

A suspension of 123 g of 4'-ammo-3',5'-dimethoxy-2-methylsulphonyl-

acetophenone and 68 g of sodium borohydride in 1.5 liters of alcohol was stirred at room temperature for 20 hours. The suspension was diluted with 1.5 liters of water. The alcohol was evaporated in vacuum and the resulting 4-amino-3,5-dimethoxy-α-(methylsulfonylmethyl)benzyl alcohol was filtered off under suction, washed with water and dried; melting point 178°-179°C.

A mixture of 8.64 g of sodium methylate, 14.6 g of p-anilinepropionitrtile and 22.0 g of 4-amino-3,5-dimethoxy-α-(methylsulfonylmethyl)benzyl alcohol in 50 ml of absolute dimethyl sulfoxide was stirred at 50°C for 1 hour under nitrogen and with the exclusion of moisture. The solution was poured into 500 ml of ice-water and the resulting emulsion was extracted with two 500 ml portions of ethyl acetate. The ethyl acetate extracts were washed with two 250 ml portions of water, dried over magnesium sulfate and evaporated in vacuum. The residue was dissolved in 60 ml ethyl acetate. After standing at room temperature for 20 hours, the crystallized 4-amino-α-(anilinemethylene)-3,5-dimethoxyhydrocinnamic acid nitrile was filtered off under suction, washed with a small amount of ethyl acetate and dried; MP: 150°-151°C.

References

G.B. Patent No. 1,484,481; Sept. 11, 1974; F. Hoffmann-La Roche and CO., Aktiengesellschaft, Swiss Company, 124-184 Grenzacherstrasse Basle, Switzerland

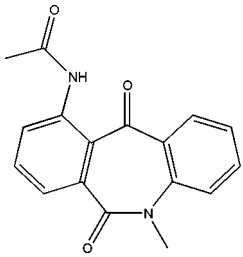
ADOSOPINE

Therapeutic Function: Urinary incontinence agent

Chemical Name: N-(6,11-Dihydro-5-methyl-6,11-dioxo-5H-dibenz[b,e] azepin-10-yl)acetamide

Common Name: Adosopine

Structural Formula:



Chemical Abstracts Registry No.: 88124-26-9

Trade Name	Manufacturer	Country	Year Introduced
Adosopine	Menarini Group	-	-

Raw Materials

Acetic anhydride	1-Aminoanthraquinone
Sodium methylate	Methyl iodide

Manufacturing Process

2 ml of acetic anhydride are added to 2.5 g of 10-amino-5,6-dihydro-11H-dibenzo[b,e]azepine-6,11-dione (prepared from 1-aminoanthraquinone in accordance with Caronna and Palazzo-Gaz. Chim. It. 83, 533, 1953) in 50 ml of dioxane. After maintaining for 2 h under reflux, the mixture is evaporated almost to dryness under reduced pressure, the residue is then poured into water, filtered and dried to give 2.0 g of crude product.

The 2.0 g of previously obtained crude product is suspended in 20 ml of N,N-dimethylformamide, and 710.0 mg of sodium methylate in 10 ml of methanol are added. After maintaining for 30 min at room temperature, 2.5 ml of methyl iodide are added, and mixture is allowed to stand for 24 h after which the mixture is poured into water, the product filtered off, dried and crystallized from ethanol, to give 5-methyl-10-acetamino-5,6-dihydro-11H-dibenzo[b,e] azepine-6,11-dione, melting point 199°-201°C.

References

Pestellini V. et al.; US Patent No. 4,551,451; Nov. 5, 1985; Assigned: A.Menarini S.a.S., Italy

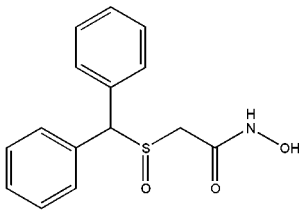
ADRAFINIL

Therapeutic Function: Psychostimulant

Chemical Name: Acetamide, 2-((diphenylmethyl)sulfinyl)-N-hydroxy-

Common Name: Adrafinil; Olmifon

Structural Formula:



Chemical Abstracts Registry No.: 63547-13-7

Trade Name	Manufacturer	Country	Year Introduced
Olmifon	Cephalon	-	-

Raw Materials

3-Chloroacetic acid	Sodium carbonate
Sulfuric acid	Hydroxylamine hydrochloride
Sodium methylate	Hydrogen chloride
Hydrogen peroxide	Thiourea
Chlorodiphenylmethane	Sodium hydroxide

Manufacturing Process

7.6 g (0.1 mol) of thiourea and 100 ml of dematerialized water are introduced into a 500 ml three-neck flask equipped with a magnetic stirrer, a dropping funnel and a condenser; the mixture is heated to 50°C and 20.25 g (18 ml; 0.1 mol) of chlorodiphenylmethane are then added all at once. The solution is left refluxing until it has become limpid, and is then cooled to 20°C, and 200 ml of 2.5 N NaOH are added dropwise. So the sodium benzhydrylthiolate is obtained.

A solution of sodium 3-chloroacetate is added to the solution of sodium benzhydrylthiolate at about 60°C. Thereafter the temperature is raised to the boil, the mixture is left under reflux for about 0.5 h and is then cooled, filtered over charcoal and acidified with concentrated HCl, and 3-(benzhydrylthio)acetic acid are thus precipitated.

To the solution of 3-(benzhydrylthio)acetic acid in 1,2-dichloroethane, methanol and concentrated H_2SO_4 have been added. The whole is heated to the reflux temperature for about 5 h, cooled, and decanted, the aqueous phase is discarded and the organic phase is washed with a saturated sodium bicarbonate solution and then with water until the wash waters have a neutral pH. After drying over $MgSO_4$ and evaporating the solvent, the 3-(benzhydrylthio)acetic acid methyl ester is obtained.

The 3-(benzhydrylthio)acetic acid methyl ester dissolved in methanol, is added to a solution of hydroxylamine base [prepared by neutralising 0.15 mol (10.4 g) of hydroxylamine hydrochloride with 0.15 mol of sodium methylate]. The whole is left at ordinary temperature (15°-25°C) for 48 h, the sodium chloride is filtered off, the methanol is evaporated, the residue is taken up with aqueous alkali, the solution is filtered over charcoal, the filtrate is acidified with concentrated HCl, and the 3-(benzhydrylthio)acethylhydroxamic acid (recrystallised from benzene) is thus obtained.

The 3-(benzhydrylthio)acethylhydroxamic acid, dissolved in anhydrous CH_3COOH, is reacted with H_2O_2. The mixture is left at 40°-45°C for about 1.5 h, the acetic acid is evaporated and the residue is taken up in 50 ml of ethyl acetate; the 2-[(diphenylmethyl)sulfinyl]-N-hydroxyacetamide (CRL 40028) crystallises (recrystallised from isopropanol).

References

Lafon L.; US Patent No. 4,066,686; Jan. 3, 1978; Assigned: Laboratoire L. Lafon, Maisons Alfort, France

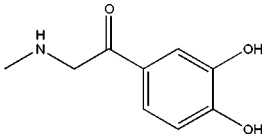
ADRENALONE

Therapeutic Function: Hemostatic, Sympathomimetic, Vasoconstrictor

Chemical Name: Ethanone, 1-(3,4-dihydroxyphenyl)-2-(methylamino)-

Common Name: Adrenalone; Adrenone

Structural Formula:



Chemical Abstracts Registry No.: 99-45-6

Trade Name	Manufacturer	Country	Year Introduced
Adrenalone	Yick-Vic Chemicals and Pharmaceuticals (HK) Ltd.	-	-

Raw Materials

ω-Chloro-3,4-dihydroxyacetophenone
Methylamine

Manufacturing Process

To a suspension of 1 part ω-chloro-3,4-dihydroxyacetophenone (prerared from chloroacetyl chloride and benzcatechole, see J. Russ. Phys. Chem. Ges., 25, 154) was added dropwise 1 part 60% solution of methylamine. Immediately was formed a residue of the salt of methylamine and ω-chloro-3,4-dihydroxyacetophenone. The dissolution of the salt was carried out by heating of the mixture. Then the salt was converted in crude 3,4-dihydroxy-α-methylaminoacetophenone. The product was dissolved in dilute hydrochloric acid. To this solution was added dropwise aqueous ammonium solution to prepare light yellow crystal of 3,4-dihydroxy-α-methylaminoacetophenone. The base and the hydrochloride of 3,4-dihydroxy-α-methylaminoacetophenone decomposed at temperature near 230°C and 240°C respectively.

References

Merck Index, Monograph number: 170, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
DE Patent No. 152,814; 1903.08.15; Assigned to Farbwerke vorm. Meister and Bruening in Hoechst a. M.

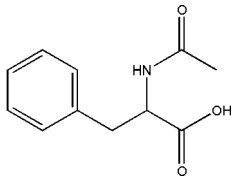
AFALANINE

Therapeutic Function: Antidepressant

Chemical Name: DL-Phenylalanine, N-acetyl-

Common Name: Afalanine

Structural Formula:



Chemical Abstracts Registry No.: 2901-75-9

Trade Name	Manufacturer	Country	Year Introduced
Afalanine	Sankyo	-	-

Raw Materials

Phenylalanine
Sodium hydroxide
Acetylbromide

Manufacturing Process

The phenylalanine was dispersed in water. A 1 N aqueous solution of sodium hydroxide was slowly added to this dispersion, and the pH of the solution reached a value of 7-8.

Then acetylbromide was dissolved in this solution, to give a N-acetylphenylalanine.

References

Shiogari T. et al.; EU Patent No. 0,178,911; April 23, 1986; Assigned: Sankyo company limited. N 1-6, 3-chome Nihonbashi Honcho Chuo-ku Tokyo (JP)

AFLOQUALONE

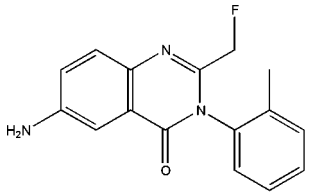
Therapeutic Function: Muscle relaxant

Chemical Name: 6-Amino-2-(fluoromethyl)-3-(o-tolyl)-4(3H)-quinazolinone

Common Name: -

Chemical Abstracts Registry No.: 56287-74-2; 56287-75-3 (Hydrochloride salt)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Arofuto	TANABE SEIYAKU	Japan	1983

Raw Materials

Fluoroacetyl chloride
Acetic anhydride
N-(2-Amino-5-nitrobenzyl)-o-toluidine
Hydrogen

Manufacturing Process

14.4 g (0.053 mol) of N-(2-amino-5-nitrobenzoyl)-o-toluidine and 6.3 g (0.08 mol) of pyridine are dissolved in 300 ml of tetrahydrofuran. 12.2 g (0.126 mol) of fluoroacetyl chloride are added to the solution for 10 minutes under ice-cooling. The solution is stirred at the same temperature for 30 minutes and then at room temperature for 2.5 hours. The reaction solution is allowed to stand at room temperature overnight. The crystalline precipitate is collected by filtration, washed with water and then dried. 16.4 g of N-(2-fluoroacetamido-5-nitrobenzoyl)-o-toluidine are obtained. Yield: 93.7%; MP 238-239°C.

16.5 g (0.05 mol) of N-(2-fluoroacetamido-5-nitrobenzoyl)-o-toluidine and 25.5 g (0.25 mol) of acetic acid anhydride are dissolved in 250 ml of glacial acetic acid. The solution is refluxed for 2 hours under heating. Then, the reaction solution is evaporated to remove solvent. The residue thus obtained is poured into ice-water, and the aqueous mixture is adjusted to pH 9 with potassium carbonate. The crystalline precipitate is collected by filtration. 15.5 g of 2-fluoromethyl-3-(o-tolyl)-6-nitro-4(3H)-quinazolinone are obtained. Yield: 98.7%; MP 155-158°C (recrystallized from ethanol).

A mixture of 2.0 g (0.064 mol) of 2-fluoromethyl-3-(o-tolyl)-6-nitro-4(3H)-quinazolinone, 0.2 g of 5% palladium-carbon and 100 ml of acetic acid is shaken for 30 minutes in hydrogen gas. The initial pressure of hydrogen gas is adjusted to 46 lb and the mixture is heated with an infrared lamp during the reaction. After 30 minutes of this reaction, the pressure of hydrogen gas decreases to 6 lb. After the mixture is cooled, the mixture is filtered to remove the catalyst. The filtrate is evaporated to remove acetic acid, and the residue is dissolved in chloroform. The chloroform solution is washed with 5% aqueous sodium hydroxide and water, successively. Then, the solution is dried and evaporated to remove solvent. The oily residue thus obtained is dissolved in 2 ml of chloroform, and the chloroform solution is passed through a column of 200 g of silica gel. The silica gel column is eluted with ethyl acetate-benzene (1:1). Then, the eluate is evaporated to remove solvent. The crude crystal obtained is washed with isopropyl ether and recrystallized from

isopropanol. 0.95 g of 2-fluoromethyl-3-(o-tolyl)-6-amino-4(3H)-quinazolinone is obtained. Yield: 52.5%; MP 195-196°C.

References

DFU 7 (8) 539 (1982)
DOT 19 (1) 581 (1983)
Inoue, L., Oine, T., Yamado, Y., Tani, J., Ishida, R. and Ochiai, T.; US Patent 3,966,731; June 29, 1976; Assigned to Tanabe Seiyaku Co., Ltd.

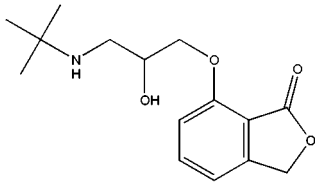
AFUROLOL

Therapeutic Function: Beta-adrenergic blocker

Chemical Name: 7-[3-[(1,1-Dimethylethyl)amino]-2-hydroxypropoxy]-1(3H)-isobenzofuranone

Common Name: Afurolol

Structural Formula:



Chemical Abstracts Registry No.: 65776-67-2

Trade Name	Manufacturer	Country	Year Introduced
Afurolol	ZYF Pharm Chemical	-	-

Raw Materials

7-Hydroxyphthalide
1-Chloro-2,3-epoxypropane
t-Butylamine

Manufacturing Process

A mixture of 18.0 g (0.12 mole) 7-hydroxyphthalide, 180.0 g of 1-chloro-2,3-epoxypropane (2 moles) and 0.5 ml of piperidine is heated at 100°C for about 5 h and then the unreacted 1-chloro-2,3-epoxypropane is distilled off in vacuum to yield 12.0 g (48%) of 7-(2,3-epoxypropoxy)phthalide, melting point 88°-90°C, (crystallized successively from methanol and ethyl acetate).

The 7-(2,3-epoxypropoxy)phthalide is dissolved in methanol and t-butylamine are added to the solution at about 20°C. The solution is allowed to stand

overnight and, the mixture is evaporated in vacuum and the residue is dried to give 7-(2-hydroxy-3-t-butylamino-propoxy)phthalide.

References

Bellasio E.; US Patent No. 3,935,236; Jan. 27, 1976; Assigned: Gruppo Lepetit, S.p.A., Milan, Italy

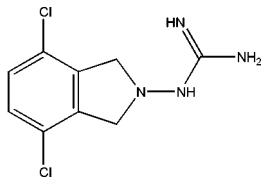
AGANODINE

Therapeutic Function: Antihypertensive

Chemical Name: Guanidine, (4,7-dichloro-2-isoindolinyl)-

Common Name: Aganodine

Structural Formula:



Chemical Abstracts Registry No.: 86696-87-9

Trade Name	Manufacturer	Country	Year Introduced
Aganodine	ZYF Pharm Chemical	-	-

Raw Materials

3,6-Dichlorophthalic anhydride
Lithium aluminum hydride
Cyanamide
Carbazic acid, tert-butyl ester
Hydrochloric acid
Sodium bicarbonate

Manufacturing Process

The solution of 3,6-dichlorophthalic anhydride in 300 ml of N,N-dimethylformamide are heated to the boiling point over 15 min with t-butylcarbazate. Subsequent to evaporation of the solvent, N-(t-butyloxycarbonylamino)-3,6-dichlorophthalimide is obtained from ethanol.

The solution of N-(t-butyloxycarbonylamino)-3,6-dichlorophthalimide in 400 ml of absolute tetrahydrofuran are slowly dripped into a suspension of aluminum lithium hydride in absolute tetrahydrofuran. The mixture is heated to the boiling point. Conventional processing yields N-(t-butyloxycarbonylamino)-4,7-dichloroisoindoline.

N-(t-Butyloxycarbonylamino)-4,7-dichloroisoindoline are introduced into concentrated hydrochloric acid and stirred at room temperature. The hydrochloride of 2-amino-4,7-dichloroisoindoline precipitates in the form of crystals is obtained, melting point 230°-232°C.

2-Amino-4,7-dichloroisoindoline hydrochloride and cyanamide are heated over 2 h to the boiling point in n-amyl alcohol. The solvent is evaporated off and the residue recrystallized from isopropyl alcohol and ethyl ether, yielding the (4,7-dichloroisoindolin-2-yl)guanidine in the form of hydrochloride, melting point 235°-237°C.

To obtained the base (4,7-dichloroisoindolin-2-yl)guanidine the salt (4,7-dichloroisoindolin-2-yl)guanidine hydrochloride is treated with sodium bicarbonicum.

References

Cohnen E, Armah B.; US Patent No. 4,526,897; July 2, 1985; Assigned: Beiersdorf Aktiengesellschaft, Hamburg, Fed.Rep. of Germany

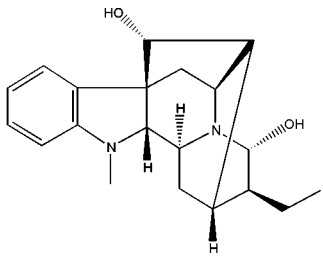
AJMALINE

Therapeutic Function: Antiarrhythmic

Chemical Name: Ajmalan-17,21-diol, (17R,21α)-

Common Name: Ajmaline; Rauwolfine

Structural Formula:



Chemical Abstracts Registry No.: 4360-12-7

Trade Name	Manufacturer	Country	Year Introduced
Ajmaline	Solvay Pharma	-	-
Aritmina	Farmacie Petrone	-	-
Aritmina	Solvay	-	-
Neo-Aritmina	Giulini Pharma	-	-
Gilurytmal	Solvay	-	-
Gilurytmal	Solvay Arzneimittel	-	-

Trade Name	Manufacturer	Country	Year Introduced
Gilurytmal	Solvay Pharmaceuticals (Spolka z o.o.)	-	-
Gilurytmal	Solvay Pharmaceuticals	-	-
Gilurytmal	Solvay Pharma, Klosterneuburg	-	-
Neo-Gilurytmal	Solvay Pharmaceuticals	-	-
Rauwolfine	Extrasynthese	-	-
Ritmos	Inverni	-	-
Serenol	Laboratoires Plantes et Medecines	-	-
Tachmalin	Arzneimittelwerk Dresden	-	-

Raw Materials

Rauwolfia canescens L. roots
Acetic acid
Ammonia

Manufacturing Process

Ajmaline isolated from *Rauwolfia sp. roots: Rauwolfia serpentine Benth., Rauwolfia vomitoria Afr., Rauwolfia canescens L.*

Threshed roots of *Rauwolfia canescens L.* extracted with 5% solution of acetic acid at room temperature for 24 h. Then extract was decanted to flask. This extract was alkalified with ammonia (alkaloid salts were converted to alkaloid bases). The obtained thus method solution was extracted with chloroform 3 or more times. Then chloroform extract was chromatographed on column through Al_2O_3 sorbent. After chromatography ajmalin was obtained, which had melting point at 205°C (recyrstallization from methanol).

References

Belikov A.S.; Alkaloids of Rauwolfia canescens L.//Chemistry of natural compounds 1969, 3. P.64

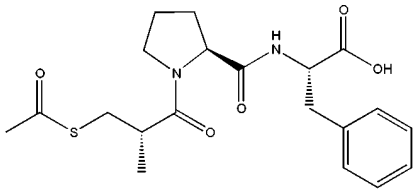
ALACEPRIL

Therapeutic Function: Antihypertensive

Chemical Name: L-Phenylalanine, N-(1-(3-(acetylthio)-2-methyl-1-oxopropyl)-L-prolyl)-, (S)-

Common Name: Alacepril; Cetapril

Structural Formula:



Chemical Abstracts Registry No.: 74258-86-9

Trade Name	Manufacturer	Country	Year Introduced
Alacepril	Sumika Fine Chemicals Co., Ltd.	-	-
Alacepril	ZYF Pharm Chemical	-	-
Cetapril	Dainippon Pharmaceutical Co., Ltd.	-	-

Raw Materials

N-Methylmorpholine
1-(D-3-Acetylthio-2-methylpropanoyl)-L-proline
Phenyl chloroformate
L-Phenylalanine t-butyl ester hydrochloride
Sodium bicarbonate
Hydrochloric acid
Anisole
Trifluoroacetic acid

Manufacturing Process

N-Methylmorpholine (1.03 g) was added to a solution of 1-(D-3-acetylthio-2-methylpropanoyl)-L-proline (2.65 g) in dry tetrahydrofuran (50 ml). The resulting solution was stirred and cooled at -20° to -15°C. Phenyl chloroformate (1.61 g) was added, and after 5 min, a solution of L-phenylalanine t-butyl ester hydrochloride (2.4 g) and N-methylmorpholine (1.03 g) in dry tetrahydrofuran (30 ml) was added. The mixture was stirred at -20° to -15°C for 1 h and then at room temperature overnight.

After removal of insoluble materials by filtration, the filtrate was concentrated under reduced pressure and the residue was dissolved in chloroform.

The chloroform solution was washed successively with 1 N sodium hydroxide, water, 10% citric acid, and water, dried and concentrated under reduced pressure. The residue was chromatographed on silica gel with chloroform-methanol (99:1) to give 4.2 g the 1-(D-3-acetylthio-2-methylpropanoyl)-L-prolyl-L-phenylalanine tert-butyl ester.

1-(D-3-Acetylthio-2-methylpropanoyl)-L-prolyl-L-phenylalanine tert-butyl ester

(2.5 g) was dissolved in a mixture of anisole (18 ml) and trifluoroacetic acid (37 ml). The solution was allowed to stand at room temperature for 1 h and then concentrated to dryness under reduced pressure. The residue was crystallized from diethyl ether. The 1-(D-3-acetylthio-2-methylpropanoyl)-L-prolyl-L-phenylalanine was obtained (1.8 g), melting point 155°-156°C (recrystallization from ethanol/n-hexane).

References

Sawayama T. et al.; US Patent No. 4,248,883; Feb. 3, 1981; Assigned: Dianippon Pharmaceutical Co., Ltd., Osaka, Japan

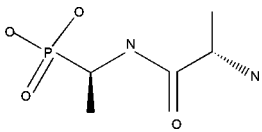
ALAFOSFALIN

Therapeutic Function: Antibacterial

Chemical Name: Phosphonic acid, ((1R)-1-(((2S)-2-amino-1-oxopropyl) amino)ethyl)-

Common Name: Alafosfalin; Alaphosfalin

Structural Formula:



Chemical Abstracts Registry No.: 60668-24-8

Trade Name	Manufacturer	Country	Year Introduced
Alafosfalin	Roche Product Limited	-	-

Raw Materials

N-Hydroxysuccinimide ester of N-benzyloxycarbonyl-L-alanine
(1R,S)-1-Aminoethylphosphonic acid
Benzylamine
Palladium on carbon
1R-(L-Alanylamino)ethanephosphonous acid
Mercuric chloride
Propylene oxide

Manufacturing Process

14.1 g (0.168 mol) of solid sodium bicarbonate were added to a solution of 7 g (0.056 mol) of (1R,S)-1-aminoethylphosphonic acid in 280 ml of water and 140 ml of ethanol while stirring at 0°C. While stirring this mixture at 0°C, a solution of 17.9 g (0.056 mol) of the N-hydroxysuccinimide ester of N-

benzyloxycarbonyl-L-alanine in 140 ml of warm ethanol was added dropwise over ca 15 minutes. The latter solution was washed in with 70 ml of ethanol. The heterogeneous mixture was stirred for 1 hour at 0°C and then for a further 16 hours at room temperature, the mixture becoming homogeneous. The mixture was evaporated and re-evaporated with 200 ml of water to give a gum, which was dissolved in 500 ml of water. The solution was extracted firstly with 500 ml of chloroform and then with 250 ml portions of chloroform, acidified to pH 2 with ca 80 ml of 2 N hydrochloric acid and again extracted with 500 ml of chloroform followed by two 250 ml portions of chloroform. The aqueous layer was concentrated and passed down a column of cation exchange resin (B.D.H., Zerolit 225, SRC 13, RSO_3H; 750 g; freshly regenerated in the acid cycle). The column was eluted with water and there were collected six 250 ml fractions. The first four fractions were combined, evaporated and re-evaporated with water to remove hydrogen chloride. There was obtained a final residue of (1R,S)-1-[(N-benzyloxycarbonyl-L-alanyl)-amino]ethylphosphonic acid which was separated as follows:

The latter residue was dissolved in 400 ml of water and titrated with 1 M benzylamine to pH 4.5. The resulting solution was concentrated and crystallized from water to give 5.3 g of the benzylamine salt of (1S)-1-[(N-benzyloxycarbonyl-L-alanyl)amino]ethylphosphonic acid of melting point 210-215°C. Concentration of the mother liquors followed by further recrystallization from water gave the benzylamine salt of (1R)-1-[(N-benzyloxycarbonyl-L-alanyl)amino]ethylphosphonic acid in a first crop of 0.59 g [melting point 226-228°C (decomposition); $[\alpha]_D^{20}$ = -32.3° (c = 1% in acetic acid)] and a second crop of 0.825 g] melting point 225-227°C (decomposition); $[\alpha]_D^{20}$ = -33.0° (c = 1% in acetic acid)]. Recrystallization of the first crop from water gave 0.333 g of pure benzylamine salt of the R-stereoisomer; melting point 226-228°C (decomposition); $[\alpha]_D^{20}$ = -33.1° (c=1% in acetic acid).

1.1 g (2.5 mmol) of the benzylamine salt of (1R)-1-[(N-benzyloxycarbonyl-L-alanyl)amino]-ethylphosphonic acid were dissolved in 4 ml of 2 N ammonium hydroxide, passed down a column of cation exchange resin (B.D.H., Zerolit 225, SRC 13, RSO_3H; 120 g; freshly regenerated in the acid cycle) and eluted with water. There were collected 200 ml of acid eluate, which was concentrated to 100 ml. To this were added 100 ml of methanol, 0.3 g of 5% palladium-on-charcoal catalyst and 3 drops of glacial acetic acid. The mixture was hydrogenated at room temperature and atmospheric pressure. The catalyst was filtered off and the solvent evaporated. The residual gum was re-evaporated with three 50 ml portions of n-propanol to give 0.6 g of a gummy solid of melting point ca 275-280°C (decomposition). After further recrystallization from water and ethanol, there was obtained 0.2 g of (1R)-1-(L-alanylamino)-ethylphosphonic acid of melting point 295-296°C (decomposition); $[\alpha]_D^{20}$ = -44.0° (c=1% in water).

The different ways of synthesis of alafosfalin were described:

1). 1R-1-(L-alanylamino)-ethanephosphonous acid (0.034 M), mercuric chloride (0.068 M) and water (175 ml) were mixed and heated to reflux for 1 hour The white insoluble mercuric chloride which formed was removed by filtration and the aqueous filtrate was evaporated to dryness. The oily residue was dissolved in ethanol (20 ml) and propylene oxide was added until

precipitation was complete. Filtration gave 1R-1-(L-alanylamino)-ethylphosphonic acid, which was recrystallised from ethanol/water. MP: 293-295°C, $[\alpha]_D^{20}$ =-49.3° (1%, H_2O). Yield was 100% of theory.

2). Papain (50 mg; 2.2 U/mg) was added to the solution of 0.5 mmol Z-L-Ala, 1.15 mmol racemic diisopropyl ester of 1-aminoethylphosphonic acid and 50 ml 2-mercaptoethanol in the mixture of 2.3 ml acetonitrile and 0.2 ml water The suspension was shaken for about 2 days until all the Z-ala was consumed (TLC-control). The enzyme was filtered off and washed with 10% $KHSO_4$, water, saturated $NaHCO_3$, dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The resulting phosphonopeptide was dissolved in 2 ml of 40% HBr in glacial acetic acid and left overnight. Anhydrous ether (10 ml) was added and the mixture was stirred for 10 min and upper phase decanted. The residue was evaporated, the remaining gum was dissolved in 2 ml of methanol and treated with excess of propylene oxide. The precipitated material was filtered off and crystallized from water water-ethanol to give pure alafosfalin, yield 60%, MP: 273-276°C (decomposition); $[\alpha]_D^{20}$ =-45° (0.2% in water). Only L-aminophosthonate is involved in the peptide bond formation because of papain presence.

References

Atherton F.R. et al.; US Patent No. 4,016,146; April 5, 1977; Assigned to Hoffmann-La Roche Inc., Nutely, N.Y.

Baylis E.; US Patent No. 4,331,591; May 25, 1982; Assigned to Ciba-Geigy Corporation, Ardsley, N.Y.

Solodenko V., Kukar V.; Tetrahedron Letters, v. 30, No. 49, pp 6917-6918, 1989

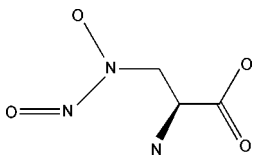
ALANOSINE

Therapeutic Function: Antineoplastic

Chemical Name: 3-(Hydroxynitrosoamino)-L-alanine

Common Name: Alanosine

Structural Formula:



Chemical Abstracts Registry No.: 5854-93-3

Trade Name	Manufacturer	Country	Year Introduced
Alanosine	Triangle Pharmaceuticals	-	-

Raw Materials

Streptomyces alanosinicus n. sp. ATCC 15710
Peptone-agar-glucose-yeast extract medium
Glucose
Dried whale meat (Pascor)
6% of Darco G-60 charcoal
Sodium methoxide

Manufacturing Process

Alanosine is an antibiotic isolated from the fermentation broth of Streptomyces alanosinicus n. sp.

Oat meal agar slants seeded with Streptomyces alanosinicus n. sp. ATCC 15710 were incubated at 20°C for 7 to 10 days and then used to inoculate 100 ml of a peptone-agar-glucose-yeast extract medium contained in 500 ml Erlenmeyer flask. The composition of this fermination medium is:

Meat extract	5.0 g./liter
Peptone	5.0 g./liter
Yeast extract	5.0 g./liter
Enzymatic casein hydrolysate	3.0 g./liter
Cerelose	2.0 g./liter
NaCl	1.5 g./liter

The medium is adjusted to pH 7.2 prior to sterilization for 20 minutes at 121°C and 15 Ibs steam pressure. The germination flasks are incubated at 28°C for 48 hours on rotary shaker having a 2 inch throw and making 240 rpm. A 3% transfer is made from the germination flask to 500 ml Erlenmeyer fermentation flaks containing 100 ml of medium TVF/5 having the following composition:

Glucose	50.0 g/L
Dried whale meat (Pascor)	10.0 g/L
$CaCO_4$	5.0 g/L
$(NH_4)_2SO_4$	1.0 g/L
$MgSO_4 \cdot 7H_2O$	1.0 g/L
$CuSO_4$ sol. 0.5%	1 ml
$FeSO_4$ sol. 0.1%	1 ml
$ZnSO_4$ sol. 0.2%	1 ml
$MnSO_4$ sol. 0.8%	1 ml

The medium is adjusted to pH 7.0 prior to sterilization for 20 minutes at 121°C. The fermentation flasks are incubated and agitated under similar conditions as the germination flasks. After 72 hours the mycelium was separated by centrifugation and the untreated broth assayed by the streak dilution method. 30 liters of broth are centrifuged and 6% of Darco G-60 charcoal is added to the clear solution, which is stirred for 30 minutes; then the charcoal is filtered off to give an almost colorless solution which is concentrated in vacuum at 45-50°C to 1.5 liters. The concentrated solution is poured under stirring into 5 liters of methanol, the formed precipitate is

filtered, washed with much acetone and dried in vacuum. Yield 230 g of crude product assaying about 10%.

Purification:

The above crude product is suspended in 400 ml of water and to the suspension, cooled to 4°C and kept stirred, sulfuric acid is added to pH 2.0-2.5; the undissolved residue is filtered off, the solution is further diluted with 400 ml of water and 1.6 liters of methanol are added to precipitate the antibiotic. The mixture is kept at 4°C for some hours to complete precipitation, then it is filtered, washed with acetone and dried in vacuum over P_2O_5. Yield 62 g of a product assaying 27%. The dried product is suspended in anhydrous methanol and the mixture is kept stirred; perchloric acid (75%) is added at about 4°C to reach a pH of 3.0, the undissolved portion is filtered off and the antibiotic is precipitated by adjusting the pH 5.5 with sodium methoxide. The suspension is allowed to decant for some hours at 4°C, then it is filtered and the precipitate is washed with diethyl ether. Yield 30 g (titer 43%). An amount of 3.2 g of the obtained antibiotic is dissolved in 60 ml of H_2O and the pH is adjusted to 8; the undissolved portion is filtered off and by the addition of glacial acetic acid, the pH is adjusted to 4-4.5. On cooling at 4°C, 1.2 g of antibiotic in crystalline form (assaying 75%) are obtained. An amount of 2.9 g of said crystalline antibiotic is dissolved in 900 ml of water heating the solution to 70-80°C, then it is filtered, concentrated to 200 ml and allowed to stand 8-10 hours at 4°C; then it is filtered and washed with cold water. Yield 1.45 g (97%). By further concentrating the solution to 100 ml a further amount of antibiotic is obtained: 1 g (80%). Alanosine melts at 190°C, $[\alpha]_D^{25}$= -37.8° (c=0.5, water).

Antibiotic was also prepared by syntheses from anhydrous hydroxylamine and methyl-2-acetamido-3-chloropropionate followed by reaction with $NaNO_2$ in dilute acetic acid. The prepared racemic product was separated on individual isomers.

References

Thiemann J. et al.; US Patent No. 3,676,490; July 11, 1972; Assigned to Lepetit S.P.A., Milan, Italy

Lancini G.C.A, Diena and E. Lassari; Tetrahedron Letters No. 16, pp. 1769-1772, 1966

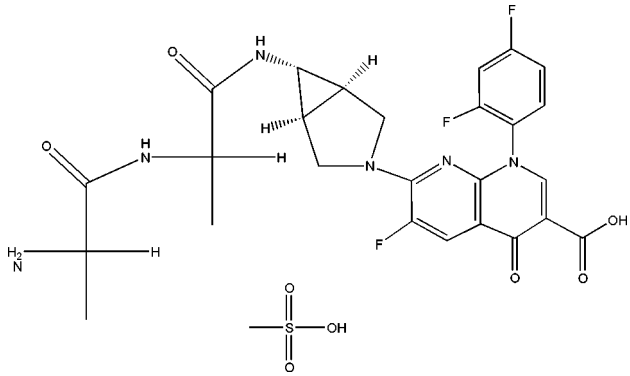
ALATROFLOXACIN MESYLATE

Therapeutic Function: Antibacterial

Chemical Name: L-Alaninamide, L-alanyl-N-(3-(6-carboxy-8-(2,4-difluorophenyl)-3-fluoro-5,8-dihydro-5-oxo-1,8-naphthyridin-2-yl)-3-azabicyclo[3.1.0]hex-6-yl)-, (1α,5α,6α)-, monomethanesulfonate

Common Name: Alatrofloxacin mesilate

Structural Formula:



Chemical Abstracts Registry No.: 146961-77-5; 146961-76-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Alatrofloxacin mesylate	Pfizer	-	-
Alatrofloxacin mesylate	Fairview Pharm	-	-
Alatrofloxacin mesilate	Cipla	-	-
Trovan Preservative Free	Pfizer	-	-
Trovan iv	Pfizer	-	-
Turvel iv	Roerig Farmaceutici Italiana S.p.A.	-	-
Turvel iv	Pfizer	-	-

Raw Materials

Diphenylphosphinous azide
Dihydropyrrole
Ethyldiazoacetate
Palladium
Alanylalanine
1-(2,4-Difluoro-phenyl)-6,7-difluoro-4-oxo-1,4-dihydro[1,8] naphthylridine-3-carboxylic acid ethyl ester

Manufacturing Process

The dipolar cycloaddition of ethyldiazoacetate to the protected dihydropyrrole (with carbobenzyloxy (CBZ) protecting group) gives the fused pyrrazolidine-(CBZ-3-ethylperoxy-1,3a,4,5,6,6a-hexahydro-pyrrolo{3,4-c}pyrazole). Pyrolysis results in loss of nitrogen and formation of the cyclopyrrolidine ring. The ester is then saponified to the corresponding carboxylic acid (CBZ-6-aza-bicyclo[3.1.0]hexene-3-carboxylic acid).This acid undergoes a version of the

Curtius rearrangement when treated with diphenylphosphinous azide to afford transient isocyanate. That reactive function adds tert-butanol from the reaction medium to afford the product as its butoxycarbonyl (BOC) derivative. CBZ-protecting group is removed by catalytic hydrogenation on Pd to afford the BOC-protected secondary amine - BOC-6-aza-bicyclo[3.1.0]hex-3-ylamine. In a standard quinolone reaction, this amine is then used to displace the more reactive fluorine at 7-position in the quinolone - 1-(2,4 difluoro-phenyl)-6,7-difluoro-4-oxo-1,4-dihydro[1,8]naphthylridine-3-carboxylic acid ethyl ester. Treatment of the displacement product with hydrogen chloride cleaves the BOC protecting group to afford the antibiotic trovafloxacin. The peptide-like alanylalanylamide derivative, alatrofloxacin can in principle be prepared by reaction of the ester precursor of trovafloxacin with alanylalanine followed by saponification and treatment by methane sulphonic acid (mesylate).

References

Lednicer D., The organic Chemistry of Drug Synthesis, vol. 5, Wiley, NY, p.123 (1985)
Brighty K.E.; US Patent No. 5,164,402; Nov. 17, 1992, Assigned to Pfizer Inc., New York, N.Y.
Lednicer D., The organic Chemistry of Drug Synthesis, vol.6, Wiley, NY, p.154 (1999)

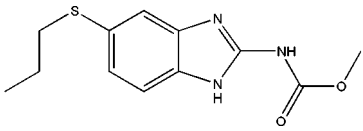
ALBENDAZOLE

Therapeutic Function: Anthelmintic

Chemical Name: [5-(Propylthio)-1H-benzimidazol-2-yl]carbamic acid methyl ester

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 54965-21-8

Trade Name	Manufacturer	Country	Year Introduced
Zentel	SK and F	France	1981

Raw Materials

3-Chloro-6-nitroacetanilide
Hydrogen
Methyl chloroformate
Propyl Mercaptan
Cyanamide

Manufacturing Process

A mixture of 6.65 g of 3-chloro-6-nitroacetanilide, 3.2 ml of propylmercaptan, 5.6 g of 50% sodium hydroxide and 100 ml of water is heated at reflux overnight. The cooled mixture is filtered to give the desired 2-nitro-5-propylthioaniline, MP 69.5-71.5°C after recrystallization from ethanol then hexane-ether. NMR ($CDCl_3$) 40%.

The aniline (2.5 g) is hydrogenated with 1.9 ml of concentrated hydrochloric acid, 100 ml ethanol and 5% palladium-on-charcoal to give 4-propylthio-o-phenylene-diamine hydrochloride.

A mixture of 2.5 ml of 50% sodium hydroxide in 5 ml of water is added to a mixture of 1.9 g of cyanamide, 2.2 g of methylchloroformate, 3.5 ml of water and 3 ml of acetone over 45 minutes below 10°C, pH raised to 6.5. A molar equivalent solution of the diamine in 100 ml of ethanol is added. The mixture is heated until the easily volatile solvents are expelled, to about 85°C, then maintained at this temperature with some water added for one-half hour. The product, methyl 5-propylthio-2-benzimidazolecarbamate, is separated, washed to give a colorless crystalline solid, MP 208-210°C.

References

Merck Index 197
DFU 2 (2) 81 (1977)
OCDS Vol.2 p. 353 (1980)
DOT 15 (3) 89 (1979)
I.N. p. 50
Gyurik, R.J. and Theodorides, V.J.; US Patent 3,915,986; October 28, 1975; Assigned to Smith Kline Corp.

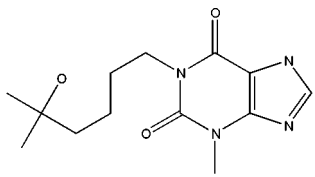
ALBIFYLLINE

Therapeutic Function: Vasodilator

Chemical Name: 3,7-Dihydro-1-(5-hydroxy-5-methylhexyl)-3-methyl-1H-purine-2,6-dione

Common Name: Albifylline

Structural Formula:



Chemical Abstracts Registry No.: 107767-55-5

Trade Name	Manufacturer	Country	Year Introduced
HWA-138	Hoechst-Roussel	-	-

Raw Materials

1-Chloro-5-hexanone
3-Methylxanthine
Palladium on carbon
Methyl magnesium chloride
Benzyl bromide

Manufacturing Process

1-(5-Hydroxy-5-methylhexyl)-3-methylxanthine may be prepared next way:

1). 1-Chloro-5-hydroxy-5-methylhexane:

A solution of 67.3 g (0.5 mol) of 1-chloro-5-hexanone in 50 ml of anhydrous ether is added dropwise to 44.9 g (0.6 mol) of methyl magnesium chloride in the form of a 20% strength solution in tetrahydrofuran and 200 ml of dry ether at 0° to 5°C, while stirring. The mixture is then subsequently stirred initially at room temperature for one hour and then while boiling under reflux for a further hour, the tertiary alkanolate formed is decomposed by addition of 50% strength aqueous ammonium chloride solution, the ether phase is separated off and the aqueous phase is extracted by shaking with ether. The combined ethereal extracts are washed in succession with aqueous sodium bisulfite solution and sodium bicarbonate solution as well as a little water, dried over sodium sulfate, filtered and concentrated in vacuo and the liquid residue is subjected to fractional distillation under reduced pressure. Yield: 64.1 g (85.1% of theory), boiling point (20 mbar) 95-97°C, refractive index n_D^{25} =1.4489.

2). 7-Benzyl-3-methylxanthine:

20 g (0.5 mol) of sodium hydroxide dissolved in 200 ml of water are added to a suspension of 83 g (0.5 mol) of 3-methylxanthine in 500 ml of methanol, the mixture is stirred at 70°C for one hour, 85.5 g (0.5 mol) of benzyl bromide are then added dropwise at the same temperature and the reaction mixture is kept between 70°C and 80°C for 5 hours. It is then cooled and filtered cold with suction, the product on the suction filter is washed with water and dissolved in 1000 ml of 1 N sodium hydroxide solution under the influence of heat, the solution is filtered and the pH is brought slowly to 9.5 with 4 N hydrochloric acid, while stirring. The crystals are filtered off from the still warm solution, washed with water until free from chloride and dried in vacuum. Yield: 81.7 g (63.8% of theory), melting point: 262-264°C.

3). 7-Benzyl-1-(5-hydroxy-5-methylhexyl)-3-methylxanthine:

A mixture of 20.5 g (0.08 mol) of 7-benzyl-3-methylxanthine, 12.4 g (0.09 mol) of potassium carbonate and 13.61 g (0.09 mol) of above 1-chloro-5-hydroxy-5-methylhexane in 300 ml of dimethylformamide is heated at 110° to 120°C for 8 hours, while stirring, and is then filtered hot and the filtrate is evaporated under reduced pressure. The residue is taken up in chloroform, the mixture is washed first with 1 N sodium hydroxide solution and then with

water until neutral and dried, the solvent is distilled off in vacuum and the solid residue is recrystallized from ethyl acetate, with the addition of petroleum ether Yield: 23.8 g (80.3% of theory), melting point: 109-111°C.

4). 1-(5-Hydroxy-5-methylhexyl)-3-methylxanthine:

14.8 g (0.04 mol) of the above mentioned 7-benzylxanthine are hydrogenated in 200 ml of glacial acetic acid over 1.5 g of palladium (5%) on active charcoal at 60°C under 3.5 bar in the course of 24 hours, while shaking. After cooling, the mixture is blanketed with nitrogen, the catalyst is filtered off, the filtrate is concentrated under reduced pressure and the solid residue is recrystallized from ethyl acetate. Yield of albifylline: 9.6 g (85.6% of theory), MP: 192-193°C.

References

Gebert U. et al.; US Patent No. 4,833,146; May 23, 1989; Assigned to Hoechst Aktiengeselschaft, Frankfurt am Main, Fed. Rep. of Germany

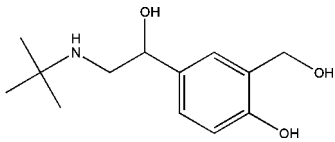
ALBUTEROL

Therapeutic Function: Bronchodilator

Chemical Name: α^1-[[(1,1-Dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol

Common Name: Salbutamol, α'-tert-Butylaminomethyl-4-hydroxy-m-xylene-α^1,α^3-diol

Structural Formula:



Chemical Abstracts Registry No.: 18559-94-9; 51022-70-9 (Sulfate)

Trade Name	Manufacturer	Country	Year Introduced
Ventolin	Allen and Hanburys	UK	1969
Sultanol	Glaxo	W. Germany	1971
Ventoline	Glaxo	France	1971
Ventolin	Glaxo	Italy	1973
Ventolin	Sankyo	Japan	1973
Ventolin	Glaxo	Switz.	1981
Ventolin	Glaxo	US	1981
Broncollenas	Llenas	Spain	-
Buto-Asma	Aldo Union	Spain	-
Proventil	Schering	US	-

Trade Name	Manufacturer	Country	Year Introduced
Rotacaps	Schering	-	-
Salbumol	Medica	Finland	-
Salbutol	Iltas	Turkey	-
Salbuvent	Leiras	Finland	-
Salbuvent	Nyegaard	Norway	-

Raw Materials

5-(N-Benzyl-N-tert-butylglycyl)salicylic acid methyl ester hydrochloride
Lithium aluminum hydride
Hydrogen

Manufacturing Process

(a) α^1-Benzyl-tert-butylaminomethyl-4-hydroxym-xylene-α^1,α^3-diol: 3.0 g of 5-(N-benzyl-N-tert-butylglycyl)-salicylic acid methyl ester hydrochloride in 40 ml of water was basified with sodium bicarbonate solution and extracted into ether. The ethereal solution was dried over $MgSO_4$ and evaporated and the basic residue in 20 ml of dry tetrahydrofuran was added with stirring to 1.0 g of lithium aluminum hydride in 100 ml of dry tetrahydrofuran, over a period of 5 minutes. The light gelatinous precipitate that formed was stirred and refluxed for 8 hours after which time 7 ml of water was carefully added and the solvents were removed under reduced pressure.

The residue was acidified with dilute hydrochloric acid and brought to pH 8 with sodium hydroxide and sodium bicarbonate. The mixture was filtered and the filtrate and orange solid were separately extracted with chloroform. The combined, dried, chloroform solutions were evaporated to give 22 g of the crude basic triol as an orange solid, when triturated with ether. A portion of the material was recrystallized from ether/light petroleum (BP 40-60°C) to give a white solid, MP 109-111°C.

In an alternative process, sodium borohydride was used as the reducing agent, as follows:

36 g of 2-(benzyl-tert-butylamino)-4'-hydroxy-3'-hydroxymethyl acetophenone, hydrochloride was shaken with 100 ml of 10% sodium carbonate solution and 100 ml of ethyl acetate. The ethyl acetate layer was separated, washed with water, dried over anhydrous sodium sulfate and evaporated in vacuum.

The residual gum was dissolved in 360 ml of ethanol and cooled to 15°C in an ice/water bath, 8 g of sodium borohydride was then added in portions over 30 minutes while maintaining the temperature at 15-20°C. After a further 30 minutes at 20°C the solution was stirred at room temperature for 2 hours. The solution was again cooled in ice and 250 ml of 2 N sulfuric acid were slowly added, then the solution was evaporated in vacuum until the ethanol had been removed. The clear aqueous solution was then treated with 250 ml of 10% sodium carbonate solution and the oil which precipitated was extracted into ethyl acetate. The ethyl acetate layer was washed with sodium carbonate solution, then with water, and was dried over anhydrous sodium

sulfate and evaporated in vacuum, to a small volume. Petroleum ether (BP 40-60°C) was added, and after standing overnight a white solid was obtained. This was filtered off to give 23 g of the product, MP 110-114°C.

(b) α^1-tert-Butylaminomethyl-4-hydroxy-m-xylene-α^1,α^3-diol: 0.8 g of α^1-benzyl-tert-butyl-aminomethyl-4-hydroxy-m-xylene-α^1,α^3-diol in 20 ml of ethanol and 2 ml of water was shaken with hydrogen in presence of 0.50 g of pre-reduced 10% palladium on charcoal catalyst. When uptake of hydrogen was complete, the solution was filtered and evaporated under reduced pressure to give 0,4 g of the base as a colorless oil which yielded a white solid, MP 144-145°C when triturated with ether/cyclohexane. Recrystallization from ethyl acetate-cyclohexane gave a white solid, MP 147-149°C.

References

Merck Index 206
DFU 4 (9) 629 (1979)
Kleeman and Engel p. 813
PDR 40 pp. 916, 1649
OCDS Vol. 2 p. 43 (1980)
DOT 16 (8) 269 (1980)
I.N. p. 860
REM p. 881
Lunts, L.H.C. and Toon, P.; US Patent 3,644,353; February 22, 1972; Assigned to Allen and Hanburys Ltd.

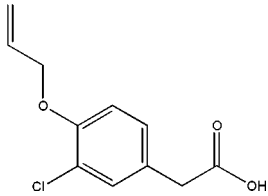
ALCLOFENAC

Therapeutic Function: Antiinflammatory

Chemical Name: 3-Chloro-4-(2-propenyloxy)benzene-acetic acid

Common Name: (4-(Allyloxy)-3-chlorophenyl]acetic acid

Structural Formula:



Chemical Abstracts Registry No.: 22131-79-9

Trade Name	Manufacturer	Country	Year Introduced
Mervan	Cooper	Switz.	-
Prinalgin	Berk	UK	1971
Neoston	Beiersdorf	W. Germany	1972

Trade Name	Manufacturer	Country	Year Introduced
Allopydin	Chugai	Japan	1976
Zumaril	Abbott	Italy	1976
Epinal	Kyorin	Japan	1976
Darkeyfenac	Cuatrecasas-Darkey	Spain	-
Desinflam	Sintyal	Argentina	-
Medifenac	Medici	Italy	-
Mervan, Mirvan	Continental Pharma	Belgium	-
Vanadian	Federico Bonet	Spain	-
ZumariI	Sidus	Italy	-
Rentenac	Tosi	Italy	-

Raw Materials

3-Chloro-4-allyloxyphenyl acetonitrile
Potassium hydroxide

Manufacturing Process

103.7 grams of 3-chloro-4-allyloxyphenylacetonitrile in 500 cc of ethanol, 100 grams of potassium hydroxide and 100 cc of water are refluxed for 4 hours. Maximum of alcohol is evaporated, the residue is diluted with water and ice, and acidified with 20% HCl. The solid is filtered and washed with petroleum ether. 91.5 grams of acid are obtained (Yield: 81%) which is recrystallized from aqueous methanol; MP 92-93°C.

References

Merck Index 209
Kleeman and Engel p. 19
OCDS Vol. 2 p. 68 (1980)
DOT 8 No. 9, 329 (1972)
I.N. p. 50
British Patent 1,174,535; December 17, 1969; Assigned to Madan AG, Switzerland

ALCLOMETASONE DIPROPIONATE

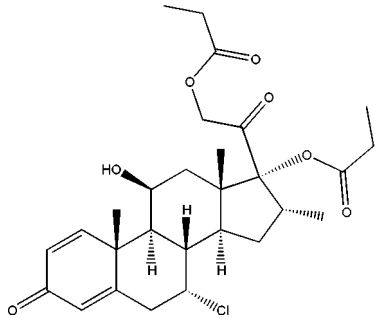
Therapeutic Function: Antiinflammatory, Antiallergic

Chemical Name: Pregna-1,4-diene-3,20-dione, 7-chloro-11-hydroxy-16-methyl-17,21-bis(1-oxopropoxy)-, (7α,11β,16α)-

Common Name: Alclometasone dipropionate; Perderm; Modrasone

Chemical Abstracts Registry No.: 66734-13-2

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Alclovate	GlaxoSmithKline	-	-
Afloderm	Belupo	-	-
Miloderme	Schering-Plough	-	-

Raw Materials

16α-Methyl-1,4,6-pregnatriene-11β,17α,21-triol-3,20-dione 17,21-dipropionate
Hydrogen chloride
Sodium borohydride

Manufacturing Process

A). Add 16α-methyl-1,4,6-pregnatriene-11β,17α,21-triol-3,20-dione 17,21-dipropionate (2.0 g) to dioxane (24 ml) which has been saturated with dry hydrogen chloride gas. Stir at room temperature for 16 hours, pour into ice water (600 ml), separate the resultant precipitate by filtration, wash the precipitate with water and dry in air. Separate the components in the foregoing precipitate on silica gel via thin layer chromatography utilizing as developing solvent ether:hexane (2:1), and elute with ethyl acetate the band containing 7α-chloro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17,21-dipropionate as shown by ultraviolet light. Evaporate the combined ethyl acetate eluates and triturate the resultant residue with acetone:ether, then filter and dry the triturated precipitate to obtain 7α-chloro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17,21-dipropionate.

Alternatively, the 7α-chloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,11,20-trione 17,21-dipropionate is prepared according to following procedures B and C.

B). Saturate dry tetrahydrofuran (137 ml) at 0°C with dry hydrogen chloride gas. Add 16α-methyl-1,4,6-pregnatriene-17α,21-diol-3,11,20-trione 17,21-dipropionate (6.85 g) and stir the reaction mixture at 0°C for 1 hour. Pour into ice water (1 liter) and stir for ½ hour. Separate the resultant precipitate by filtration, wash with water, and air dry to give 7v-chloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,11,20-trione 17,21-dipropionate. Purify from methanol:acetone containing a trace of propylene oxide; $[\alpha]_D^{26}$ +76.2°

(dimethylformamide).

C). To a solution of 7v-chloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,11,20-trione 17,21-dipropionate (3.2 g) in tetrahydrofuran (24 ml) and methanol (8 ml) at 0°C under an atmosphere of nitrogen add sodium borohydride (0.697 g) and stir the reaction mixture for 15 min at 0°C. Pour into ice water (1.8 liters) and 250 ml of 1 N hydrochloric acid. Separate the resultant precipitate by filtration and air dry to give 7α-chloro-16α-methyl-11β,17α,21-triol-3,20-dione 17,21-dipropionate. Purify by crystallizing twice from acetone:methanol:isopropyl ether; m.p. 212°-216°C; $[\alpha]_D^{26}$ +42.6° (dimethylformamide). λ_{max} 242 nm (methanol, ε 15,600).

By saponification of 7α-chloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,11,20-trione 17,21-dipropionate is prepared (7α,11β,16α)-7-chloro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione.

References

Green M., Shue Ho-Jane; US Patent No. 4,124,707; Nov. 7, 1978; Schering Corporation (Kenilworth, NJ)

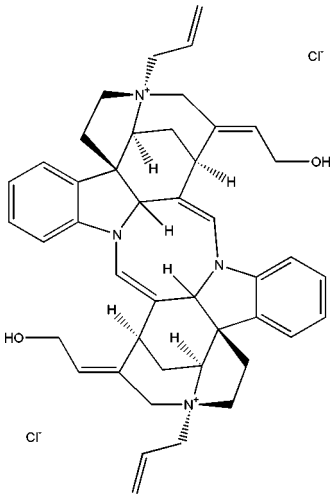
ALCURONIUM CHLORIDE

Therapeutic Function: Muscle relaxant

Chemical Name: N,N'-Diallylnortoxiferinium dichloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 15180-03-7

Trade Name	Manufacturer	Country	Year Introduced
Alloferin	Roche	UK	1966
Alloferin	Roche	W. Germany	1968
Alloferine	Roche	France	1968
Dialferin	Nippon Roche	Japan	1969
Toxiferin	Roche	-	-

Raw Materials

Diallyl Nortoxiferine Diiodide
Chloride Ion Exchange Resin

Manufacturing Process

31 g of diallylnortoxiferine diiodide are suspended in 1 liter of water and shaken with 1,100 ml of Amberlite IRA-400 [chloride ion form, described Merck Index, 7th edition, Merck and Co., Inc., Rahway, New Jersey (1960), page 1584], for 2 hours. The diiodide thereby goes into solution. The ion exchanger is filtered off and then washed in 3 portions with a total of 1 liter of water. The combined filtrates are then allowed to run through a column of 300 ml of Amberlite IRA-400 (chloride ion form), rinsed with 300 ml of water and the eluate evaporated to dryness in a vacuum while excluding air. The residue gives on recrystallization from methanol/ethanol crystalline pure colorless diallylnortoxiferine dichloride in a yield of 18.6 g. The compound contains 5 mols of water of crystallization after equilibration in air.

References

Merck Index 215
Kleeman and Engel p. 19
I.N. p.51
Boller, A., Els, H. and Furst, A.; US Patent 3,080,373; March 5, 1963; Assigned to Hoffman La Roche, Inc.

ALDOSTERONE

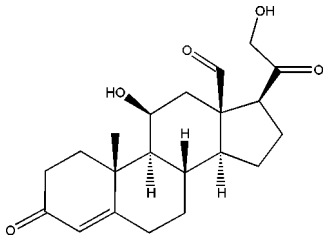
Therapeutic Function: Mineralocorticoid

Chemical Name: Pregn-4-en-18-al, 11,21-dihydroxy-3,20-dioxo-, (11β)-

Common Name: Aldosterone; Elektrocortin; Oxocorticosterone; Reichstein's substance X

Chemical Abstracts Registry No.: 52-39-1

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Aldosterone	Sigma Chemical Company	-	-
Aldosterone	Andard-Mount Company Limited	-	-
Aldocorten	Ciba	-	-

Raw Materials

3α,11β-Dihydroxy-D-homo-18-noretiocholan-17α-one

Sodium hydride	Potassium hydroxide
Acrylonitrile	4-Toluenesulfonic acid monohydrate
Acetic acid	Sodium borohydride
Ozone	Sodium metaperiodate
Sodium arsenite	Sodium bicarbonate
Potassium iodide	Piperidine
Pyridine	Acetic anhydride
Zinc	Diazomethane
Lithium	Bromobenzene
Thyonyl chloride	Palladium
Chromic oxide	Dinitrophenylhydrazine
Furfural	Hydrogen chloride

Manufacturing Process

In 1.0 L of methanol (purified by distillation from potassium hydroxide) was dissolved 27.02 g of 3α,11β-dihydroxy-D-homo-18-noretiocholan-17α-one (melting point 169°-173°C Patent No. 2,847,457; May 26, 1955). The solution was cooled to 5°C, and 54 ml of freshly distilled furfural was added. The air in the flask was replaced by nitrogen, 400 ml of 15% aqueous potassium hydroxide was added and the flask was sealed tightly. The solution was allowed to stand at room temperature overnight. The precipitate was collected on a filter, washed generously with water, and was dried to constant weight in vacuo, yielding 28.45 g of 3α,11β-dihydroxy-D-homo-18-noretiocholan-17-furfurylidene-17α-one as colorless lustrous plates, melting point 193°-194°C (after repeated recrystallization from methanol and acetone-petroleum ether).

A solution of 48 mg of sodium hydride in 6 ml of anhydrous methanol was cooled to 5°C, and to it was added slowly 1.20 ml of acrylonitrile (b.p. 75°-78°C). The solution was allowed to stand at room temperature for an 1 h and then cooled again to 5°C. The 3α,11β-dihydroxy-D-homo-18-noretiocholan-17-

furfurylidene-17α-one was added and the solution was stirred at room temperature for 2 h and then heated at reflux for 2 h. After a total of 8 h of heating at reflux the mixture was cooled to 5°C, and acetic acid was added until the solution was acidic. It was then diluted with water and extracted with ethyl acetate. The extract was washed with aqueous sodium bicarbonate and water, dried over magnesium sulfate, and distilled to dryness under reduced pressure. The product was crystallized from a small volume of acetone, and the crystals were washed with hot petroleum ether and then ether. This gave 750 mg of 3α,11β-dihydroxy-13α-(2-cyanoethyl)-D-homo-18-noretiocholan-17-furfurylidene-17α-one as colorless plates, melting point 193°-194°C (after repeated recrystallization from methanol).

A solution of 1.02 g of 3α,11β-dihydroxy-13α-(2-cyanoethyl)-D-homo-18-noretiocholan-17-furfurylidene-17α-one in 60 ml of methanol and 5 ml of pyridine was cooled to -70°C, and a stream of oxygen containing ozone was passed through until the solution turned a faint blue color (25 min). The solution was quickly put under reduced pressure to remove any dissolved ozone, and after 3 min a solution of 1.0 g of sodium borohydride in 10 ml of water was added slowly, allowing the solution to warm to 0°C. Within two min after the borohydride was added (an acidified portion of the solution gave no starch-iodide test, indicating absence of ozonide). An additional 3.0 g of borohdride was added in 1 g portions at 1 h intervals, and the solution was allowed to stand for a total of 35 h. Acetic acid was added slowly and stirring until the solution yield pH 5. The methanol was distilled, under reduced pressure, the last portions being co-distilled with ethyl acetate and water. The aqueous solution was then extracted three times with ethyl acetate. The extracts were washed in turn with 5% aqueous hydrochloric acid (cold), water, aqueous sodium bicarbonate, and water. The combined ethyl acetate solutions were dried over sodium sulfate and concentrated to dryness under reduced pressure. The crude product (71%) of 3α,11β,17,17a-tetrahydroxy-13α-(2-cyanoethyl)-D-homo-18-noretiocholan was obtained as colorless rods, melting point 137°-140°C (several recrystallization from aqueous methanol).

To a solution of 280 mg of 3α,11β,17,17a-tetrahydroxy-13α-(2-cyanoethyl)-D-homo-18-noretiocholan in 17 ml of methanol at room temperature contained in a 25 ml volumetric flask there was added 162 mg of sodium metaperiodate in 8 ml of water. A small amount of water was added to bring the volume to 25 ml. After 15 min an aliquot was withdrawn and added to a measured amount of sodium arsenite solution containing sodium bicarbonate and potassium iodide. After 10 min, the solution was titrated with standard iodine solution. The solution was diluted with water and extracted twice with ethyl acetate, each extract being washed in turn with sodium combined, dried over magnesium sulfate and concentrated to dryness under reduced pressure, yielding 265 mg of a colorless, amorphous product of 4b-methyl-1β-(2-formylethyl)-2β-formyl-2-(2-cyanoethyl)-4β,7α-dihydroxyperhydrophenanthrene.

A solution of 240 mg of 4b-methyl-1β-(2-formylethyl)-2β-formyl-2-(2-cyanoethyl)-4β,7α-dihydroxyperhydrophenanthrene dissolved in 30 ml of anhydrous methanol containing 20 mg of p-toluenesulfonic acid monohydrate was allowed to stand at room temperature for 36 h. Aqueous sodium bicarbonate was added and the methanol was evaporated under reduced pressure. An ether extraction of the aqueous layer afforded 260 mg of a benzene soluble oil, which was chromatographed on 12 g of florisil. The 4b-

methyl-1β-(2-formylethyl)-2β-formyl-2-(2-cyanoethyl)-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether was eluted between 20% benzene in ether and ether.

A solution of 560 mg of the 4b-methyl-1β-(2-formylethyl)-2β-formyl-2-(2-cyanoethyl)-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether in 10 ml of pyridine and 5 ml of acetic anhydride was heated at 100°C for 10 min. The solution was cooled and poured on iced aqueous sodium bicarbonate. The mixture was extracted with ether, the extract being washed with water, dried over magnesium sulfate and concentrated to dryness at aspirator pressure. The pyridine was removed at 2 mm with as little heating as possible. From a small volume of methanol, the colorless oil remaining gave a heavy precipitate of crystals which was washed with petroleum ether (b.p. 32°-35°C). The pure 4b-methyl-1β-(2-formylethyl)-2β-formyl-2-(2-cyanoethyl)-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether 7α-acetate was obtained as colorless prisms, melting point 126°-127°C, by several recrystallizations from methanol.

The 4b-methyl-1β-(2-formylethyl)-2β-formyl-2-(2-cyanoethyl)-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether 7α-acetate (360 mg) was stirred in 3 ml of ether. Upon the addition of 9 ml of 70% aqueous acetic acid the crystals dissolved immediately. The solution was allowed to stand at room temperature for 16 h and was then extracted with ether. The extract was washed thoroughly with water and aqueous sodium bicarbonate, dried over magnesium sulfate and concentrated to dryness under reduced pressure, yielding 337 mg of oil. On trituration with ether there was obtained 305 mg of crystals of 4b-methyl-1β-(2-formylethyl)-2β-formyl-2-(2-cyanoethyl)-4β,7α-dihydroxyperhydrophenanthrene 2β,4β-lactol methyl ether 7α-acetate as platelets, melting point 85°-105°C after recrystallizations from benzene-petroleum ether.

After standing at room temperature for 10 min, a solution of 710 mg of the 4b-methyl-1β-(2-formylethyl)-2β-formyl-2-(2-cyanoethyl)-4β,7α-dihydroxyperhydrophenanthrene 2β,4β-lactol methyl ether 7α-acetate in 5 ml of piperidine and 10 ml of benzene was heated at brisk reflux in a nitrogen atmosphere. After 3 h the solvents were removed under reduced pressure, leaving 820 mg of 4b-methyl-1β-[3-(1-piperidyl)-2-propenyl]-2β-formyl-2-(2-cyanoethyl)-4β,7α-dihydroxyperhydrophenanthrene 2β,4β-lactol methyl ether 7α-acetate as colorless oil.

Through a solution of 810 mg of crude 4b-methyl-1β-[3-(1-piperidyl)-2-propenyl]-2β-formyl-2-(2-cyanoethyl)-4β,7α-dihydroxyperhydrophenanthrene 2β,4v-lactol methyl ether 7α-acetate in 60 ml of methylene chloride and 1.5 ml of pyridine at -70°C was passed a stream of oxygen containing ozone until the solution turned blue (17 min). 3 g of zinc dust and 6 ml of glacial acetic acid were added immediately. The stirred solution was allowed to warm to 0°C and to remain at that temperature for 30 min. The solution was filtered and washed with aqueous sodium bicarbonate. The organic solvent was dried over magnesium sulfate and was distilled below room temperature, affording 750 mg of a benzene soluble, pale yellow oil. The product was chromatographed and eluted 310 mg (45%) of 4b-methyl-1β-(2-formylmethyl)-2β-formyl-2-(2-cyanoethyl)-4β,7α-dihydroxyperhydrophenanthrene 2β,4β-lactol methyl ether 7α-acetate.

A solution of 310 mg of the chromatographed noncrystalline 4b-methyl-1β-(2-formylmethyl)-2β-formyl-2-(2-cyanoethyl)-4β,7α-dihydroxyperhydrophenanthrene 2β,4β-lactol methyl ether 7α-acetate in 60 ml of anhydrous methanol containing 40 mg of p-toluenesulfonic acid monohydrate was allowed to stand at room temperature for 9 h. Aqueous sodium bicarbonate was added, and methanol was evaporated under reduced pressure. The remaining mixture was extracted with ether and extract was dried over magnesium sulfate and concentrated to dryness in vacuo, affording 325 mg of oil. This was chromatographed on 12 g of florisil. Ether eluted 285 mg of oil which crystallized from petroleum ether, giving 230 mg of 4b-methyl-1β-(2-formylmethyl)-2β-formyl-2-(2-cyanoethyl)-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether 7α-acetate as irregular prisms, melting point 149°-152°C.

A solution of 220 mg of the 4b-methyl-1β-(2-formylmethyl)-2β-formyl-2-(2-cyanoethyl)-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether 7α-acetate in 5 ml of methanol and 10 ml of 10% aqueous potassium hydroxide was heated at reflux 17 h. The methanol was distilled off and the remainder was extracted with chloroform. The aqueous solution was cooled to 5°C and was acidified to pH 4 with cold 3 N hydrochloric acid. The solution was rapidly extracted twice with cold ethyl acetate, each extract being washed in turn 3 times with water. To the combined extracts (300 ml) was added 10 ml of methanol followed by solution excess diazomethane in 50 ml of ether. After 10 min the diazomethane was blown off, and the solvent was evaporated under reduced pressure, affording 235 mg of an oil. Chromatography of this material on 6 g of florisil and elution gave 220 mg of 4b-methyl-1β-(2-formylmethyl)-2β-formyl-2-(2-methylcarboxyethyl)-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether.

Excess phenyllithium (prepared from 0.210 g of lithium wire and 2.4 g of bromobenzene following the directions given by J.C.W. Evans and C.F.H. Allen, Org. Syntheses, vol. 2, p. 22 (1943)) in 20 ml of ether was added to 215 mg of the 4b-methyl-1β-(2-formylmethyl)-2β-formyl-2-(2-methylcarboxyethyl)-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether in 20 ml of anhydrous ether under an atmosphere of nitrogen. After the solution was stirred at room temperature for 2 h, the excess reagent was decomposed by the drop wise addition of ethanol. Water was added, and the mixture was extracted with ether. The extract was washed with water, dried over magnesium sulfate and concentrated to dryness under reduced pressure, yielding 310 mg of an oil which was chromatographed ed on 6 g of florisil; ether eluted 267 mg of an oil which giving 252 mg of 4b-methyl-1β-(2-formylmethyl)-2β-formyl-2-(3,3,3-hydroxydiphenylpropyl)-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether as needles, melting point 116°-119°C (from ether).

A solution of 250 mg of the 4b-methyl-1β-(2-formylmethyl)-2β-formyl-2-(3,3,3-hydroxydiphenylpropyl)-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether, in 10 ml of pyridine and 5 ml of acetic anhydride was heated at 100°C for 10 min. The solution was cooled and poured onto iced aqueous sodium bicarbonate. The mixture was extracted with ether, dried over magnesium sulfate and concentrated to dryness under reduced pressure, affording 255 mg (95.2%) of the colorless 4b-methyl-1β-(2-formylmethyl)-2β-formyl-2-(3,3,3-hydroxydiphenylpropyl)-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether

7α-acetate.

To a solution of 250 mg of the 4b-methyl-1β-(2-formylmethyl)-2β-formyl-2-(3,3,3-hydroxydiphenylpropyl)-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether 7α-acetate in 10 ml of benzene and 1.0 ml of pyridine at 0°C was added 0.5 ml of thyonyl chloride. After standing at 0°C for 15 min, the solution was poured onto iced sodium bicarbonate, and resulting mixture was extracted with ether. The extract was dried over magnesium sulfate, and the ether was removed under reduced pressure. Pyridine (20 ml) was added and solution was heated at 100°C for 20 min. The solution was then concentrated to dryness under reduced pressure and the residue was dissolved in a small volume of benzene. The benzene solution was poured on 6 g of florisil; elution with ether provided 230 mg of colorless 4b-methyl-1β-(2-formylmethyl)-2β-formyl-2-(3,3-diphenyl-2-propenyl)-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether 7α-acetate.

Through a solution of 225 mg of the 4b-methyl-1β-(2-formylmethyl)-2β-formyl-2-(3,3-diphenyl-2-propenyl)-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether 7α-acetate in 30 ml of methylene dichloride and 0.15 ml of pyridine at -70°C was passed a stream of oxygen containing ozone. When the solution turned a faint blue color, 3 g of zinc dust and 6 ml of glacial acetic were added immediately. The solution was stirred at 0°C until it gave a negative starch iodide test (10 min); the mixture was filtered, washing the zinc with additional methylene dichloride. The organic solution was washed with aqueous sodium bicarbonate, dried over magnesium sulfate and concentrated to dryness in vacuo, giving 230 mg of oil. This was chromatographed on 5 g of florisil; elution with ether gave 110 mg of 4b-methyl-1β,2α-bis-(2-formylmethyl)-2β-formyl-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether 7α-acetate.

In 1 ml of ether was dissolved 20 mg of the crude 4b-methyl-1β,2α-bis-(2-formylmethyl)-2β-formyl-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether 7α-acetate. To this was added 3 ml of 70% aqueous acetic acid, and the homogeneous solution was allowed to stand at room temperature to 10 h. The material was extracted with ether, and extract was washed with aqueous sodium bicarbonate, dried over magnesium sulfate and concentrated to dryness under reduced pressure, yielding 15 mg of 4b-methyl-1β,2α-bis-(2-formylmethyl)-2β-formyl-4β,7α-dihydroxyperhydrophenanthrene 2β,4β-lactol 7α-acetate.

A benzene solution (5 ml) of 15 mg of the 4b-methyl-1β,2α-bis-(2-formylmethyl)-2β-formyl-4β,7α-dihydroxyperhydrophenanthrene 2β,4β-lactol 7α-acetate containing 3.4 mg of piperidine and 6.2 mg of acetic acid was heated at 60°C in slow stream of nitrogen with an azeotropic separator. After 1 h, half the solution was withdrawn, diluted with benzene, and washed with diluted aqueous hydrochloric acid and with aqueous sodium bicarbonate. The benzene extract dried over magnesium sulfate and concentrated to dryness under reduced pressure, giving 3α-acetoxy-17-formyl-16-etiocholen-11β-ol-18-one 11β,18-lactol as colorless oil.

The 3α-acetoxy-17-formyl-16-etiocholen-11β-ol-18-one 11β,18-lactol can be converted to aldosterone by conventional methods as follows.

The unsaturated 3α-acetoxy-17-formyl-16-etiocholen-11β-ol-18-one 11β,18-lactol is hydrogenated in the presence of palladium catalyst to saturate the 16,17-double bond, and then saturated aldehyde are oxidized by treatment with chromic oxide in pyridine to give 3α-acetoxy-11β-ol-18-one-pregnane 11β,18-lactone 17-carboxylic acid.

Then as a result of reaction of 3α-acetoxy-11β-ol-18-one-pregnane 11β,18-lactone 17-carboxylic acid and HCl the 3α-acetoxy-11β-ol-18-one-pregnane 11β,18-lactone 17-carboxylic acid chloride was obtained. The 3α-acetoxy-11β-ol-18-one-pregnane 11β,18-lactone 17-carboxylic acid chloride was treated with diazomethane to give 3α-acetoxy-11β-ol-18-one-pregnane 11β,18-lactone 17-diazoketone.

The saponification of acetoxy group and reacting of 3α-acetoxy-11β-ol-18-one-pregnane 11β,18-lactone 17-diazoketone with acetic acid were carried out to afford acetic acid 3α,11β-dihydroxy-18,20-dione-pregnane 11β,18-lactone 17-oxoethyl ether.

The 3-keto-δ^4 system is introduced by conventional methods, that is, by oxidation of the 3-hydroxy group to a 3-keto group with chromic oxide. Bromination at the 4-position, and finally dehydrobromination with dinitrophenylhydrazine or with lithium chloride in dimethylformamide were carried out to give acetic acid 11β-hydroxy-3,18,20-trione-pregn-4-ene 11β,18-lactone 17-oxoethyl ether.

2 Methods of producing of aldosterone:

1. Further, acetic acid 11β-hydroxy-3,18,20-trione-pregn-4-ene 11β,18-lactone 17-oxoethyl ether has been converted to 11β,21-dihydroxy-3,18,20-trione-pregn-4-ene by methods of reduction of the lactone group and deacetylation of 17-oxoethyl group, described by Schmidlin, Anner, Biller and Wettstein (Experimentia, XI, 365 (1955).

2. Further, acetic acid 11β-hydroxy-3,18,20-trione-pregn-4-ene 11β,18-lactone 17-oxoethyl ether has been converted to 11β-hydroxy-18-one-pregn-4-ene 11β,18-lactone-3,20-bis-ethylenketal 17-oxoethyl ether, which was reduced with lithium-aluminum hydride to 3,20-bis-ethylenketal aldosterone. Then by hydrolisation of 3,20-bis-ethylenketal aldosterone with $HClO_4$ aldosterone can be obtained.

References

Johnson W.S., Johns W.F.; US Patent No. 3,049,539; August 14, 1962; Assigned: Wisconsin Alumini Research Foundation, Madison,Wis., a corporation of Wisconsin

Chaletsky A.M.; Pharmaceutical Chemistry, 'Medicina', L., 1966. 761p.

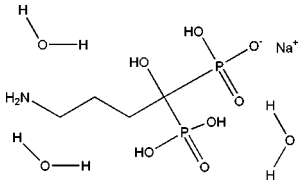
ALENDRONATE SODIUM TRIHYDRATE

Therapeutic Function: Antiosteoporotic

Chemical Name: (4-Amino-1-hydroxybutylidene)diphosphonic acid monosodium salt trihydrate

Common Name: Alendronate sodium

Structural Formula:



Chemical Abstracts Registry No.: 129318-43-0; 66376-36-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Adronat	Neopharmed	Italy	-
Adronat	Tecnifar	Portugal	-
Alendronate sodium	BARR	-	-
Arendal	Syncro	Argentina	-
Alendros	Abiogen	Italy	-
Brek	TRB	Argentina	-
Dronal	Sigma Tau	Italy	-
Elandur	Sidus	Argentina	-
Endronax	Sintofarma	Brazil	-
Fosalan	Merck Pharmaceutical Corporation	-	-
Fosamax	Merck Sharp and Dohme	Netherlands	-
Holadren	Laboratorio Chile S.A.	-	-
Lafedam	Elvetium	Argentina	-
Marvil	Elisium	Argentina	-
Onclast	Teijin Pharma Ltd.	Japan	-
Osteoral	Ache	-	-
Phostarac	Rontag	Argentina	-
Regenesis	Elea	Argentina	-
Teiroc	Teijin Pharma Ltd.	Japan	-

Raw Materials

Phosphorous acid
Phosphorus trichloride
4-Aminobutyric acid

Manufacturing Process

4-Amino-1-hydroxybutylidene-1,1-diphosphonic acid (ABDT).

Orthosphophorous acid (102.7 g; 1.25 moles) is introduced into a 2 liter-flask with condenser, stirrer and dropping funnel, placed on a thermostatized bath; the air is then removed with a nitrogen stream which is continued during all the reaction. The acid is melted by heating the bath to 95°C. When melting is complete, 4-aminobutyric acid (103.3; 1 mole) is added under stirring which is continued till obtaining a doughy fluid. Phosphorous trihalide (176 ml; 2 moles) is added dropwise causing the mixture to boil and evolution of gaseous hydrochloric acid which is damped by means of a suitable trap. The addition rate is adjusted so as to keep a constant reflux for about 60 minutes. When the addition is nearly over, the mixture swells, slowly hardening. Stirring is continued as long as possible, whereafter the mixture is heated for further 3 hours. Without cooling, but removing the bath, water (300 ml) is added, first slowly and then quickly. Heating and stirring are started again. Decolorizing charcoal is added and the mixture is boiled for about 5 minutes, then hot-filtered on paper and the filtrate is refluxed for 6 hours. After cooling is slowly poured in stirred methanol (1500 ml) causing thereby the separation of a white solid which collected and dried (161 g; 64.6%). The structure of ABDT is confirmed by IR spectrum, proton magnetic and nuclear magnetic resonance spectrum and elemental analysis.

The sodium salt of this acid may be prepared by adding of equivalent of sodium hydroxide.

References

G. Staibano; US Patent No. 4,705,651; Nov. 10, 1987; Assigned to Instituto Gentili S.p.A., Pisa, Italy

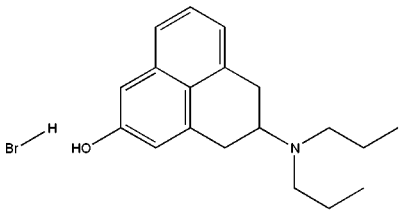
ALENTAMOL

Therapeutic Function: Antipsychotic, Dopamine agonist

Chemical Name: 1H-Phenalen-5-ol, 2-(dipropylamino)-2,3-dihydro-, hydrobromide, (+/-)

Common Name: Alentamol

Structural Formula:



Chemical Abstracts Registry No.: 121514-27-0

Trade Name	Manufacturer	Country	Year Introduced
U 68553B	Upjohn Company	-	-

Raw Materials

Triethylamine	5-Methoxy-2,2-dicarboxy-2,3-dihydro-1H-phenalene
Hydrogen chloride	Diphenyl phosphoryl azide
Trifluoroacetic acid	t-Butyl carbamate
Sodium hydroxide	Hydrogen bromide
n-Propyl bromide	Potassium carbonate

Manufacturing Process

The solid 5-methoxy-2,2-dicarboxy-2,3-dihydro-1H-phenalene, was decarboxylated (one carboxyl group removed) by heating in an oil bath at 190°-210°C for 50 min. The resulting liquid was cooled, and the solid was ground to a fine powder to obtain 37.1 g (98% yield) of the subtitled 2-carboxyl-5-methoxy-2,3-dihydro-1H-phenalene, melting point 194°-196°C.

A mixture of the 5-methoxy-2,3-dihydro-1H-phenalen-2-yl-carboxylic acid, (37.1 g; 0.153 mole), 42.1 g (0.153 mole) of diphenyl phosphoryl azide, 17.0 g (0.168 mole) of triethylamine and 1950 ml of dry tert-butyl alcohol was refluxed for 21 h. The initially formed solution became a suspension. The solvent was evaporated in vacuo and the residue was taken up in a chloroform/water mixture. The resulting suspension was filtered. The filtrate was separated, the aqueous phase was extracted with chloroform, and the combined organic liquid phases was washed with 5% w/v sodium hydroxide aqueous solution (3x100 ml), with water and with saturated sodium chloride salt solution and then dried over magnesium sulfate and evaporated.The resulting residual yellow solid, 35.9 g, was extracted with boiling SKELLYSOLVE B brand of hexanes (5x200 ml), the resulting solution was concentrated to about 300 ml, clarified with diethyl ether and allowed to crystallize at 0°C to obtain 28.6 g of the 5-methoxy-2-(tert-butoxycarbonylamino)-2,3-dihydro-1H-phenalene, melting point 113°-115°C.

Trifluoroacetic acid, 85 ml, was added to 30.5 g (0.0958 mole) of the 5-methoxy-2-(tert-butoxycarbonylamino)-2,3-dihydro-1H-phenalene. The resulting solution was stirred for 20 min. Ice was then added, and the resulting mixture was made pH basic with 20% w/w sodium hydroxide in water solution and stirred for 1 h at room temperature. The mixture was extracted well with chloroform, the chloroform extract was separated and washed with water, with saturated sodium chloride solution; dried with magnesium sulfate, and evaporated to give 18.8 g (92% yield) of the 2-amino-5-methoxy-2,3-dihydro-1H-phenalene as a brown oil.

This 2-amino-5-methoxy-2,3-dihydro-1H-phenalene was converted to its hydrochloride salt in methanol with 1.5 N hydrogen chloride in diethyl ether solution to give 18.11 g of the 2-amino-5-methoxy-2,3-dihydro-1H-phenalene hydrochloride as colorless needle crystals, melting point 252°C (dec.).

A mixture of 2-amino-5-methoxy-2,3-dihydro-1H-phenalene, 2.6 g (0.0122 mole), released from its hydrochloride, 6.46 g (0.0525 mole) of n-propyl

bromide, 7.25 g (0.0525 mole) of potassium carbonate and 50 ml of acetonitrile was refluxed for 20 h. Another 3.3 g of n-propyl bromide, 3.6 g of potassium carbonate and 25 ml of acetonitrile were added to the reaction mixture. The mixture was refluxed for 26 h. GC analysis of a sample of the reaction mixture indicated complete reaction. The mixture was evaporated, and the residue was taken up in a diethyl ether/water mixture. The organic liquid layer was washed with saturated sodium chloride (salt) solution and dried with magnesium sulfate, and evaporated. The residue was dissolved in petroleum ether (boiling point 30°-60°C), and filtered from some insoluble brown material, and the filtrate was evaporated to leave the 2-(di-n-propylamino)-5-methoxy-2,3-dihydro-1H-phenalene.

The 2-(di-n-propylamino)-5-methoxy-2,3-dihydro-1H-phenalene was dissolved in diethyl ether, treated with ethereal hydrogen chloride which resulted in the formation of the crude gummy solid hydrogen chloride salt. 2.67 g (66% yield) of the 2-(di-n-propylamino)-5-methoxy-2,3-dihydro-1H-phenalene hydrochloride, melting point 196°-197°C (crystallized from a methanol/diethyl ether).

A mixture of 2-(di-n-propylamino)-5-methoxy-2,3-dihydro-1H-phenalene, (1.65 g; 5.55 mmol), released from the hydrochloride salt, and 20 ml of 48% aqueous hydrogen bromide solution was heated for 15 min in an oil bath at 125°-130°C. The reaction mixture was evaporated, the residue was dissolved in a minimum amount of methanol, diethyl ether was added until the mixture became cloudy, and the mixture was filtered through a filter aid (CELITE) to remove some oily impurity. The filtrate was diluted with diethyl ether and seeded. There was obtained 1.28 g (63% yield) of the 2-(di-n-propylamino)-2,3-dihydro-lH-phenalen-5-ol hydrobromide, melting point 233°-234°C (dec.).

References

Szmuszkovicz J. et al.; Patent Coop. Treaty (WIPO), 1987, 87/04153; July 16, 1987; Assigned: The UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US)

ALEXIDINE

Therapeutic Function: Antiseptic

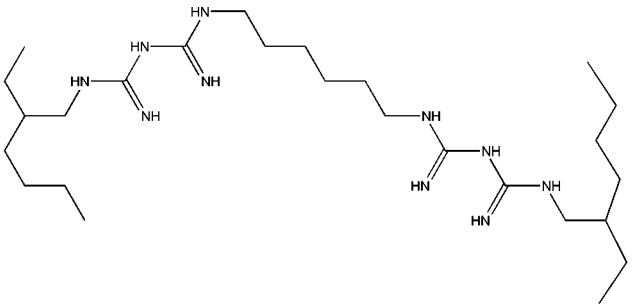
Chemical Name: 2,4,11,13-Tetraazatetradecanediimidamide, N,N''-bis(2-ethylhexyl)-3,12-diimino-

Common Name: Alexidine

Chemical Abstracts Registry No.: 22573-93-9

Trade Name	Manufacturer	Country	Year Introduced
Alexidine	Science Lab.	-	-
Alexidine	Chemos GmbH	-	-

Structural Formula:



Raw Materials

1,1'-Hexamethylene-bis(3-cyanoguanidine)
Ethylhexylamine hydrochloride

Manufacturing Process

A mixture of 16 g (0.09 mole) 1,1'-hexamethylene-bis(3-cyanoguanidine) and 20 d (0.12 mole) 2-ethylhexylamine hydrochloride is heated at 150-155°C for 3 hours. The mixture is cooled and the product is dissolved in 75 ml of hot water. The solution is treated with activated charcoal. 1,1'-Hexamethylene-bis-(5-(ethylhexyl)biguanide) is recrystalluized from methanol-ether, melting point 220.6-223.4°C.

References

Fr. Patent No. 1,463,818; Apr. 8, 1965; Assigned to Sterling Drug Inc. Residant in USA

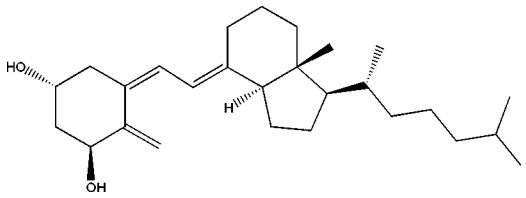
ALFACALCIDOL

Therapeutic Function: Calcium regulator, Vitamin

Chemical Name: 9,10-Secocholesta-5,7,10(19)-triene-1,3-diol

Common Name: 1α-Hydroxycholecalciferol; 1α-Hydroxyvitamin D_3

Structural Formula:



Chemical Abstracts Registry No.: 41294-56-8

Trade Name	Manufacturer	Country	Year Introduced
One-Alpha	Leo	UK	1978
Eins-Alpha	Thomae	W. Germany	1980
Alfarol	Chugai	Japan	1981
One-Alpha	Teljin	Japan	1981
Delakmin	Roussel	France	-
Etalpha	Leo	Denmark	-
Un-Alfa	Leo	-	-

Raw Materials

Cholesta-1,5,7-trien-3β-ol
m-Chloroperbenzoic acid
4-Phenyl-1,2,4-triazoline-3,5-dione
Lithium aluminum hydride

Manufacturing Process

1. Preparation of 1,4-cyclized adduct of cholesta-1,5,7-trien-β-ol and 4-phenyl-1,2,4-triazoline-3,5-dione: a solution of 400 mg of cholesta-1,5-7-trien-3β-ol in 30 ml of tetrahydrofuran is cooled with ice, and 190 mg of 4-phenyl-1,2,4-triazoline-3,5-dione is added little by little to the solution under agitation. The mixture is agitated at room temperature for 1 hour and the solvent is distilled under reduced pressure. The residue is purified by chromatography using a column packed with silica gel. Fractions eluted with ether-hexane (7:3 v/v) are collected and recrystallization from ether gives 550 mg of a 1,4-cyclized adduct of cholesta-1,5,7-trien-3β-ol and 4-phenyl-1,2,4-triazoline-3,5-dione having a melting point of 178°C to 182°C.

2. Preparation of 1,4-cyclized adduct of cholesta-5,7-dien-3β-ol-1α-epoxide and 4-phenyl-1,2,4-triazoline-3,5-dione: 1.25 g of the 1,4-cyclized adduct of cholesta-1,5,7-trien-3β-ol and 4-phenyl-1,2,4-triazoline-3,5-dione is dissolved in 50 ml of chloroform, and 560 mg of m-chloroperbenzoic acid is added to the solution. The mixture is agitated for 20 hours at room temperature, and 200 mg of m-chloroperbenzoic acid is further added and the mixture is agitated again for 20 hours. The reaction mixture liquid is diluted with chloroform, washed with a 10% aqueous solution of potassium carbonate and dried with magnesium sulfate. Then, the solvent is distilled under reduced pressure. The residue is purified by silica gel chromatography, and first effluent fractions eluted with ether are collected, and recrystallization from methanol gives 680 g of a crystal melting at 172°C to 173°C. The second ether effluent fractions are collected, and recrystallization from methanol gives 400 mg of a 1,4-cyclized adduct of cholesta-5,7-dien-3β-ol-1α,2α-epoxide and 4-phenyl-1,2,4-triazoline-3,5-dione having a melting point of 152°C to 154°C.

3. Preparation of cholesta-5,7-diene-1α,3β-diol: a solution of 500 mg of the 1,4-cyclized adduct of cholesta-5,7-dien-3β-ol-1α,2α-epoxide and 4-phenyl-1,2,4-triazoline-3,5-dione in 40 ml of tetrahydrofuran is added dropwise under agitation to a solution of 600 mg of lithium aluminum hydride in 30 ml of THF. Then, the reaction mixture liquid is gently refluxed and boiled for 1 hour and cooled, and a saturated aqueous solution of sodium sulfate is added to the reaction mixture to decompose excessive lithium aluminum hydride. The organic solvent layer is separated and dried, and the solvent is distilled. The

residue is purified by chromatography using a column packed with silica gel. Fractions eluted with ether-hexane (7:3 v/v) are collected, and recrystallization from the methanol gives 400 mg of cholesta-5,7-diene-1α,3β-diol.

4. Preparation of 1α,3β-dihydroxyprovitamin D_3: a solution of 25 mg of cholesta-5,7-diene-1α,3β-diol in 650 ml of ether is subjected to radiation of ultraviolet rays for 14 minutes in an argon gas atmosphere by passing it through a Vycor filter using a 200-W high pressure mercury lamp (Model 654A-36 manufactured by Hanobia). The solvent is distilled at room temperature under reduced pressure. This operation is repeated twice, and 50 mg of the so obtained crude product is fractionated by chromatography using a column packed with 20 g of Sephadex LH-20. The first effluent fractions eluted with chloroform-hexane (65:35 v/v) give 13.5 mg of oily 1α,3β-dihydroxyprovitamin D_3. The composition exhibits a maximum ultraviolet absorption at 260 nm in an ether solution.

5. Preparation of 1α-hydroxycholecalciferol: a solution of 13.5 mg of 1α,3β-dihydroxyprovitamin D_3 in 200 mi of ether is allowed to stand still in the dark at room temperature in an argon gas atmosphere for 2 weeks. During this period, the position of the maximum ultraviolet absorption is shifted from 260 nm to 264 nm, and the absorption intensity becomes 1.6 times as high as the original intensity. The solvent is distilled at room temperature under reduced pressure, and the residue is purified by chromatography using a column packed with 10 g of Sephadex LH-20. The fractions eluted with chloroform-hexane (65:35 v/v) give 6.5 mg of oily 1α-hydroxycholecalciferol.

References

Merck Index 4730
Kleeman and Engel p. 21
DOT 6 (3) 104 (1970); 14 (10) 441 (1978)
I.N. p. 52
Ishikawa, M., Kaneko, C., Suda, T., Yamada, S., Eguchi, Y., Sugimoto, A. and Sasaki, S.; US Patent 3,929,770; December 30, 1975; Assigned to Wisconsin Alumni Research Foundation

ALFADOLONE

Therapeutic Function: Anesthetic

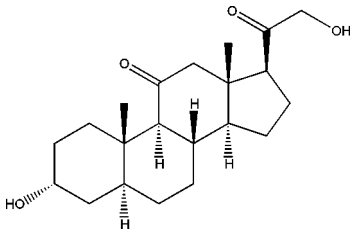
Chemical Name: 5α-Pregnane-11,20-dione, 3α,21-dihydroxy-

Common Name: Alfadolone; Alphadolone

Chemical Abstracts Registry No.: 14107-37-0

Trade Name	Manufacturer	Country	Year Introduced
Alphadolone	RiboTargets Ltd.	-	-

Structural Formula:



Raw Materials

Acetic acid	3β-Acetoxy-5α-pregn-16-ene-11,20-dione
Potassium hydroxide	4-Toluenesulfonyl chloride
Potassium acetate	Palladium on carbon
Hydrogen	Boron trifluoride etherate
Lead tetraacetate	Sodium bicarbonate

Manufacturing Process

A solution of 3β-acetoxy-5α-pregn-16-ene-11,20-dione (Chamberlin et al., J.Amer. Chem Soc., 1951, 73, 2396) (25.7 g) in dioxan (Analar, 500 ml) was treated with potassium hydroxide (10 g) and water 250 ml and the mixture allowed to stand at room temperature for 1 h. After a further 1 h at 40°C the mixture was diluted with water and the product filtered off. The crude material was dissolved in chloroform and filtered through a column of grade III neutral alumina (100 g). The material obtained was crystallized from acetone-petroleum to give pure 3β-hydroxy-5α-pregn-16-ene-11,20-dione (17.65 g, 77.5%) as small plates, melting point 217.5°C.

A solution of 3β-hydroxy-5α-pregn-16-ene-11,20-dione (39.6 g) in dry pyridine (165 ml) was treated with toluene-p-sulfonyl chloride (43.9 g) to give the toluene sulfonate (56.7 g), melting point 147-151°C. A portion (10.7 g) of this material was crystallized from ethyl acetate-petroleum to give the pure 3β-toluene-p-sulfonyloxy-5α-pregn-16-ene-11,20-dione (9.2 g) as plates, melting point 154°-155°C.

2 Methods of producing of 3α-hydroxy-5α-pregn-16-ene-11,20-dione from 3β-toluene-p-sulfonyloxy-5α-pregn-16-ene-11,20-dione:

1. A solution of 3β-toluene-p-sulfonyloxy-5α-pregn-16-ene-11,20-dione (19.1 g) in N,N-dimethylformamide (160 ml) and water (16.0 ml) was treated with potassium acetate (29.2 g) and the mixture heated at 115°C for 2.5 h. The solvents were removed in vacuo and residue partitioned between chloroform and water. The chloroform extract was washed with water, dried and evaporated. The residue was taken up in methanol (500 ml) and solution flushed with nitrogen. Potassium hydroxide (17 g) in water (70 ml) was added and the solution refluxed for 1 h. Glacial acetic acid was added to bring the pH to about 6 and most of the methanol evaporated in vacuo. Dilution with water gave a gummy precipitate which was extracted into chloroform to give the crude product. This material was extracted with ether and the residue boiled with benzene. The insoluble material was crystallized from chloroform-petroleum to give 3α-hydroxy-5α-pregn-16-ene-11,20-dione (3.28 g) as large

prisms, melting point 243°-244°C.

2. A mixture of the 3β-toluene-p-sulfonyloxy-5α-pregn-16-ene-11,20-dione (60 g; 0.124 mole) in N,N-dimethylformamide (350 ml) and potassium acetate (92 g, 0.94 mole) in water (935 ml) was stirred at 115°C for 4 h. The brown solution was cooled and most of the N,N-dimethylformamide removed by evaporation at 50°C and 4 mm to give a brown solid mass. Another run with to sylate (58 g, 0.12 mole), potassium acetate (90 g, 0.91 mole), N,N-dimethylformamide (350 ml) and water (35 ml) was carried out as described above. The combined aqueous fractions were extracted with chloroform (3 x 100 ml) and dried over magnesium sulfate. The chloroform was removed in vacuo and residual N,N-dimethylformamide was evaporated at 50°C and 4 mm to give the crude 3α-acetate-5α-pregn-16-ene-11,20-dione (92 g) as a brown solid.

A solution of 3α-acetate-5α-pregn-16-ene-11,20-dione (92 g) in dioxin (1000 ml) was mixed with a solution of potassium hydroxide (45 g, 0.8 mole) in water (500 ml) to give a two-phase system. A homogeneous solution was obtained by the addition of dioxin (440 ml) and water (625 ml). Nitrogen was bubbled through the solution which was heated at 50°C for 2 h. The port colored solution was treated with glacial acetic acid (40 ml) to bring the pH about 7 and two thirds of the solvent was removed by distillation in vacuo (water pump). Water (3 L) was added to the resultant mixture (which had already begun to crystallize) and the precipitated solid was filtered off, washed with water and dried over phosphorus pentoxide to give the crude 3α-hydroxy-5α-pregn-16-ene-11,20-dione (73.9 g).

Producing of 3α,21-dihydroxy-5α-pregnane-11,20-dione from 3α-hydroxy-5α-pregn-16-ene-11,20-dione:

A solution of 3α-hydroxy-5α-pregn-16-ene-11,20-dione (200 mg) in freshly distilled tetrahydrofuran (8 ml) with 5% palladium on carbon (100 mg) was hydrogenated till hydrogen uptake ceased. The mixture was filtered through a pad of kieselguhr and the tetrahydrofuran removed in vacuo to give 3α-hydroxy-5α-pregnane-11,20-dione (196 mg), melting point 171°-172°C.

Boron trifluoride etherate (37.9 ml) was added to a stirred solution of 3α-hydroxy-5α-pregnane-11,20-dione (6.64 g, 20 mmol) and lead tetraacetate (10.1 g, 22 mmol) in dry benzene (280 ml) and methanol (15.1 ml) at room temperature. After 2 h the mixture was poured into water (2 L) and extracted with ether (1 L). The combined ether extracts were washed successively with sodium bicarbonate solution and water, dried over magnesium sulfate, and concentrated in vacuo to give a white crystalline mass. Four recrystallizations from acetone-petroleum (b.p. 40°-60°C) gave 21-acetoxy-3α-hydroxy-5α-pregnane-11,20-dione as fine needles (4.22 g, 54%), melting point 172°-173°C.

The 3α,21-dihydroxy-5α-pregnane-11,20-dione is conveniently prepared by the deacylation of 21-acetoxy-3α-hydroxy-5α-pregnane-11,20-dione under basic conditions, for example, in the presence of potassium or sodium hydrogen carbonate, conveniently in the presence of a solvent e.g. methanol, ethanol or tetrahydrofuran, reesterifying the resultant product.

References

Davis B. et al.; US Patent No. 3,781,435; December 25, 1973

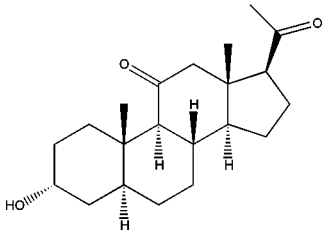
ALFAXALONE

Therapeutic Function: Anesthetic component

Chemical Name: 3-Hydroxypregnane-11,20-dione

Common Name: Alphaxolone

Structural Formula:



Chemical Abstracts Registry No.: 23930-19-0

Trade Name	Manufacturer	Country	Year Introduced
Althesin	Glaxo	UK	1972
Alfadion	Nippon Glaxo	Japan	1978
Alfathesin	Glaxo	France	-
Aurantex	Glaxo	W. Germany	-

Raw Materials

3α-Hydroxy-5α-pregn-16-ene-11,20-dione
Hydrogen

Manufacturing Process

A solution of 3α-hydroxy-5α-pregn-16-ene-11,20-dione (200 mg) in freshly distilled tetrahydrofuran (8 ml) with 5% palladium on carbon (100 ml) was hydrogenated until hydrogen uptake ceased. The mixture was filtered through a pad of kieselguhr and the tetrahydrofuran removed in vacuum to give 196 mg, MP 171°C to 172°C.

References

Merck Index 225
Kleeman and Engel p. 23
DOT 8 (11) 407 (1972)

I.N. p. 53
Davis, B., Pearce, D.R. and Phillips, G.H., British Patent 1,317,184; May 16, 1973; Assigned to Glaxo Laboratories, Ltd.
Davis, B. and Phillips, G.H.; US Patent 3,714,352; January 30, 1973; Assigned to Glaxo Laboratories, Ltd.

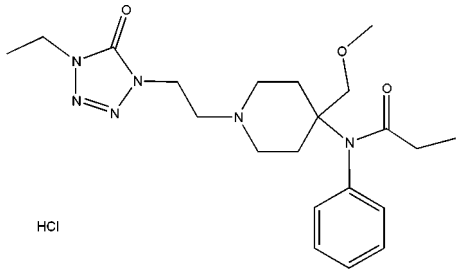
ALFENTANIL HYDROCHLORIDE

Therapeutic Function: Narcotic analgesic

Chemical Name: N-[1-[2-(4-Ethyl-4,5-dihydro-5-oxo-1H-tetrazol-1-yl)ethyl]-4-(methoxy-methyl)-4-piperidinyl]-N-phenylpropaneamide hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 69049-06-5

Trade Name	Manufacturer	Country	Year Introduced
Rapifen	Janssen	Belgium	1983
Rapifen	Janssen	Netherlands	1983
Rapifen	Janssen	W. Germany	1983
Rapifen	Janssen	UK	1983
Rapifen	Janssen	Switz.	1983

Raw Materials

1-Ethyl-1,4-dihydro-5H-tetrazol-5-one
1-Bromo-2-chloroethane
N-[4-(Methoxymethyl)-4-piperidinyl]-N-phenylpropanamide

Manufacturing Process

A mixture of 22 parts of 1-ethyl-1,4-dihydro-5H-tetrazol-5-one, 45 parts of 1-bromo-2-chloroethane, 26 parts of sodium carbonate, 0.3 part of potassium iodide and 240 parts of 4-methyl-2-pentanone is stirred and refluxed overnight with water-separator. The reaction mixture is cooled, water is added and the layers are separated. The aqueous phase is extracted three times with

dichloromethane. The combined organic phases are dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using trichloromethane as eluent. The pure fractions are collected and the eluent is evaporated, yielding 28.4 parts (80%) of 1-(2-chloroethyl)-4-ethyl-1,4-dihydro-5H-tetrazol-5-one as a residue.

A mixture of 1.8 parts of 1-(2-chloroethyl)-4-ethyl-1,4-dihydro-5H-tetrazol-5-one, 3.45 parts of N-[4-(methoxymethyl)-4-piperidinyl]-N-phenylpropanamide, 5 parts of sodium carbonate, 0.2 part of potassium iodide and 240 parts of 4-methyl-2-pentanone is stirred and refluxed overnight with water-separator. The reaction mixture is poured onto water and the layers are separated. The organic phase is dried, filtered and evaporated. The residue is purified by column-chromatography over silicagel using a mixture of trichloromethane and methanol (97:3 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is converted into the hydrochloride salt in 2-propanone. The salt is filtered off and crystallized from 2-propanone, yielding 1.5 parts (33.3%) of N-[1-[2-(4-ethyl-4,5-dihydro-5-oxo-1H-tetrazol-1-yl]-4-(methoxymethyl)-4-piperidinyl]-N-phenylpropanamide monohydrochloride monohydrate; melting point 140.8°C.

References

DFU 6 (6)335 (1981)
OCDS Vol. 3 p. 118 (1984)
DOT 19 (12) 683 (1983)
I.N. p. 53
Janssens, F.; US Patent 4,167,574; September 11, 1979; Assigned to Janssen Pharmaceutica NV.

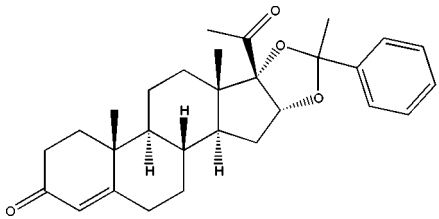
ALGESTONE ACETOPHENIDE

Therapeutic Function: Progestin, Contraceptive

Chemical Name: 16,17-[(1-Phenylethylidene)bis(oxy)]pregn-4-ene-3,20-dione

Common Name: 16α,17α-Dihydroxyprogesterone acetophenide; Alphasone acetophenide

Structural Formula:



Chemical Abstracts Registry No.: 24356-94-3

Trade Name	Manufacturer	Country	Year Introduced
Neolutin Depo	Medici	Italy	1982
Neolutin Depositum	Orma	Italy	-
Droxone	Squibb	US	-
Decadroxone	Squibb	-	-
Decadroxate	Sauibb	-	-

Raw Materials

16α,17α-Dihydroxyprogesterone
Acetophenone

Manufacturing Process

To a suspension of 500 mg of 16α,17α-dihydroxyprogesterone in 25 ml of freshly redistilled acetophenone is added 0.125 ml of 72% perchloric acid and the mixture is agitated at room temperature for one hour. The clear solution is washed with dilute sodium bicarbonate to remove excess acid and the acetophenone layer, after addition of chloroform is separated from the aqueous phase. The organic layer is dried over sodium sulfate and after removal of the chloroform and acetophenone in high vacuum the residue is crystallized from 95% alcohol. The pure acetophenone derivative has a melting point of about 142°C to 144°C.

References

Merck Index 227
Kleeman and Engel p. 24
OCDS Vol. 2 p. 171 (1980)
DOT 19 (2) 110 (1983)
I.N. p. 54
Fried, J.; US Patent 2,941,997; June 21, 1960; Assigned to Olin Mathieson Chemical Corp.
Fried, J. and Diassi, P.A.; US Patent 3,008,958; November 14, 1961; Assigned to Olin Mathieson Chemical Corp.

ALIBENDOL

Therapeutic Function: Choleretic, Spasmolytic

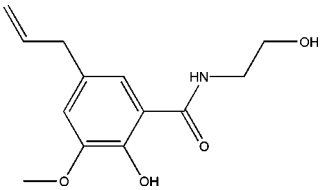
Chemical Name: 2-Hydroxy-N-(2-hydroxyethyl)-3-methoxy-5-(2-propenyl) benzamide

Common Name: -

Chemical Abstracts Registry No.: 26750-81-2

Trade Name	Manufacturer	Country	Year Introduced
Cebera	Bouchara	France	1981

Structural Formula:



Raw Materials

2-Hydroxy-3-methoxy-5-allylbenzoic acid
Ethanol
Ethanolamine

Manufacturing Process

36 g of ethyl ester of 2-hydroxy-3-methoxy-5-allyl-benzoic acid [obtained by the process described by Pearl, et al., J. Amer. Chem. Soc., Vol. 71, 1067-1068 (1949)] and 61 g of ethanolamine were admixed and left to stand for 1 hour at ambient temperature after which it was heated for 1 hour at 120°C. The mixture was extracted with chloroform and the organic phases were washed with half diluted hydrochloric acid, then with water, and the chloroform evaporated off. The residue, after recrystallization from benzene, was a 78% yield of 2-hydroxy-3-methoxy-5-allyl-N-(β-hydroxyethyl)-benzamide having a melting point of 95°C. The product appeared in the form of colorless crystals which were insoluble in water and soluble in dilute sodium hydroxide.

References

Merck Index 230
DOT 18 (10) 525 (1982)
Clemence, F. and Le Martret, O.; US Patent 3,668,238; June 6, 1972; Assigned to Roussel Uclaf.

ALIFEDRINE HYDROCHLORIDE

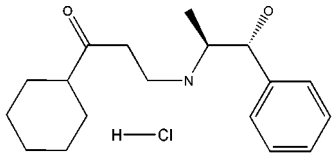
Therapeutic Function: Sympathomimetic; Cardiotonic

Chemical Name: 1-Propanone, 1-cyclohexyl-3-((2-hydroxy-1-methyl-2-phenylethyl)amino)-, (R-(R*,S*))-, hydrochloride

Common Name: Alifedrine

Chemical Abstracts Registry No.: 72913-80-5

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Alifedrine hydrochloride	Chemiewerk Homberg	-	-

Raw Materials

1-Acetyl-1-cyclohexene
1-Norephedrine
Palladium on carbon
Aluminum chloride
Dimethylamine hydrochloride
Cyclohexanecarboxylic acid chloride
Cyclohexyl-β-chloroethyl ketone

Manufacturing Process

There are some means to produce aliflurane:

1). 2.2 g (0.01 mol) of (2-dimethylaminoethyl)cyclohexylketone hydrochloride (produced by Mannich reaction from 1-acetyl-1-cyclohexene with formaldehyde and dimethylamine hydrochloride and subsequent hydrogenation with Pd/C as catalyst) and 1.5 g (0.01 mol) of 1-norephedrine were dissolved in 20 ml of warm isopropanol. The product crystallizing out in the cooling was filtered off with suction and recrystallized from ethanol. Yield of desired 1-propanone, 1-cyclohexyl-3-((2-hydroxy-1-methyl-2-phenylethyl)amino)-, (R-(R*,S*) hydrochloride 24%, M.P: 219-221°C.

2). 13.8 g (0.1 mol) of cyclohexylvinyl ketone (obtainable by the splitting off of HCl during the distillation of cyclohexyl-β-chloroethyl ketone) and 15.1 g (0.1 mol) of 1-norephedrine were dissolved in 50 ml of isopropanol. The desired compound crystallized out as the free base in the standing overnight. The hydrochloride was made with isopropanolic hydrochloric acid. M.P. of the hydrochloride: 219-221°C.

3). The oily cyclohexyl-β-chloroethyl ketone obtained from a solution of 200 g (1.36 mol) of cyclohexanecarboxylic acid chloride in 500 ml of dried 1,2-dichloroethane by portion-wise addition of 182 g (1.3 mol) of AlCl3 at -5°C, then leading ethylene through, subsequent hydrolysis with 500 ml of water at room temperature and concentration of the organic phase dried with Na2SO4 in a vacuum (analogous to U.S. Pat. No. 2,792,406) was added to a solution of 164 g (1.09 mol) of 1-norephedrine in 1000 ml of dioxane. The desired product crystallized out overnight, was filtered off with suction and recrystallized from ethanol/water 1:1 (by volume). Yield: 67% (based on the cyclohexane carboxylic acid chloride). M.P. of the hydrochloride: 219-221°C.

References

Engel J. et al.; US Patent No. 4,542,159; September 17, 1985; Assigned to Degussa Aktiengeselschaft, Frankfurt, Fed. Rep. of Germany

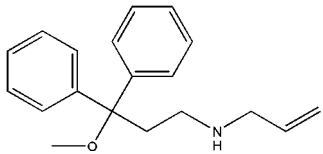
ALIMADOL

Therapeutic Function: Analgesic

Chemical Name: N-(3-Methoxy-3,3-diphenylpropyl)allylamine

Common Name: Alimadol

Structural Formula:



Chemical Abstracts Registry No.: 52742-40-2

Trade Name	Manufacturer	Country	Year Introduced
Alimadol	ZYF Pharm Chemical	-	-

Raw Materials

Trifluoroacetic anhydride
Allyl bromide
3,3-Diphenyl-3-methoxypropylamine
Hexamethyl phosphoric acid amide

Manufacturing Process

12 g 3,3-diphenyl-3-methoxypropylamine, 13.5 g trifluoroacetic acid anhydride, 6.0 g pyridine and 100 ml benzene was heated by stirring for 1 hour at 40°C. Then in was cooled to 0°C and poured in water. The organic layer was separated, washed with diluted HCl and water, and evaporated to dryness. The residue N-(3,3-diphenyl-3-methoxypropyl)trifluoroacetamide melted at 108°-110°C. Yield: 98%.

8 g above amide was in 80 ml hexamethyl phosphoric acid amide dissolved mixed with 1.7 g sodium hydride and stirred for 3 hours. Then 5.7 g allyl bromide was added dropwise and the mixture was stirred for 30 minutes. It was diluted with water and extracted with benzene. Benzene layer was separated, evaporated to dryness. The residue was mixed with 100 ml of 75% ethanol and 1 g sodium hydroxide and heated for 1 hour. Ethanol was distilled off and reaction product was extracted with ether. Yield of N-(3-methoxy-3,3-diphenylpropyl)allylamin (or 1,1-diphenyl-1-methoxy-3-allylaminopropane) was 6.5 g (97%). MP: 40°-50°C. Hydrochloride melted at 137°-138°C.

References

Hollinger R. et al.; DE Patent No. 2,339,528; Sept. 11, 1972; Lenia GmdH, Chem. u. pharm. Erzeugnisse-Indusriebedarf, 8000 Munchen

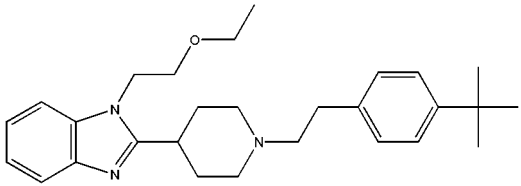
ALINASTINE

Therapeutic Function: Antihistaminic, Antiallergic

Chemical Name: Benzimidazole, 2-(1-(p-tert-butylphenethyl)-4-piperidyl)-1-(2-ethoxyethyl)-

Common Name: Alinastine

Structural Formula:



Chemical Abstracts Registry No.: 154541-72-7

Trade Name	Manufacturer	Country	Year Introduced
Alinastine	Fabrica Espanola de Productos Quimicos y Farmaceuticos	-	-

Raw Materials

Sodium hydride
2-(2-Ethoxyethyl)tosylate
2-[1-(2-(4-(1,1-Dimethylethyl)phenyl)ethyl)piperidin-4-yl]-1H-benzimidazole

Manufacturing Process

1.5 g of a sodium hydride suspension in oil are added to another suspension of 10.83 g of 2-[1-(2-(4-(1,1-dimethylethyl)phenyl)ethyl)piperidin-4-yl]-1H-benzimidazole in 150 ml of dimethylformamide and the mixture is stirred for 1 h at room temperature, then a solution of 2-(2-ethoxyethyl)tosylate in dimethylformamide are slowly added. The mixture is heated at 60°C for 16 h, poured onto water and extracted with ether. The extracts are washed with water, dried over anhydrous sodium sulfate and concentrated. The obtained oil is purified by column chromatography yielding 6.0 g of 1-(2-ethoxyethyl)-2-[1-(2-(4-(1,1-dimethylethyl)phenyl)ethyl)piperidine-4-yl]-1H-benzimidazole, melting point 138°-140°C.

References

Orjales-Venero A., Rubio-Royo V.; US Patent No. 5,322,850; June 21, 1994; Assigned: Fabrica Espanola de Productos Quimicos y Farmaceuticos, S.A., Leiva-Lamiaco, Spain

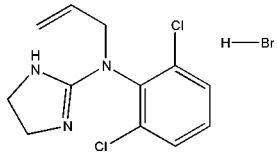
ALINIDINE HYDROBROMIDE

Therapeutic Function: Antiarrhythmic, Bradycardic, Analgesic

Chemical Name: N-(2,6-Dichlorophenyl)-4,5-dihydro-N-2-propenyl-1H-imidazol-2-amine monohydrobromide

Common Name: Alinidine hydrobromide

Structural Formula:



Chemical Abstracts Registry No.: 71306-36-0

Trade Name	Manufacturer	Country	Year Introduced
Alinidine hydrobromide	Boehringer Ingelheim Laboratories	-	-

Raw Materials

2-(2',6'-Dichlorophenylamino)-2-imidazoline
Allyl bromide

Manufacturing Process

2-(N-Allyl-N-(2,6-dichlorophenyl)amino)-2-imidazoline:

A mixture consisting of 2.0 g of 2-(2',6'-dichlorophenylamino)-2-imidazoline, 3 ml of allyl bromide, 1 ml of pyridine and 10 ml of absolute methanol was heated for about 15 hours at 100°C in a closed tube. Thereafter, the reaction mixture was evaporated to dryness in vacuum, the residue was dissolved in a small amount of dilute hydrochloric acid, the resulting solution was purified by extraction with ether, and the ether extracts were discarded. The acidic aqueous solution was made alkaline with 5 N sodium hydroxide where upon an oily substance separated out which crystallized through upon standing for some time on an ice bath. The crystalline product was collected by vacuum filtration, washed with distilled water and dried. 1.5 gm (83% of theory) of the compound having a melting point of 130-131°C was obtained.

References

Stahle H. et al.; US Patent No. 3,708,485; January 2, 1973; Assigned to Bohehringer Ingelheim am Rein, Germany

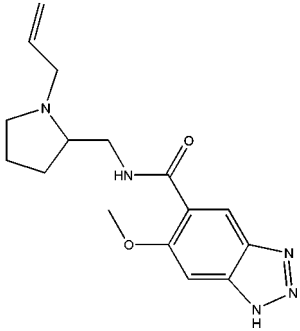
ALIZAPRIDE

Therapeutic Function: Neuroleptic, Antiemetic

Chemical Name: 6-Methoxy-N-[[1-(2-propenyl)-2-pyrrolidinyl]methyl]-H-benzotriazole-5-carboxamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 59338-93-1

Trade Name	Manufacturer	Country	Year Introduced
Plitican	Delagrange	France	1981
Vergentan	Delagrange	W. Germany	1981

Raw Materials

2-Methoxy-4,5-azimidobenzoic acid
1-Allyl-2-aminomethylpyrrolidine
Phosphoric anhydride

Manufacturing Process

38.6 g (0.2 mol) of 2-methoxy-4,5-azimidobenzoic acid were dissolved in anhydrous toluene and 56 g (0.4 mol) of 1-allyl-2-amino-methylpyrrolidine were added. The mixture was heated to 50°C and then 42 g (0.3 mol) of phosphoric anhydride were added. The mixture was warmed at reflux temperature for 3 hours and then cooled to 80°C. After adding water, the aqueous layer was alkalized. The crystals were filtered, washed with water and then dissolved in 450 ml of acetone. After crystallization, the product was

filtered, washed and dried.

40.4 g (yield 65%) of N-(1'-allyl-2'-pyrrolidylmethyl)-2-methoxy-4,5-azimidobenzamide having a melting point of 139°C were obtained.

References

Merck Index 231
DFU 6 (1) 11 (1981)
DOT 18 (4) 162 (1982)
I.N. p.55
Bulteau, G., Acher, J., Collignon, C. and Monier, J.C.; US Patent 4,039,672; August 2, 1977; Assigned to Societe D'Etudes Scientifiques et Industrielles de I'lle-de-France

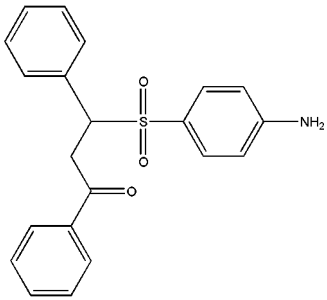
ALKOFANONE

Therapeutic Function: Antidiarrheal

Chemical Name: 3-[(4-Aminophenyl)sulfonyl]-1,3-diphenyl-1-propanone

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 7527-94-8

Trade Name	Manufacturer	Country	Year Introduced
Clafanone	Roche	US	1956

Raw Materials

Benzal acetophenone
p-Aminobenzene sulfinic acid

Manufacturing Process

38 g benzal-acetophenone and 25 g p-aminobenzene-sulfinic acid are refluxed

for 5 hours in 700 cc of 85% ethyl alcohol. Fine crystals soon begin to appear and fill the reaction vessel. While still hot, the mixture is suction-filtered. The reaction product is washed first with 750 cc warm absolute alcohol, then with 500 cc water, and finally again with 300 cc alcohol, and then dried in vacuum. Yield 32 g. MP 210-212°C with decomposition.

References

Merck Index 240
Goldberg, M.W.; US Patent 2,421,836; June 10, 1947; Assigned to Hoffmann-La Roche, Inc.

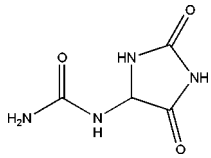
ALLANTOIN

Therapeutic Function: Vulnerary, Antiulcer (topical), Antipsoriatic

Chemical Name: Urea, (2,5-dioxo-4-imidazolidinyl)-

Common Name: Allantoin

Structural Formula:



Chemical Abstracts Registry No.: 97-59-6

Trade Name	Manufacturer	Country	Year Introduced
Allantoin	Arocor Holdings Inc.	-	-
Allantoin	Hunan Xinyu	-	-
Allantoin	Akema Fine Chemicals	-	-
Allantoin	Allan Chemical Corporation	-	-
Allantoin	Hangzhou Greenda Chemical Co., Ltd.	-	-
Allantoin	Kunshan Hua Xin Daily Chemicals Co., Ltd.	-	-
Allantoin	Omikron	-	-
Allantoin	Xiamen Linyo Technology Co., Ltd.	-	-
Cutemol	Summers Laboratories Inc.	-	-
Egopsoryl	Ego Pharmaceuticals	-	-
Egopsoryl	SMP Vet	-	-
Herker	Herker Industries	-	-
Soothex	Jamieson Laboratories Ltd.	-	-

Raw Materials

Urea	Glyoxal
Sulfuric acid	Cobalt(II) nitrate hexahydrate
Sodium nitrite	Hydrogen chloride
Ammonium sulfate	

Manufacturing Process

To a mixture of 13.14 kg 40% solution of glyoxal in water and a solution of 0.5 L of concentrated HCl in 3 L of water was added 1.8 g $Co(NO_3)_2 \cdot 6H_2O$. The mixture was heated at 50-60°C, to the solution was added 20 g of sodium nitrite and then at 40-60°C was added dropwise the mixture of 6 L of concentrated HNO3, 4.2 L of water and 30 g of sodium nitrite. The product obtained was mixed with 2.4 kg ammonium sulfate and filtrated. The filtrate was heated with 14.5 kg urea at 70°C for 10 hours. Allantoin was filtrated and recrystallized from the water; M.P. 233-235°C.

References

Merck Index, Monograph number: 255, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
DE Patent No. 1,939,924, 18 Feb., 1971
Christmann et al.; US Patent No. 2,802,011; Aug. 6, 1957; Assigned to Carbogen Corporation, New York
DE Patent No. 2,714,938; 11.05.1978

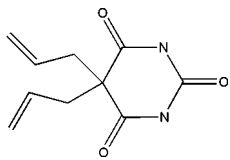
ALLOBARBITAL

Therapeutic Function: Sedative, Hypnotic

Chemical Name: Barbituric acid, 5,5-diallyl-

Common Name: Diallylbarbituric acid, Allobarbital, Diallymal

Structural Formula:



Chemical Abstracts Registry No.: 52-43-7

Trade Name	Manufacturer	Country	Year Introduced
Allobarbital	Fluorochem Ltd.	-	-
Dorm	Funke	-	-

Raw Materials

Allyl bromide
Barbituric acid
Sodium hydroxide

Manufacturing Process

To a mixture of 43 parts barbituric acid, 200 parts of water and 5 parts of cuprous sulfate in 10 parts of water is added 82 parts of allylbromide. Then at room temperature is added 27 parts of sodium hydroxide (10% aqueous solution). 5,5-Diallylbarbituric acid is isolated by filtration. After recrystallization from water 5,5-diallylbarbituric acid has melting polint 169-170°C.

References

Patent DE 268158; 30.June 1911; Assigned to Geselschaft fur Chemische Industrie in Basel
Patent DE 526854; 22. Feb. 1930; Assigned to F.Hoffmann-La Roche and Co. Act.-Ges. in Basel

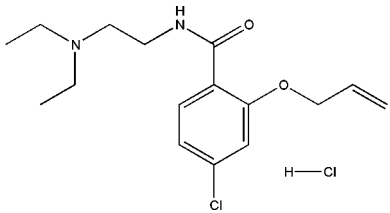
ALLOCLAMIDE HYDROCHLORIDE

Therapeutic Function: Antitussive

Chemical Name: Benzamide, 4-chloro-N-(2-(diethylamino)ethyl)-2-(2-propenyloxy)-, monohydrochloride

Common Name: Alloclamide hydrochloride; Depryn; Pectex

Structural Formula:



Chemical Abstracts Registry No.: 5107-01-7; 5486-77-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Alloclamide hydrochloride	ZYF Pharm Chemical	-	-

Raw Materials

2-Hydroxy-4-chlorobenzoic aci
β-Diethylaminoethylamine
Allyl bromide
Thionyl chloride

Manufacturing Process

(a) 200 g of 2-hydroxy-4-chlorobenzoic acid and 1 liter of methanol are brought to reflux. Dry hydrogen chloride gas is bubbled through the mixture during a time period of 8 hours. The excess of methanol is evaporated, the residue is poured into cold water, neutralized and extracted with ether. After evaporation of the solvent the product is distilled under vacuum. The boiling point of the compound at 15 mm Hg is 127°C, and the yield is 85% of the theoretical.

(b) The production of 2-allyloxy-4-chloromethyl benzoate:

4-Chloro-2-hydroxymethyl benzoate 186 g (1 mole), 152 g anhydrous potassium carbonate, 133 g redistilled allyl bromide in 350 ml acetone are heated of refluxing under agitation. At the end of 6 hours the reaction is completed. The reaction mixture is filtered for removal of the mineral salts. The acetone is evaporated. There is thus obtained an oily residue, which rapidly crystallizes. After recrystallization from methanol the obtained product is a white crystal solid, which melts at 56°C. The yield is 84%.

(c) The production of 2-allyl-oxy-4-chlorobenzoyl chloride:

The 2-allyloxy-4-chloromethyl benzoate obtained under (b) above is saponified under the usual conditions on for obtaining the corresponding acid, and the corresponding acid is obtained in a yield of 91%, the acid melting at 87°C.

The chloride of the acid is prepared by treating 1 mol of the acid with 1.5 moles of thionyl chloride (freshly rectified on linseed oil) in the presence of benzene. There is thus obtained a pale yellow viscous liquid, which can be further used without preliminary distillation.

(d) Preparation of the amide and of the hydrochloride:

115.5 g (0.5 mol) of the benzoyl chloride produced under (c) above is dissolved in 500 ml of anhydrous chloroform. There is added to this solution drop by drop while agitating and under cooling in an ice bath 116 g of β-diethylaminoethylamine. After the addition is completed the agitation is continued for 1 hour at ambient temperature. The reaction mass is then washed with water, the chloroform is evaporated, the residue is taken up the minimum of absolute alcohol, and there is then added a slight excess of absolute alcohol saturated with hydrogen chloride. The hydrochloride crystallizes by the addition of anhydrous ether. After recrystallization in absolute alcohol plus ether there is obtained white crystals, which are soluble in water and in alcohol. The 2-allyloxy-4-chloro-N-(β-diethylaminoethyl)benzamide hydrochloride melts at 125°-127°C.

References

Mauvernay R-Y.; US Patent No. 3,160,557; Dec. 8, 1964; Assigned to Centre European de Recherches Mauvernay, Chateau de Bardon, Riom, Puy-de-Dome, France

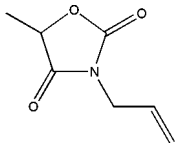
ALLOMETHADIONE

Therapeutic Function: Anticonvulsant, Antiepileptic

Chemical Name: 2,4-Oxazolidinedione, 5-methyl-3-(2-propenyl)-

Common Name: Allomethadione, Aloxidone

Structural Formula:



Chemical Abstracts Registry No.: 526-35-2

Trade Name	Manufacturer	Country	Year Introduced
Aloxidone	ZYF Pharm Chemical	-	-

Raw Materials

Allyl bromide
Urea
5-Methyloxazolidine-2,4-dione
Ethyl lactate

Manufacturing Process

A mixture of 11.4 parts of 5-methyloxazolidine-2,4-dione and 15 parts anhydrous potassium carbonate in 150 parts of dry acetone is stirred for 0.5 hour. 15 parts of allyl bromide are then added and the mixture boiled under reflux with stirring for 4 hours. After cooling and filtering, the solvent and any unchanged allyl bromide are removed by distillation. The residue is extracted with ether end the extract washed with saturated aqueous sodium bicarbonate until the subsequent water-washings are either neutral or just alkaline to litmus paper. The solvent is then distilled and the residue fractionated when 3-allyl-5-methyloxazolidine-2,4-dione is obtained in 65% yield as a colorless oil, BP: 88°-90°C/1.8 mm, n_d^{20} = 1.4710.

The dry sodium salt of 5-methyloxazolidine-2,4-dione, obtained from 4.6 parts of sodium, 100 parts of ethanol, 12 parts of urea and 23.6 parts of ethyl lactate, is suspended in 100 parts of dry benzene and 30.25 parts of allyl bromide are added. The mixture is boiled under reflux for 20 hours and the benzene decanted or filtered from any solid. The solution is washed with

saturated aqueous sodium bicarbonate until the subsequent water-washings are neutral or just alkaline to litmus paper. The dried benzene solution is then distilled to remove solvent and the residue fractionated, when 3-allyl-5-methylosazolidine-2,4-dione is obtained in 27% yield as a colorless oil, BP: 89°-90°C/1 mm, n_d^{20} = 1.4712.

The dry sodium salt of 5-methyloxazolidine-2,4-dione obtained as above is mixed with 100 parts of dry dioxane and 31.25 parts of allyl bromide are added. After boiling under reflex for 24 hours, decanting the solution and distilling off the dioxane under reduced pressure, the residue is dissolved in ether and the ethereal extract mashed with aqueous sodium bicarbonate as above. Fractionation of the residue after removing the olvent furnishes 3-allyl-5-methyloxazolidine-2,4-dione in 48.5% yield as a colorless oil; BP: 94°-95°C/11.75 mm; n_d^{20} = 1.4710.

References

Davis J.S.H. and Hook W.H.; GB Patent No. 632,423; June 28, 1948; British Schering Research Laboratories, Great Britain

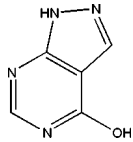
ALLOPURINOL

Therapeutic Function: Xanthine oxidase inhibitor, Gout therapy

Chemical Name: 1H-Pyrazolo[3,4-d]pyrimidin-4-ol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 315-30-0

Trade Name	Manufacturer	Country	Year Introduced
Zyloprim	Burroughs-Wellcome	US	1966
Zyloric	Wellcome	Switz.	-
Zyloric	Burroughs-Wellcome	UK	1966
Zyloric	Wellcome	W. Germany	1967
Zyloric	Wellcome	Italy	1968
Zyloric	Wellcome	Japan	1969
Zyloric	Wellcome	France	1969
Lopurin	Boots	UK	1980
Adenock	Tanabe	Japan	-
Adenock	Shiraimatsu	Japan	-
Allopin	Yeni	Turkey	-

Trade Name	Manufacturer	Country	Year Introduced
Allomaron	Nattermann	W. Germany	-
Alloprim	Iltas	Turkey	-
Alloprin	ZCN	Canada	-
Allopur	Gea	Denmark	-
Allopur	Nyegaard	Norway	-
Allopurinol	Sigfried	W. Germany	-
Allopurinol	Efeka	W. Germany	-
Allopurinol	Woelm Pharma	W. Germany	-
Allopurinol	Lederle	Japan	-
Allopurinol	Kowa	Japan	-
Allopurinol	Showa	Japan	-
Allorin	Towa	Japan	-
Allozym	Sawai	Japan	-
Allural	Nativelle	Italy	-
Allural	Pan Quimica	Spain	-
Allurit	Schoum	Italy	-
Aloc	Toho Iyaku	Japan	-
Alositol	Tanabe	Japan	-
Anoprocin	Nippon Shoji	Japan	-
Antigot	Yurtoglu	Turkey	-
Anzief	Nippon Chemiphar	Japan	-
Aprinol	Daisan	Japan	-
Apurin	Gea	Denmark	-
Apurin	Madica	Finland	-
Apurol	Siegfried	Switz.	-
Bleminol	Desitin	W. Germany	-
Caplenal	Berk	UK	-
Capurate	Fawns and McAllan	Australia	-
Cellidrin	Henning	W. Germany	-
Cosuric	DDSA	UK	-
Dabroson	Hoyer	W. Germany	-
Embarin	Diabetylin	W. Germany	-
Epidropal	Fresenius	W. Germany	-
Flogorex	Lancet	Italy	-
Foligan	Henning	W. Germany	-
Geapur	Gea	Denmark	-
Gichtex	Gerot	Austria	-
Ketawrift	Ohta	Japan	-
Ketobun A	Isei	Japan	-
Lopurin	Generics Corp.	US	-
Lysuron	Boehringer Mannheim	W. Germany	-
Masaton	Zensei	Japan	-
Melianin	Kohjin	Japan	-
Mephanol	Mepha	Switz.	-
Milurit	EGYT	Hungary	-

Trade Name	Manufacturer	Country	Year Introduced
Monarch	SS Pharmaceutical	Japan	-
Nektronan	ICN Pharmaceuticals Inc.	W. Germany	-
Neufan	Teikoku	Japan	-
Neufan	Teisan	Japan	-
Novopurol	Novopharm	Canada	-
Progout	Protea	Australia	-
Puricos	Lennon	S. Africa	-
Purinol	Horner	Canada	-
Riball	Mitsui	Japan	-
Roucol	Rougier	Canada	-
Serviprinol	Servipharm	Switz.	-
Suspendol	Merckle	W. Germany	-
Takanarumin	Takata	Japan	-
Urbol	Heilit	W. Germany	-
Urbol	Gea	Denmark	-
Uredimin	Chassot	Switz.	-
Uricemil	Farnex	Italy	-
Uricemil	Fardeco	Italy	-
Uriconorm	Streuli	Switz.	-
Uridocid	Reig Jofre	Spain	-
Uriscel	Armour Med.	Italy	-
Urobenyl	Endopharm	W. Germany	-
Urolit	Magis	Italy	-
Urosin	Boehringer Mannheim	W. Germany	-
Urozyl-SR	Restan	S. Africa	-
Urtias	Sabona	W. Germany	-
Vedatan	Corvi	Italy	-
Xanturat	Gruenenthal	W. Germany	-
Zylol	Teva	Israel	-

Raw Materials

Cyanoacetamide
Morpholine
Triethylorthoformate
Hydrazine hydrate

Manufacturing Process

3-Morpholino-2-cyanoacrylamide: A stirred mixture of cyanoacetamide (63 g), triethylorthoformate (134 g), morpholine (82.5 g) and acetonitrile (37.5 ml) was heated under reflux for 4 hours. The initial reflux temperature was 117°C and the final reflux temperature was 82°C.

At the end of the reflux period the mixture was cooled to 30°C and the heavy

crystalline precipitate was collected and washed with 2 x 75 ml of ethanol. The product was dried in vacuum at 30°C. Wt = 111 g. Yield = 82%, MP 173-175°C.

3-Aminopyrazole-4-carbxamide hemisulfate: To water (253 ml) at 60°C was added 3-morpholino-2-cyanoacrylamide (63.4 g) and 85% technical hydrazine hydrate (22.7 g). The mixture was rapidly heated to 95°C and the temperature was maintained at >90°C for 20 minutes. The mixture was then cooled to 60°C and the pH carefully adjusted to 1.5 by the addition of a mixture of sulfuric acid (45.7 g) and ice. The acidified reaction was cooled to 5°C and the crystalline product collected and washed with cold water (2 x 100 ml) and acetone (2 x 50 ml). The product was dried in vacuum at 80°C. Wt =5.8 g. Yield =95%, MP 237-239°C.

4-Hydroxypyrazolo[3,4-d]pyrimidine: A suspension of 3-aminopyrazole-4-carboxamide hemisulfate (113 g) in formamide (325 g) was stirred and heated to 145°C. The reaction was held at 145°C for 5 hours. The reaction was then cooled to 30°C and the product collected and washed with formamide (2 x 50 ml), water (2 x 150 ml) and acetone (2 x 100 ml). Wt of crude product = 79 g. The crude product was recrystallized by dissolution in a solution made from sodium hydroxide (25 g) in water (1,200 ml) with treatment at 25°C with charcoal (8 g), followed by reprecipitation by the addition of concentrated hydrochloric acid to pH 5. The product was collected and washed with cold water (2 x 300 ml), acetone (2 x 200 ml) and dried in vacuum at 60°C. Wt = 70 g. Yield = 80%.

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Hitchings, G.H. and Falco, E.A.; US Patent 3,474,098; October 21, 1969; Assigned to Burroughs Wellcome and Co.
Cresswell, R.M. and Mentha, J.W.; US Patent 4,146,713; March 27, 1979; Assigned to Burroughs Wellcome and Co.

ALLYLESTRENOL

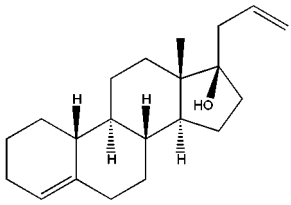
Therapeutic Function: Progestin; Antiandrogen

Chemical Name: 17α-Allylestr-4-en-17β-ol

Common Name: Alilestrenol; Allylestrenol; Allyloestrenol

Chemical Abstracts Registry No.: 432-60-0

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Alilestrenol	Terapia	-	-
Alilestrenol PA	AAA Principio Activo	-	-
Allyloestrenol	Belco Pharma	-	-
Allyloestrenol	Huei-Ho Industries	-	-
Anin	Ind-Swift Ltd.	-	-
Astanol	Rekvina Pharma	-	-
Gestanin	Organon	-	-
Gestanin	Donmed	-	-
Gestanon Tab.	Organon	-	-
Gestin	Walter Bushnell	-	-
Gestormone	Zorka	-	-
Gravidin	Alidac	-	-
Gynonys	Sankyo	-	-
Fetugard	Biddle Sawyer	-	-
Fulterm	Micro Nova	-	-
Maintane Tab.	Jagsonpal	-	-
Nidagest	Systopic	-	-
Orageston	Akzo	-	-
Pregular	Helios	-	-
Profar	Infar	-	-
Premaston	Kalbe	-	-
Profar	Infar	-	-
Turinal	Richter Co.	-	-
Turinal	Gedeon Richter	-	-
Turinal	Medimpex	-	-
Turinal	Mekim	-	-
Turinal Tab.	October Pharma Co.	-	-

Raw Materials

Methylamine
Chromium trioxide
Acetic acid
Allyl bromide
Lithium
Oestradiol-3-methylether
Magnesium

Manufacturing Process

To 145 ml of dry methylamine which is cooled to -20°C 1.5 g of lithium cut to

small pieces are added. To the solution which is blue in color after 10-20 min, a solution of 3.0 g of oestradiol-3-methylether in 145 ml of absolute ether is added drop wise. Subsequently the reaction mixture is stirred at -10°C for 40 h, after which 50 ml of absolute ethanol are added. Then the methylamine is distilled off at law pressure.

To the remaining solution 50 ml of ether and 50 ml of water are added. The water layer is separated and extracted with ether. The ethereal layer is washed with a 2 N hydrochloric acid solution, subsequently with a saturated sodium bicarbonate solution, and then with water. The ethereal solution is dried and evaporated to dryness. The resulting crude reaction product is dissolved in a mixture of benzene and petroleum ether (1:3) and chromatographed over aluminium oxide. The δ^4-17β-hydroxy-oestrene obtained after chromatographic purification has a melting point of 80°-90°C and 95°-100°C after repeated crystallization from petroleum ether.

A solution of 13.2 g of chromium trioxide in a mixture of 120 ml of water and 20 ml of acetic acid is added, with stirring, to a solution of 20 g of δ^4-17β-hydroxy-oestrene in 400 ml of benzene. Subsequently the reaction mixture is vigorously stirred at room temperature for 16 h, after which the benzene layer is separated.

The remaining aqueous layer is extracted a few times with benzene and the benzene extracts collected are then added to the separated benzene layer. The benzene extracts are successively washed with dilute sulfuric acid and water and then evaporated to dryness. The residue is crystallized from acetone, and the δ^4-17β-oxo-oestrene, melting point 114°-116°C is obtained.

To a mixture of 22.4 ml of absolute ether and 1.84 g of magnesium, a mixture of 2.72 ml of allyl bromide and 2.72 ml of absolute ether is added in nitrogen atmosphere. Subsequently a solution of 2 g of δ^4-17β-oxo-oestrene in 30 ml of absolute ether is added to this reaction mixture, after which the whole is stirred for 4 h. Then the reaction mixture is poured into acidified ice water. The aqueous mixture is extracted with ether; the ether layer is separated, washed with water, dried over sodium sulfate and evaporated to dryness. The residue is recrystallized from a mixture of ether and petroleum ether, giving δ^4-17β-hydroxy-17α-allyl-oestrene, melting point 79.5°-80°C.

References

GB Patent No. 841,411; April 2, 1958; Assigned: Organon Laboratories Limited, a British Company of Brettenham House, Lancaster Place, London

ALMAGATE

Therapeutic Function: Antacid

Chemical Name: Magnesium, (carbonato(2-))heptahydroxy(aluminum)tri-, dihydrate

Common Name: Almagate

Structural Formula: $AlMg_3(CO_3)(OH)_7$

Trade Name	Manufacturer	Country	Year Introduced
Almagate	AGARWAL PHARCHEM (I) PVT. LTD.	-	-

Chemical Abstracts Registry No.: 66827-12-1

Raw Materials

Aluminum hydroxide
Magnesium hydroxide
Triethylamine
Ammonium hydroxide
Water

Manufacturing Process

2 Methods of producing of basic aluminium magnesium carbonate:

1. A suspension of aluminum hydroxide (9.57 g, corresponding to 5.09 g of Al_2O_3 0.05 mol), magnesium hydroxide of 92.09% purity (18.87 g; 0.3 mol), concentrated ammonium hydroxide (4.89 ml; 0.33 mol) and water (500 ml) was boiled under reflux for 6 h while a stream of carbon dioxide was passed through the mixture. Then the reaction mixture was cooled, and the insoluble compound was filtered off, washed several times with water and dried in vacuum at a temperature of 60°C. Basic aluminum magnesium carbonate (31.1 g) was obtained.

2. A suspension of aluminium hydroxide (9.57 g, corresponding to 5.09 g of Al_2O_3 0.05 mol) magnesium hydroxide of 92.09% purity (18.87 g; 0.3 mol), triethylamine (33.4 g; 0.33 mol) and water (500 ml) was boiled under reflux for 8 h while a stream of carbon dioxide was passed through the mixture. After cooling, the insoluble compound was filtered off, washed several times with water and dried at 60°C under reduced pressure. Basic aluminum magnesium carbonate (30.8 g) was obtained.

References

Spickett R.G.W. et al.; US Patent No. 4,447,417; May 8, 1984; Assigned: Anphar S.A., Madrid, Spain

ALMASILATE

Therapeutic Function: Antacid

Chemical Name: Magnesium aluminosilicate (MgAl2Si2O8) hydrate

Common Name: Simagel; Almasilate

Structural Formula: $MgAl_2Si_2O_8 \cdot H_2O$

Trade Name	Manufacturer	Country	Year Introduced
Megalac Almasilat	Krewel Meuselbach	-	-
Simagel	Philopharm	-	-

Chemical Abstracts Registry No.: 71205-22-6

Raw Materials

Magnesium chloride
Aluminum sulfate
Caustic soda
Sodium silicate (Na_2O, 9%, SiO_2, 29%)

Manufacturing Process

203 g of crystalline magnesium chloride such as is used as a food additive, containing 46% $MgCl_2$, is dissolved in 600 ml of water, to which 96 g of caustic soda dissolved in 250 ml of water is added with stirring and a solution comprising 50 ml of water with 207 g of sodium silicate (Na_2O, 9%, SiO_2, 29%) is further added and is then vigorously stirred to produce basic sodium magnesium silicate (which is designated as Slurry A).

Secondly 593 g of aluminum sulfate containing 17.2% Al_2O_3, dissolved in 1,700 ml of water is gently added with stirring to 216 g of caustic soda dissolved in 600 ml of water, to which 50 ml of water added to 207 g of sodium silicate (Na_2O 9%, SiO_2, 29%) is slowly added and is then vigorously stirred to produce tetrabasic dialuminum silicate (which is designated as Slurry B). Slurry A and Slurry B are mixed up vigorously with stirring for 3 hours at room temperature. The thus obtained white gel-like precipitate is washed by decantation to remove free alkali, sodium sulfate, sodium chloride, etc. produced as reaction by-products. The residue is filtered and dried at 105°-110°C and 340 g of white powder of fine particle size is obtained as the final product. The molar ratio of MgO to Al_2O_3, to SiO_2, in this product is approximately 1: 1: 2.

203 g of crystalline magnesium chloride such as is used as a food additive, containing 46% $MgCl_2$, and 593 g of aluminum sulfate containing 17.2% Al_2O_3, are dissolved in 2,300 ml of water, to which a solution comprising 272 g of caustic soda with 800 ml of water, is slowly added with stirring. Thereafter, a solution comprising 414 g of sodium silicate (Na_2O, 9%, SiO_2, 29%) with 100 ml of water is added, the mixture is heated and is stirred for five hours, while keeping the temperature at 60°C. When the reaction mixture becomes neutral it is allowed to cool and to stand, the supernatant fluid is withdrawn and the white gel-like precipitate is washed by decantation to remove the impurities and dried at 105°-110°C and 350 g of white powder of fine particle size is obtained as the final product (almasilate).

References

Hidetaka Uoda et al.; GB Patent No. 1,153,513; Feb. 17, 1967; Fuji Kagaku Kogyo Kaushiki Kaisha, a Japanese Company, of 55 Yokohooji, Kamiichimachi, Naka-Niikawa-gun, Toyama-ken, Japan

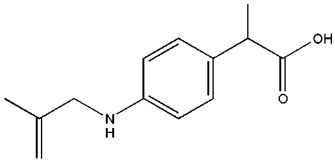
ALMINOPROFEN

Therapeutic Function: Analgesic, Antiinflammatory

Chemical Name: Benzeneacetic acid, α-methyl-4-((2-methyl-2-propenyl) amino)-

Common Name: Alminoprofen; Minalfene

Structural Formula:



Chemical Abstracts Registry No.: 39718-89-3

Trade Name	Manufacturer	Country	Year Introduced
Alminoprofen	ZYF Pharm Chemical	-	-
Minalfene	Bouchara-Recordati	-	-

Raw Materials

Methyl 2-(p-nitrophenyl)acrylate
Methallyl chloride
Palladium on charcoal
Pyridine

Manufacturing Process

Methyl 2-(p-aminophenyl)propionate:

Methyl 2-(p-nitrophenyl)acrylate (52 g) is hydrogenated in ethanol (500 ml) in the presence of 5% palladium-over-charcoal, while maintaining the temperature at +5°C. The theoretical amount of hydrogen is taken up within one hour. After separation of the catalyst and concentration to dryness, the resulting material gives methyl 2-(p-aminophenyl)proprionate which crystallizes: MP: = 40°-43°C.

Methyl 2-(p-methallylaminophenyl)propionate hydrochloride:

A mixture of methyl 2-(p-aminophenyl)propionate (44.75 g), methallyl chloride (34 g) and pyridine (30 ml) in isopropanol (400 ml) is boiled during 30 hours. The solvent is removed in vacuo and the residue is taken up into water and ether. After separation, the organic phase is washed repeatedly with water, after which it is dried and concentrated in vacuo. The resulting oil is fractionally distilled in vacuo (0.1 mm Hg; 5 g of oil essentially consisting of methyl 2-(p-aminophenyl)propionate are collected at 115°-120°C; 30 g of oil consisting of a mixture of mono- (80%) and disubstituted (20%) amines is collected at 128°-130°C. This oil is used to prepare the hydrochloride, which is recrystallized from ethyl acetate, to give white crystals (22.7 g) melting at

115°C. Saponification in the cold methanolic hydroxide gives the desired 2-(4-(methallylamino)phenyl)propionic acid (alminoprofen). MP: 120°C.

References

Bouchara E.; US Patent No. 3,957,850; May 18, 1976

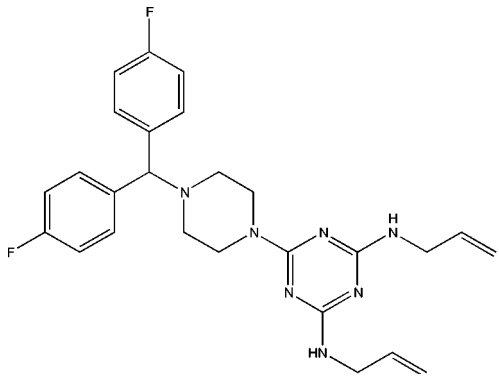
ALMITRINE

Therapeutic Function: Respiratory stimulant

Chemical Name: 1,3,5-Triazine-2,4-diamine, 6-(4-(bis(4-fluorophenyl) methyl)-1-piperazinyl)-N,N'-di-2-propenyl-

Common Name: Almitrine

Structural Formula:



Chemical Abstracts Registry No.: 27469-53-0

Trade Name	Manufacturer	Country	Year Introduced
Armanor	Les Laboratoires Servier	-	-
Duxaril	Les Laboratoires Servier	-	-
Duxil	Servier-Egypt Co.	-	-
Vectarion	Les Laboratoires Servier	-	-

Raw Materials

4,6-Bis(allylamino)-2-chloro-s-triazine
1-p,p'-Difluorobenzhydryl piperazine dihydrochloride
Sodium hydroxide

Manufacturing Process

A solution of 4,6-bis(allylamino)-2-chloro-s-triazine, melting point 204°C

(Kofler) and dihydrochloride of 1-p,p'-difluorobenzhydryl piperazine, melting point 178°-180°C (capillary) in anhydrous dimethylformamide are heated under reflux. On completion of this operation the solvent is removed under vacuum and the residue taken up in a mixture of chloroform and of water (1:1). The organic phase is separated, and repeatedly extracted with aqueous N-methanesulphonic acid and the aqueous acidic layers separated. The aforementioned acidic solutions are then combined and rendered alkaline (pH 10) with dilute aqueous sodium hydroxide, the base extracted with ether, the extract dried over anhydrous potassium carbonate, and filtered. The etheral filtrate, upon evaporation yields the 2,4-bis(allylamino)-6-(4-(bis(p-fluorophenyl)methyl)-1-piperazinyl)-s-triazine, melting point 175°-180°C.

References

Regnier G. et al.; US Patent No. 3,647,794; March 7, 1972; Assignee: Societe en nom collectiff "Science Union et Cie", Societe Francaise de Recherche Medicale

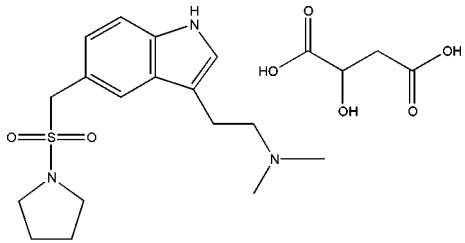
ALMOTRIPTAN MALATE

Therapeutic Function: Migraine therapy

Chemical Name: Pyrrolidine, 1-[[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]sulfonyl]-, hydroxybutanedioate salt (1:1)

Common Name: Almotriptan malate

Structural Formula:



Chemical Abstracts Registry No.: 181183-52-8; 154323-57-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Almogran	Lundbeck	-	-
Axert	Aetna Inc.	-	-
Axert	Jannsen-Ortho	-	-
Axert	Pharmacia Corporation	-	-

Raw Materials

1-[[2-Carboxy-3-(2-dimethylaminoethyl)-5-indolyl]methanesulphonyl]-pyrrolidine
Quinoline
Copper oxide

Manufacturing Process

To a solution of previously dried 1-[[2-carboxy-3-(2-dimethylaminoethyl)-5-indolyl]methanesulphonyl]-pyrrolidine (1.6 g; 0.0442 moles) in anhydrous quinoline (75 ml) and under atmosphere of nitrogen, cuprous oxide (160 mg; 0.0011 moles) was added. The reaction mixture was heated to 190°C for 15 minutes, stirred to room temperature, poured into a mixture of 1 N hydrochloric acid (150 ml) and ethyl acetate (50 ml), shaken and decanted. The aqueous solution was washed several times with ethyl acetate, then solid sodium bicarbonate was added until pH = 7.8, and washed with n-hexane to eliminate the quinoline. The aqueous solution was made alkaline with solid potassium carbonate and extracted with ethyl acetate. The organic solution was dried (Na_2SO_4), the solvent removed under reduced pressure when a dark oil was obtained (1.3 g; yield 92%). This product was purified by column chromatography with silica gel and methylene chloride:ethanol:ammonium hydroxide (60:8:1) as eluent and a white foam (0.8 g) of 1-[[3-(2-dimethylaminoethyl)-5-indolyl]methanesulphonyl]-pyrrolidine was obtained. To a solution of the above product (0.8 g) in acetone (30 ml), a few drops of hydrogen chloride saturated dioxan solution, were added. The precipitated solid was collected by filtration, washed with acetone and dried to give 1-[(3-(2-(dimethylamino)ethyl)-5-indolyl)methanesulphonyl]-pyrrolidine hydrochloride (0.75 g). Melting point 218°-220°C.

In practice it is usually used as malate salt.

References

F. Former et al.; WO 94/02460; 28.07.92
D. Lednicer; The organic chemistry of drug synthesis; p. 124, 1999; Wiley and Sons

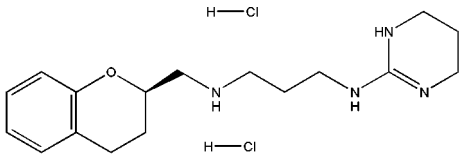
ALNIDITAN DIHYDROCHLORIDE

Therapeutic Function: Migraine therapy

Chemical Name: 1,3-Propanediamine, N-((3,4-dihydro-2H-1-benzopyran-2-yl)methyl)-N'-(1,4,5,6-tetrahydro-2-pyrimidinyl)-, dihydrochloride, (2R)-

Common Name: Alniditan dihydrochloride; Pasmigren

Structural Formula:



Chemical Abstracts Registry No.: 155428-00-5; 152317-89-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Pasmigren	Janssen-Cilag	-	-

Raw Materials

Methylbenzene	3,4-Dihydro-2H-1-benzopyran-2-carboxylic acid, (+)-
2-Chloropyrimidine	2,2'-Oxybispropane
Thionyl chloride	Acetamide, N,N-dimethyl-
Thiophene	Palladium on charcoal
Hydrogen	Benzenemethanamine
Potassium acetate	2-Propenenitrile
Sodium hydroxide	Sodium carbonate
Nickel Raney	

Manufacturing Process

To a stirred and heated +80°C mixture of 3,4-dihydro-2H-1-benzopyran-2-carboxylic acid and methylbenzene were added dropwise thionyl chloride during a period of 85 min. Upon complete addition, stirring was continued for 2 h at 80°C. After cooling to room temperature, the reaction mixture was evaporated. The residue was taken up in methylbenzene and the solvent was evaporated again, yielding (R)-3,4-dihydro-2H-1-benzopyran-2-carbonyl chloride.

A mixture of (R)-3,4-dihydro-2H-1-benzopyran-2-carbonyl chloride in N,N-dimethylacetamide and 2,2'-oxybispropane was hydrogenated in the presence of palladium-on-charcoal catalyst (10%) and a solution of thiophene in methanol (4%). After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was added to a mixture of benzenemethanamine, potassium acetate and methanol. This mixture was hydrogenated again in the presence of palladium-on-charcoal catalyst (10%) and a solution of thiophene in methanol (4%). After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was poured into water and the whole was basified with NaOH (50%). The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was converted into the hydrochloride salt in 2-propanone by adding 2-propanol saturated with HCl. The salt was filtered off and dried, yielding (R)-3,4-dihydro-N-(phenylmethyl)-2H-1-benzopyran-2-methanamine.

A mixture of 28.0 g of (R)-3,4-dihydro-N-(phenylmethyl)-2H-1-benzopyran-2-methanamine and 300 ml of methanol was hydrogenated in the presence of 2.0 g of palladium-on-charcoal catalyst (10%). After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated, yielding 18.2 g (100%) of (-)-(R)-3,4-dihydro-2H-1-benzopyran-2-methanamine as crude residue.

A mixture of 18.0 g of (-)-(R)-3,4-dihydro-2H-1-benzopyran-2-methanamine, 60.0 g of 2-propenenitrile and 400 ml of ethanol was stirred for 4 h at reflux temperature. The reaction mixture was evaporated and the residue was dried, yielding 20.0 g (84%) of (-)-(R)-3-[[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]amino]propanenitrile.

A mixture of 20.0 g (-)-(R)-3-[[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]amino]propanenitrile and 300 ml of methanol was hydrogenated in the presence of 5.0 g of Raney Nickel. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated, yielding 21.0 g (100%) of (-)-(R)-N-[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]-1,3-propanediamine as crude residue.

A mixture of (-)-(R)-N-[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]-1,3-propanediamine, 2-chloropyrimidine, sodium carbonate and ethanol was stirred for 4 h at reflux temperature. The reaction mixture was evaporated. The residue was purified by column chromatography (silica gel; $CHCl_3/CH_3OH$ 90:10). The eluent of the desired fraction was evaporated and the residue was converted into the hydrochloride salt in 2-propanol. The salt was filtered off and dried in vacuum, yielding (-)-(R)-N-[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]-N'-(2-pyrimidinyl)-1,3-propanediamine dihydrochloride hemihydrate.

A mixture of 3.6 g of (-)-(R)-N-[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]-N'-(2-pyrimidinyl)-1,3-propanediamine dihydrochloride hemihydrate in 150 ml of methanol and 20 ml of 2-propanol saturated with HCl was hydrogenated in the presence of 1.5 g of palladium-on-charcoal catalyst (2%). After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The product was crystallized from acetonitrile, filtered off and dried, yielding 2.7 g (74.0%) of (-)-(R)-N-[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]-N'-(1,4,5,6-tetrahydro-2-pyrimidinyl)-1,3-propanediamine dihydrochloride hemihydrate; melting point 200.2°C.

The base (-)-(R)-N-[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]-N'-(1,4,5,6-tetrahydro-2-pyrimidinyl)-1,3-propanediamine may be obtained by treatment of (-)-(R)-N-[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]-N'-(1,4,5,6-tetrahydro-2-pyrimidinyl)-1,3-propanediamine dihydrochloride hemihydrate with NaOH.

References

Van Lommen G.R.E. et al.; US Patent No. 5,541,180; July 30, 1996; Assigned: Janssen Pharmaceutica N.V., Beerse, Belgium

ALONACIC

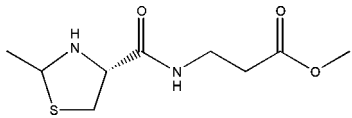
Therapeutic Function: Mucolytic

Chemical Name: N-(((2RS,4R)-2-Methyl-4-thiazolidinyl)carbonyl)-β-alanine, methyl ester

Common Name: Alonacic

Chemical Abstracts Registry No.: 105292-70-4

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Alonacic	Onbio Inc.	-	-

Raw Materials

β-Alanine methyl ester hydrochloride
N-Methylmorpholine
Dicyclohexylcarbodiimide
N-Hydroxybenzotriazole
N-t-Butoxycarbonyl-2-methylthiazolidine-4-carboxylic acid

Manufacturing Process

Preparation of (2-methylthiazolidin-4-carbonyl)-β-alanine methyl ester:

To a solution of β-alanine methyl ester hydrochloride (5.08 g, 36.4 mmol) in dimethylformamide (35 ml) kept under stirring at -5°C, N-methylmorpholine (4.01 ml, 36.4 mmol) and then a solution of N-t-butoxycarbonyl-2-methylthiazolidine-4-carboxylic acid (9 g, 36.4 mmol) in dimethylformamide (15 ml) were added. To the resulting solution kept under stirring at -5°C, dicyclohexylcarbodiimide (9 g, 43.68 mmol) and N-hydroxybenzotriazole (5.89 g, 43.68 mmol) were added. After 24 hours under stirring at +4°C, the precipitate (dicyclohexylurea) was filtered and the filtrate was evaporated to dryness. An oil was obtained which was dissolved in ethyl acetate and the solution was washed with an aqueous solution of citric acid at 10%, with an aqueous sodium bicarbonate solution at 10% and with water. The organic solution, dried on sodium sulphate was evaporated to dryness under vacuum at 40°C. (N-t-Butoxycarbonyl-2-methylthiazolidine-4-carbonyl)-β-alanine methyl ester (10.7 g) was thus obtained as oil. The obtained product (7.9 g) was treated at room temperature under nitrogen, with ethyl acetate (90 ml) containing 13% (w/v) of hydrogen chloride. After 1 hour the solution was evaporated to dryness under vacuum at 35°C.

The residue, after crystallization from isopropyl alcohol diethyl ether, afforded (2-methylthiazolidine-4-carbonyl)-β-alanine methyl ester hydrochloride (5.4 g). $[\alpha]_D^{20}$=-85° (c=1, CH_3OH); MP:=124°-125°C.

The base form may be prepared by adding of equivalent of any basic product ($NaHCO_3$, Et3N and so on).

References

Pilotto A. et al.; US Patent No. 4,761,399; Aug. 2, 1988; Assigned to Zambon S.P.A., Vicenza, Italy

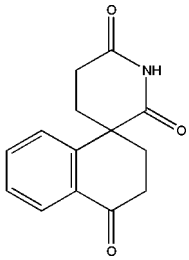
ALONIMID

Therapeutic Function: Sedative, Hypnotic

Chemical Name: Spiro[naphthalene-1(4H),3'-piperidine]-2',4,6'-trione, 2,3-dihydro-

Common Name: Alonimid

Structural Formula:



Chemical Abstracts Registry No.: 2897-83-8

Trade Name	Manufacturer	Country	Year Introduced
Alonimide	ZYF Pharm Chemical	-	-
Alomid	Merrel	-	-

Raw Materials

Phenylacetonitrile
Ethyl acrylate
Polyphosphoric acid

Manufacturing Process

To a stirred mixture of 58.6 g (0.5 M) of phenyl-acetonitrile and 150 g (1.5 M) of ethyl acrylate was carefully added sodium methoxide in small increments (about 0.1 g). The exothermic reaction was controlled by ice bath cooling to keep the reaction mixture at 50°C. When further additions of sodium methoxide were no longer exothermic, the reaction mixture was stirred for one half hour more and the excess ethyl acrylate removed under reduced pressure on a steam bath. The resulting oil was added to 1.500 g of polyphosphoric acid and stirred on a steam bath for three hours. After cooling to about 50°C, 0.5 liter of chloroform was added followed by additions of crushed ice until the aqueous phase was free flowing. The chloroform layer was separated and combined with three 150 ml chloroform extracts of the aqueous layer. The organic phase was then dried over anhydrous magnesium sulfate, filtered and concentrated to a semi-solid residue.

Recrystallization from acetone gave 2,3-dihydrospiro[naphthalene-1(4H),3'-piperidine]-2',4,6'-trione, melting point 197°-199°C.

References

Carr et al.; US Patent No. 3,647,797; March, 7, 1972; Assigned to Richardson-Merrell Inc., New York, N.Y.

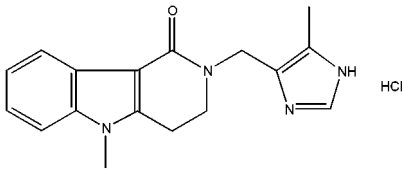
ALOSETRON HYDROCHLORIDE

Therapeutic Function: Antidiarrheal

Chemical Name: 1H-Pyrido[4,3-b]indol-1-one, 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-, monohydrochloride

Common Name: Alosetron hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 122852-69-1; 122852-42-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Alosetron hydrochloride	GlaxoSmithKline	-	-
Lotronex	GlaxoSmithKline	USA	-

Raw Materials

Thionyl chloride
Maleic acid
Sodium hydride
Polyphosphoric acid
1-(Triphenylmethyl)-1H-imidazole-4-methanol
Hydroxylamine hydrochloride
3,4-Dihydro-4-methylcyclopent[b]indol-1-(2H)-one

Manufacturing Process

4-(Chloromethyl)-1-(triphenylmethyl)-1H-imidazole.

Thionyl chloride (0.829 g) was added over 1 min to a stirred suspension of 1-(triphenylmethyl)-1H-imidazole-4-methanol (1.3 g) in a mixture of dichloromethane (50 ml) and DMF (1.0 ml) at 23°C. The solution so obtained was stirred for 15 min. and extracted with 8% sodium bicarbonate solution (80 ml). The organic phase was washed with water (50 ml), dried and evaporated to give an oil which solidified. The solid was slurried in hexane and filtered to give the title compound (1.28 g), m.p. 139-141°C.

3,4-Dihydro-4-methylcyclopent[b]indol-1(2H)-one oxime.

3,4-Dihydro-4-methylcyclopent[b]indol-1(2H)-one (1.7 g) and hydroxylamine hydrochloride (1.925 g) in pyridine were heated at 60°C for 18 h and cooled. The reaction mixture was evaporated in vacuo to a residue to which was added 8% sodium bicarbonate (150 ml). Extraction with ethyl acetate (300 ml) produced a suspension in the organic layer; this layer and associated solid was separated from the aqueous layer. The aqueous layer was re-extracted with ethyl acetate (250 ml). The combined organic extracts (and suspended solid) were evaporated to a residue, boiled with a mixture of ethanol (150 ml) and methanol (150 ml) and cooled to 50°C. The residue was adsorbed from this solution on to FCC silica and applied to an FCC column. Elution with ethyl acetate/3-10% methanol provided the title compound (1.69 g), m.p. 219-224°C (decomp.).

2,3,4,5-Tetrahydro-5-methyl-1H-pyrido[4,3-b]indol-1-one.

3,4-Dihydro-4-methylcyclopent[b]indol-1(2H)-one oxime (1.53 g), polyphosphoric acid (409 g) and dioxan (15 ml) were heated at 110-120°C for 2.2 h under nitrogen. The reaction mixture was cooled, and treated with 2 N sodium carbonate solution (1 L). The suspension was extracted with ethyl acetate (4x400 ml) and the combined extracts were dried. Evaporation gave a solid (1.43 g) which was recrystallised from ethyl acetate/cyclohexane. This solid was purified by FCC, eluting with dichloromethane:ethanol:ammonia solution (200:10:1) to give a solid (1.26 g) which was recrystallised from ethanol to provide the title compound (960 mg), m.p. 234-238°C.

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one maleate.

A mixture of 2,3,4,5-tetrahydro-5-methyl-1H-pyrido[4,3-b]indol-1-one (0.6 g) and 78% sodium hydride dispersion in mineral oil (0.109 g) in dry DMF (15 ml) was stirred under nitrogen at 50°C until hydrogen evolution ceased (ca. 1.5 h). The mixture was cooled to 40°C and a solution of 4-(chloromethyl)-5-methyl-1-(triphenylmethyl)-1H-imidazole (1.12 g) in dry THF (15 ml) was added. The reaction was then stirred at 40°C for 3 h, at 20°C for 16 h and a further portion of 4-(chloromethyl)-5-methyl-1-(triphenylmethyl)-1H-imidazole (1.12 g) in dry THF (15 ml) was added. The resulting mixture was heated at 40°C for 3 h, quenched with water (20 ml) and acetic acid (20 ml), and heated at 100°C for 2 h. The mixture was then concentrated in vacuo to ca. 60 ml, diluted with 1 M hydrochloric acid (40 ml) and washed with ethyl acetate (3x50 ml). The organic phase was discarded and the acidic aqueous phase was basified (pH=9) with potassium carbonate and extracted with ethyl acetate:ethanol (20:1; 3x100 ml). The extracts were combined, dried and evaporated to give a brown gum (ca. 1 g). This gum was adsorbed onto silica and purified by FCC eluting with dichloromethane:ethanol:ammonia solition (100:8:1) to give a pale brown solid (0.8 g); m.p. 238-240°C (decomp.). This solid was dissolved in a mixture of (hot ethanol and methanol (1:1; 100 ml) and treated with an ethanolic solution of maleic acid (3.18 g). The resulting solution was concentrated to ca. 20 ml and diluted with dry diethyl ether (ca. 8 ml) to precipitate the title compound (0.75 g) as an off-white solid melting point 160-162°C. Hydrochloride may be prepared by treating the above solid with an equivalent of an ethanolic solution of HCl.

References

Harold I.H. et al.; European Patent Office No 0 306 323 A2; 02.09.88

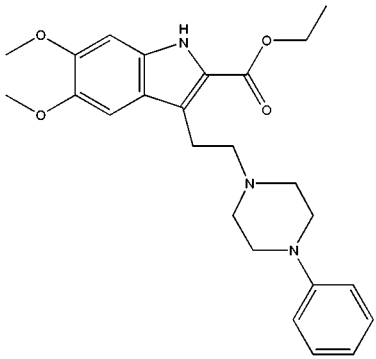
ALPERTINE

Therapeutic Function: Antipsychotic; Neuroleptic

Chemical Name: 1H-Indole-2-carboxylic acid, 5,6-dimethoxy-3-(2-(4-phenyl-1-piperazinyl)ethyl)-, ethyl ester

Common Name: Alpertine

Structural Formula:



Chemical Abstracts Registry No.: 27076-46-6

Trade Name	Manufacturer	Country	Year Introduced
Alpertine	ZYF Pharm Chemical	-	-
Win 31665	Sterling-Winthrop	-	-

Raw Materials

γ-Butyrolactone
Ethyl oxalate
3,4-Dimethoxyphenylhydrazine hydrochloride

Manufacturing Process

1-[2-(2-Carbethoxy-5,6-dimethoxy-3-indolyl)ethyl]-4-phenylpiperazine:

To a suspension of 23 g (1.0 mole) of sodium pellets in 800 ml of absolute ether was added 80 ml of a mixture of 86 g (1.0 mole) of γ-butyrolactone and 146 g (1.0 mole) of ethyl oxalate. The reaction mixture began to boil gently and was allowed to reflux spontaneously for two hours, after which time the remainder of the γ-butyrolactone and ethyl oxalate mixture was added

cautiously. When addition was complete, the mixture was refluxed for one hour, allowed to stand overnight, and the ether removed in vacuo. The residue was mixed with ice, acidified with cold, dilute sulfuric acid, extracted with ether, and the ether extracts dried over sodium sulfate and taken to dryness. Distillation of the residue in vacuo at 0.05 mm afforded 98 g of α-ethoxalyl-γ-butyrolactone, collected between 110-126°C.

Forty grams (0.215 mole) of the latter were heated under reflux in 100 ml of 2 N sulfuric acid until the evolution of carbon dioxide ceased, giving a solution of α-keto-δ-valerolactone.

3,4-Dimethoxyphenylhydrazine hydrochloride (44 g, 0.22 mole) was dissolved in 300 ml of water, treated with a solution of 12.3 g (0.22 mole) of potassium hydroxide in 50 ml of water, and cooled. To this mixture was added the above described solution of α-keto-δ-valerolactone, and the pH of the mixture was adjusted to about 2 with 10% sodium hydroxide. The mixture was warmed on a hot plate for five minutes, allowed to cool, extracted with chloroform, and the extracts dried over magnesium sulfate and concentrated to dryness giving 66 g of crude hydrazone.

The latter was dissolved in 100 ml of absolute ethanol, the mixture acidified with 400 ml of saturated ethanolic hydrogen chloride, and a stream of hydrogen chloride gas was passed through the mixture causing the temperature to rise to 80°C. The solid which separated from the reaction mixture was collected after standing overnight, and washed with cold absolute ethanol to give 38 g of crude 2-carboxy-5,6 -dimethoxy-3-(2-hydroxyethyl)indole.

The latter was suspended in 300 ml of absolute ethanol and the solution saturated with anhydrous hydrogen chloride for one hour. The mixture was allowed to stand for two hours, and the solid which separated was collected and dried to give 24 g of 2-carbethoxy-5,6-dimethoxy-3-(2-chloroethyl)indole, M.P. 179-181°C.

The latter was added to 15 ml of 1-phenylpiperazine and the mixture heated at 140-160°C for one hour and twenty minutes. The cooled mixture was triturated with 100 ml of ether, filtered, and the ether filtrate concentrated to dryness. The residue was mixed with water and acetic acid, the pH adjusted to about 5.0, and the insoluble material was collected by filtration giving 5 g of crude product which was recrystallized from methanol to give 2.2 g of 1-[2-(2-carbethoxy-5,6-dimethoxy-3-indolyl)ethyl]-4-phenylpiperazine, M.P. 142.5-144.0°C.

References

Archer S.; US Patent No. 3,562,278; Feb. 9, 1971; Assigned to Sterling Drug Inc., New York, N.Y., a corporation of Delawere

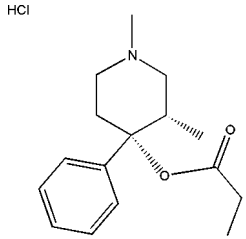
ALPHAPRODINE HYDROCHLORIDE

Therapeutic Function: Narcotic analgesic

Chemical Name: cis-1,3-Dimethyl-4-phenyl-4-piperidinolpropanoate hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 77-20-3 (Base); 49638-24-6 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Nisentil	Roche	US	1949

Raw Materials

Lithium
Bromobenzene
Hydrogen chloride
1,3-Dimethyl-4-piperidone
Propionic anhydride

Manufacturing Process

In a round-bottom flask provided with stirrer, dropping funnel, condenser and a gas outlet for keeping the system under nitrogen, 200 cc of dry ether is placed and 4.6 grams of lithium cut into thin strips is added. 52 grams of bromobenzene in 50 cc of dry ether are added dropwise and after addition, the mixture is refluxed for 2 hours. This procedure results in the formation of phenyl-lithium. Other aryl-lithium compounds can be prepared in a similar manner by reacting lithium metal or a lithium compound capable of transferring lithium and a compound having an exchangeable halogen group as, for example, bromonaphthalene.

The solution of phenyl-lithium is cooled to -20°C and to this a solution of 12.7 grams of 1,3-dimethyl-4-piperidone, prepared according to the method of Howton, J. Org. Chem. 10, 277 (1945), in ether is added dropwise with stirring. After the addition, the stirring is continued for a further 2 hours at -20°C. The lithium complex, 1,3-dimethyl-4-phenyl-4-oxylithium piperidine, which forms is soluble in the ether and can be recovered there from. To prepare the piperidinol, the lithium complex, while in the reaction mixture is decomposed by the addition of an ice and hydrochloric acid mixture. The acidified layer is separated, basified and extracted with ether. After drying the ether solution and removing the solvent, the residue on distillation in vacuum distills chiefly at 155°C/10 mm, yielding the product, 1,3-dimethyl-4-phenyl-4-hydroxypiperidine, which, on crystallization from n-hexane melts at 102°C. On treatment with propionic anhydride catalyzed with a trace of sulfuric acid,

1,3-dimethyl-4-propionoxy-4-phenylpiperidine is attained. The latter compound can be converted into the hydrochloride salt by reaction with hydrogen chloride. This salt after crystallization from acetone has a melting point of 209°C.

References

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Kleeman and Engel p. 29
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OCDS Vol. 1 pp. 304 and 2328 (1977)
I.N. p.60
REM p. 1107
Lee, J. and Ziering, A.; US Patent 2,498,433; February 21, 1950; Assigned to Hoffmann-La Roche Inc.

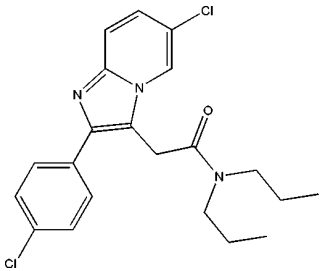
ALPIDEM

Therapeutic Function: Anxiolytic

Chemical Name: Imidazo[1,2-a]pyridine-3-acetamide, 6-chloro-2-(4-chlorophenyl)-N,N-dipropyl-

Common Name: Ananxil

Structural Formula:



Chemical Abstracts Registry No.: 82626-01-5

Trade Name	Manufacturer	Country	Year Introduced
Ananxil	Synthelabo	-	-

Raw Materials

Formic acid
6-Chloro-2-(4-chlorophenyl)imidazo[1,2-a]pyridine-3-acetonitrile
Hydrogen chloride
Ammonia
Potassium hydroxide
Acetic acid

Manufacturing Process

Two methods of synthesis of 6-chloro-2-(4-chlorophenyl)imidazo[1,2-a]-pyridine-3-N,N-dimethylacetamide:

1. 22 g (0.0788 mol) of 6-chloro-2-(4-chlorophenyl)imidazo[1,2-a]pyridine-3-acetonitrile are added to 85 ml of 99% formic acid and the solution is treated with a stream of dry hydrogen chloride for 3 to 4 hours. When all the nitrile has been converted, the solution is heated slightly to degas it, and the cooled solution is then poured into 1 liter of water; the mixture is stirred for 10 min and then rendered alkaline with 200 ml of concentrated ammonia solution. The solid is filtered off, washed copiously with water and dried under a waterpump vacuum. The 6-chloro-2-(4-chlorophenyl)imidazo[1,2-a]pyridine-3-acetamide is recrystallised from ethanol. Melting point = 285-287°C.

2. 19.2 g of 6-chloro-2-(4-chlorophenyl)imidazo[1,2-a]pyridine-3-acetamide and 19 g of KOH are added successively to 550 ml of 75% ethanol. The suspension is heated at the reflux temperature for 10-16 hours. When the reaction has ended, the solution is concentrated in vacuo and the residue is dissolved in ½ liter of water. The small amount of insoluble material is filtered off and the filtrate is treated with 50 ml of acetic acid. The expected acid precipitates and it is filtered off and roughly dried. The crude product is taken up in 500 ml of acetone and the 6-chloro-2-(4-chlorophenyl)imidazo[1,2-a]pyridine-3-acetic acid is filtered off hot. Melting point=258-260°C.

References

Kaplan J.-P., George Pascal; US Patent No. 4,460,592; July 17, 1984; Assigned to Synthelabo

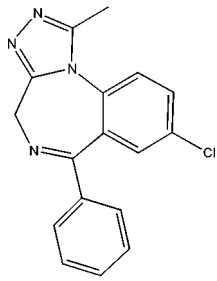
ALPRAZOLAM

Therapeutic Function: Tranquilizer

Chemical Name: 8-Chloro-1-methyl-6-phenyl-4H-s-triazolo[4,3-a][1,4] benzodiazepine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 28981-97-7

Trade Name	Manufacturer	Country	Year Introduced
Xanax	Upjohn	US	1981
Xanax	Upjohn	Switz.	1982
Xanax	Upjohn	UK	1983
Xanax	Upjohn	Australia	1983

Raw Materials

2,6-Dichloro-4-phenylquinoline
Hydrazine hydrate
Triethyl orthoacetate
Sodium periodate
Paraformaldehyde
Phosphorus tribromide
Ammonia

Manufacturing Process

6-Chloro-2-hydrazino-4-phenylquinoline: A stirred mixture of 2,6-dichloro-4-phenylquinoline (2.7 g, 0.01 mol) and hydrazine hydrate (6.8 g) was refluxed under nitrogen for 1 hour and concentrated in vacuum. The residue was suspended in warm water, and the solid was collected by filtration, dried and recrystallized from ethyl acetate-Skelly B hexanes to give 1.81 g (67% yield) of 6-chloro-2-hydrazino-4-phenylquinoline of melting point 156.5-157°C.

7-Chloro-1-methyl-5-phenyl-s-trizolo[4,3-a]quinoline: A stirred mixture of 6-chloro-2-hydrazino-4-phenylquinoline (1.4 g, 0.0052 mol), triethyl-orthoacetate (0.925 g, 0.0057 mol) and xylene (100 ml) was refluxed, under nitrogen, for 2 hours 40 minutes. During this period the ethanol formed in the reaction was removed by distillation through a short, glass helix-packed column. The mixture was concentrated to dryness in vacuum and the residue was crystallized from methanol-ethyl acetate to give: 1.28 g of 7-chloro-1-methyl-5-phenyl-s-triazolo[4,3-a]quinoline (83.9% yield). The analytical sample was crystallized from methylene chloride:methanol and had a melting point 252.5-253.5°C.

5-Chloro-2-(3-methyl-4H-1,2,4-triazol-4-yl)benzophenone (Oxidation of 7-chloro-1-methyl-5-phenyl-s-trizolo[4,3-a]quinoline): A stirred suspension of 7-chloro-1-methyl-5-phenyl-s-triazolo[4,3-a] quinoline (2,94 g, 0.01 mol) in acetone (110 ml) was cooled in an ice-bath and treated slowly with a solution prepared by adding sodium periodate (2 g) to a stirred suspension of ruthenium dioxide (200 mg) in water (35 ml). The mixture became dark. Additional sodium periodate (8 g) was added during the next 15 minutes. The ice-bath was removed and the mixture was stirred for 45 minutes. Additional sodium periodate (4 g) was added and the mixture was stirred at ambient temperature for 18 hours and filtered. The solid was washed with acetone and the combined filtrate was concentrated in vacuum. The residue was suspended in water and extracted with methylene chloride. The extract was dried over anhydrous potassium carbonate and concentrated. The residue was chromatographed on silica gel (100 g) with 10% methanol and 90% ethyl acetate; 50 ml fractions were collected. The product was eluted in fractions 10-20 and was crystallized from ethyl acetate to give: 0.405 g of melting

point 168-169.5°C and 0.291 g of melting point 167.5-169°C (23.4% yield) of 5-chloro-2-(3-methyl-4H-1,2,4-triazol-4-yl)benzophenone. The analytical sample had a melting point of 168°C.

5-Chloro-2-[3-(hydroxymethyl)-5-methyl-4H-1,2,4-triazol-4-yl]benzophenone: A stirred mixture of 5-chloro-2-(3-methyl-4H-1,2,4-triazolo-4-yl)benzophenone, (2.98 g, 0.01 mol) paraformaldehyde (3 g) and xylene (100 ml) was warmed under nitrogen, in a bath maintained at 125°C for 7 hours. The mixture was then concentrated in vacuum. The residue was chromatographed on silica gel (150 g) with 3% methanol-97% chloroform. Fifty ml fractions were collected. The product was eluted in fractions 20-44. The fractions were concentrated and the residue was crystallized from ethanol-ethyl acetate to give: 1.64 g of melting point 138-142°C; 0.316 g of melting point 138.5-141°C; 0.431 g of melting point 139-141°C (72.8% yield) of 5-chloro-2-[3-(hydroxymethyl)-5-methyl-4H-1,2,4-triazol-4-yl]benzophenone. The analytical sample had a melting point of 138-139°C.

5-Chloro-2-[3-(bromomethyl)-5-methyl-4H-1,2,4-triazol-4-yl]-benzophenone: A solution of 5-chloro-2-[3-(hydroxymethyl)-5-methyl-4H-1,2,4-triazol-4-yl]-benzophenone (328 mg, 0.001 mol) in dry, hydrocarbon-stabilized chloroform (5 ml) was cooled in an ice-bath and treated with phosphorus tribromide (0.1 ml). The colorless solution was kept in the ice-bath for 55 minutes, at ambient temperature (22-24°C), for 5 hours. The resulting yellow solution was poured into a mixture of ice and dilute sodium bicarbonate. This mixture was extracted with chloroform. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was crystallized from methylene chloride-ethyl acetate to give: 0.285 g of melting point 200-240°C (decomposition) and 0.030 g of melting point 200-220°C (decomposition) of 5-chloro-2-[3-(bromomethyl)-5-methyl-4H-1,2,4-triazol-4-yl]benzophenone. The analytical sample had a melting point of 200-240°C.

8-Chloro-1-methyl-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine: A stirred suspension of 5-chloro-2-[3-(bromomethyl)-5-methyl-4H-1,2,4-triazol-4-yl]-benzophenone (391 mg, 0.001 mol) in tetrahydrofuran (15 ml) was cooled in an ice-bath and treated with a saturated solution of ammonia in methanol (12.5 ml). The resulting solution was allowed to warm to ambient temperature and stand for 24 hours. It was then concentrated in vacuum. The residue was suspended in water, treated with a little sodium bicarbonate and extracted with methylene chloride. The extract was washed with brine, dried with anhydrous potassium carbonate and concentrated. The residue was crystallized from methylene chloride-ethyl acetate to give 0.220 g of crude product of melting point 227-228.5°C. Recrystallization of this material from ethyl acetate gave 0.142 g of melting point 228-229.5°C of 8-chloro-1-methyl-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine.

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Hester, J.B., Jr.; US Patent 3,781,289; December 25, 1973; Assigned to The Upjohn Company
Hester, J.B., Jr.; US Patent 3,709,898; January 9, 1973; Assigned to The Upjohn Company

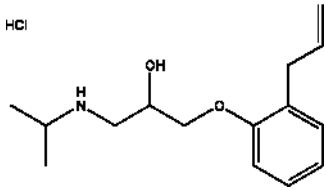
ALPRENOLOL HYDROCHLORIDE

Therapeutic Function: Beta-adrenergic blocker

Chemical Name: 1-[(1-Methylethyl)amino]-3-[2-(2-propenyl)phenoxy]-2-propanol hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 13655-52-2 (Base); 13707-88-5 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Aptol	Globopharm	Switz.	-
Aptin	Astra France	W. Germany	1967
Aptine	Lematte/Boinot	France	1971
Aprobal	Fujisawa	Japan	1971
Aptin	Byk Gulden	Italy	1972
Apllobal	Hassle	Sweden	-
Aptina	Made	Spain	-
Aptol-Duriles	Astra	-	-
Betacard	Beecham	UK	-
Elperl	Sawai	Japan	-
Gubernal	Geigy	France	-
Regletin	Teikoku	Japan	-
Sinalol	Kaken	Japan	-
Yobir	Maruko	Japan	-

Raw Materials

Ammonia
Hydrogen chloride
Acetone
o-Allyl epoxy propoxy benzene
Sodium borohydride

Manufacturing Process

A solution of 24.6 g of o-allyl-epoxypropoxybenzene dissolved in 250 ml of absolute ethanol saturated with ammonia was placed in an autoclave and heated on a steam-bath for 2 hours. The alcohol was then removed by distillation and the residue was redissolved in a mixture of methanol and ethylacetate. Hydrogen chloride gas was introduced into the solution. The hydrochloride salt was then precipitated by the addition of ether to yield 11.4 g of product. Five grams of the amine-hydrochloride thus formed were dissolved in 50 ml of methanol and 9 ml of acetone. The resulting solution was cooled to about 0°C. At this temperature 5 g of sodium borohydride were added over a period of 1 hour. Another 2.2 ml of acetone and 0.8 g of sodium borohydride were added and the solution was kept at room temperature for 1 hour, after which 150 ml of water were added to the solution. The solution was then extracted with three 100-ml portions of ether which were combined, dried over potassium carbonate, and evaporated. The free base was then recrystallized from petrol ether (boiling range 40-60°C) to yield 2.7 g of material having a melting point of 57°C.

The corresponding hydrochloride was prepared by dissolving 2 g of the product, prepared above, in 20 ml of acetone, and adding to the resulting solution acetone saturated with hydrogen chloride until the pH was reduced to about 3. The precipitated hydrochloride salt was then recrystallized from acetone.

References

Merck Index 304
Kleeman and Engel p. 31
OCDS Vol. 1 p. 177 (1977)
DOT 9 (6) 245 (1973)
I.N. p. 60
Brandstrom, A.E., Corrodi, H.R. and Alblad, H.R.G.; US Patent 3,466,376; September 9, 1969; Assigned to Aktiebolaget Hassie

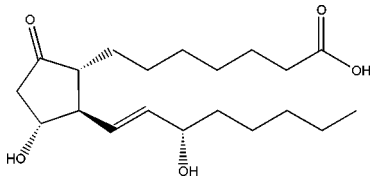
ALPROSTADIL

Therapeutic Function: Vasodilator, Abortifacient, Antihypertensive, Bronchodilator

Chemical Name: Prost-13-en-1-oic acid, 11,15-dihydroxy-9-oxo-, (11α,13E,15S)-

Common Name: Alprostadil; Prostaglandin E_1

Structural Formula:



Chemical Abstracts Registry No.: 745-65-3

Trade Name	Manufacturer	Country	Year Introduced
Alprostadil	Schwarz Pharmacia	-	-
Alprostapint	BAG	Germany	-
Alprostan	Leciva	Czech Republic	-
Alpostin	Samarth Pharma Pvt. Ltd.	India	-
Alprox-TD	NexMed, Inc.	-	-
Befar	Nexmed Pharmaceutical	USA	-
Bondil	Meda	-	-
Caverject	Pharmacia and Upjohn	Belgium	-
Muse	Meda	UK	-
Prostin VR	Pharmacia India (P) Ltd.	India	-
Topiglan	MacroChem Copr.	-	-
Vazaprostan	Schwarz Pharma	Germany	-

Raw Materials

3α,6,7,7α-Tetrahydro-4-methyl-2-oxo-1β-indaheptanoic acid methyl ester
4-Toluenesulfonic acid monohydrate
Ethylene glycol
Sodium hydride
Sodium periodate
Trifluoroperacetic acid
Etheral diazomethane
Sodium methoxide
Osmium tetroxide
Potassium t-butoxide

Manufacturing Process

Manufacturing process for prostaglandin E_1 includes 15 steps.

1. A mixture of 11.8 g of (+/-)-3α,6,7,7α-tetrahydro-4-methyl-2-oxo-1β-indaheptanoic acid methyl ester, 27 ml of ethylene glycol and 300 mg of p-toluene sulfonic acid mono-hydrate in 600 ml of benzene was refluxed with stirring for 18 hours using a Dean-Stark trap to separate the water formed in the reaction. The reaction mixture was cooled and added to 300 ml of cold 5% potassium bicarbonate. The aqueous layer extracted twice with 2:1 benzene-hexene. The combined organic fractions were washed 3 times with saturated aqueous NaCl, dried over sodium sulfate and evaporated to dryness

affording 12.6 g of (+/-)-3α,6,7,7α-tetrahydro-4-methyl-2-oxo-1β-indaheptanoic acid methyl ester, 2-cyclic ethylene acetal.

2. To 5.69 g of this acetal in 410 ml of t-butanol and 11 ml of water was added a mixture of 5.80 g of potassium carbonate, 22,8 g of sodium periodate, and 270 mg of potassium permanganate in 1230 ml of water. The reaction mixture was stirred at 20-25°C for 20 hours and concentrated in vacuo to remove t-butanol. Ethylene glycole (0.5 ml) was added and reaction mixture extracted with 1:1 ether-benzene to remove neutral material. The aqueous layer acidified with solid sodium dihydrogen phosphate and extracted 4 times with 1:1 ethyl acetate-benzene. The organic layer was dried over sodium sulfate and evaporated to dryness in vacuo affording (+/-)-3-acetyl-2α-(2-carboxyethyl)-5-oxo-1β-cyclopentaneheptanoic acid methyl ester, 5-cyclic ethylene acetal as a mixture of the 3α and 3β isomers.

3. (+/-)-3β-Acetyl-2α-(2-methoxycarbonylethyl)-5-oxo-1β-cyclopentaneheptanoic acid methyl ester, 5-cyclic ethylene acetal, NMR ($CDCl_3$) δ 2.13 [3H - CH_3CO], was prepared from above (+/-)-3-acetyl-2α-(2-carboxyethyl)-5oxo-1β-cyclopentaneheptanoic acid methyl ester, 5-cyclic ethylene acetal with etheral diazomethane and subsequent stirring with sodium methoxide in methanol for 18 hours at room temperature.

4. (+/-)-3β-Acetoxy-2α-(2-methoxycarbonylethyl)-5-oxo-1β-cyclopentaneheptanoic acid methyl ester, 5-cyclic ethylene acetal was produced by stirring the solution of 4.5 g of (+/-)-3β-acetyl-2α-(2-methoxycarbonylethyl)-5-oxo-1β-cyclopentaneheptanoic acid methyl ester, 5-cyclic ethylene acetal in 25 ml methylene chloride, containing 60 g of solid disodium monohydrogen phosphate, with 85 ml freshly prepared 0.3 M trifluoroperacetic acid in methylene chloride for 42 hours at room temperature. The reaction mixture was filtered, the precipitate washed with methylene chloride and the organic extract was washed with cold aqueous potassium iodide and cold thiosulfate. Organic layer was washed with potassium bicarbonate, dried over sodium sulfate and evaporated in vacuo.

5. The reaction 4.25 g of (+/-)-3β-acetoxy-2α-(2-methoxycarbonylethyl)-5-oxo-1β-cyclopentaneheptanoic acid methyl ester, 5-cyclic ethylene acetal in 25 ml of methanol with 6 ml of 1.00 N sodium methoxide under nitrogen at room temperature for 2 hours produced pure (+/-)-2α-(2-methoxycarbonylethyl)-3β-hydroxy-5-oxo-1β-cyclopentaneheptanoic acid methyl ester, 5-cyclic ethylene acetal after chromatographical purification with silica gel (eluent 25% acetone in chloroform).

6. (+/-)-2α-(2-Carboxyethyl)-3β-hydroxy-5-oxo-1β-cyclopentaneheptanoic acid methyl ester δ-lactone, 5-cyclic ethylene acetal was prepared as follows: 1.66 g of (+/-)-2α-(2-methoxycarbonylethyl)-3β-hydroxy-5-oxo-1β-cyclopentaneheptanoic acid methyl ester, 5-cyclic ethylene acetal in 350 ml of benzene was refluxed with 0.25 ml of 0.66 M potassium t-butoxide in butanol and 140 ml of benzene in a nitrogen atmosphere for 4 hours. Above lacton was produced after washing of organic fraction with of saturated aqueous solutions of sodium dihydrogen phosphate and NaCl and evaporating in vacuo to dryness.

7. 210 mg of 50% sodium hydride was added to a stirred solution above δ-lactone under nitrogen at 0°C. The mixture was stirred for 1 hour at 0°C and

4 hours at 20°C. The solvent was removed in vacuo and residue washed with ether and filtered. The residue was recrystallized from ether-hexane affording (+/-)-2α-(2-carboxy-2-formylethyl)-3β-hydroxy-5-oxo-1β-cyclopentaneheptanoic acid methyl ester δ-lactone, 5-cyclic ethylene acetal, m.p. 88-90°C.

8. A solution of 460 mg of (+/-)-2α-(2-carboxy-2-formylethyl)-3β-hydroxy-5-oxo-1β-cyclopentaneheptanoic acid methyl ester δ-lactone, 5-cyclic ethylene acetal in 6 ml of methylene chloride and 4.4 ml of pyridine was treated with a 5% ozone-oxygen mixture at - 70°C until the mixture had persistent pale blue color. The excess of ozone was evaporated by bubbling nitrogen into reaction and the solvents were removed in vacuo. The residue was tirturaed with ether affording crystalline (+/-)-2α-(2-carboxy-2-oxoethyl)-3β-hydroxy-5-oxo-1β-cyclopentaneheptanoic acid methyl ester δ-lactone, 5-cyclic ethylene acetal, m.p. 114-116°C.

9. The product of ozonolysis was acetylated in 6 ml of pyridine and 3 ml acetic anhydride at room temperature for 17 hours, 6 ml xylene was added and the reaction mixture evaporated in vacuo. The residue was triturated with ether-hexane affording crystalline (+/-)-2α-(2-acetoxy-2-carboxyvinyl)-3β-hydroxy-5-oxo-1β-cyclopentaneheptanoic acid methyl ester δ-lactone, 5-cyclic ethylene acetal, m.p. 82-84°C.

10. 14 mg of osmium tetroxide in 1.4 ml methanol was added to a stirred solution of δ-lactone (step 9) in 16 ml of methanol. The reaction mixture darkened in 10-15 minutes and 440 mg of sodium periodate was added portionwise over 3 hours. The mixture was stirred 1 additional hours and filtered, filtrate evaporated to dryness in vacuo. The residue was dissolved in 2.5 ml of 1:1 ethyl acetate - benzene and the solution washed in usual way, dried over sodium sulfate and evaporated according (+/-)-2α-formyl-3β-[(methoxyalyl)oxy]-5-oxo-1β-cyclopentaneheptanoic acid methyl ester δ-lactone, 5-cyclic ethylene acetal as an oil.

11. 230 mg of dimethyl-2-oxoheptyl phosphonate in 4 ml of tetrahydofuran was stirred with 50 mg of 50% sodium hydride in 10 ml tetrahydrofuran under a nitrogen at 0°C for 30 minutes. A solution of 420 mg of (+/-)-2α-formyl-3β-[(methoxyalyl)oxy]-5-oxo-1β-cyclopentaneheptanoic acid methyl ester δ-lactone, 5-cyclic ethylene acetal in 4 ml of tetrahydrofuran was added dropwise over 5 min. After 10 min the mixture was allowed to warm to room temperature and stirred 2 hours. The reaction mixture was added to saturated aqueous dihydrogen phosphate at 10°C and extracted with ethyl acetate. After usual washing and drying procedure, extract was evaporated to dryness affording (+/-)-3β-[(methoxyalyl)oxy]-2α-(3-oxo-1-octenyl)-5-oxo-1β-cyclopentaneheptanoic acid methyl ester, 5-cyclic ethylene acetal.

12. The above product was dissolved in 7.5 ml of methanol and 60 mg of ethylenediamine in 5 ml of methanol was added dropwise at 0°C and the mixture stirred for 45 min at 20°C. And the solvent evaporated in vacuo. The residue was chromatographed on 35 g silica gel eluting with 30% acetone and chloroform taking 40 fractions of 4 ml each. Fraction 5-14 was evaporated to dryness in vacuo affording 250 mg (+/-)-3β-hydroxy-2α-(3-oxo-1-octenyl)-5-oxo-1β-cyclopentaneheptanoic acid methyl ester, 5-cyclic ethylene acetal, λ_{max} (methanol, 232 nm, E 12500).

13. Prostaglandin E_1, methyl ester, cyclic ethylene acetal was prepared from 245 mg of (+/-)-3β-hydroxy-2α-(3-oxo-1-octenyl)-5-oxo-1β-cyclopentaneheptanoic acid methyl ester, 5-cyclic ethylene acetal, in 6 ml of methanol by stirring with 23 mg of sodium borohydride in 2 ml of methanol at -10°C for 40 min. After usual washing and evaporating to dryness the residue was chromatographed on 20 g of silica gel eluting with 50% acetone-chloroform. (+/-)-3β-hydroxy-2α-(3β[R]-hydroxy-1-octenyl)-5-oxo-1β-cyclopentaneheptanoic acid methyl ester, 5-cyclic ethylene acetal and (+/-)-3β-hydroxy-2α-(3β[S]-hydroxy-1-octenyl)-5-oxo-1β-cyclopentaneheptanoic acid methyl ester, 5-cyclic ethylene acetal, m.p. 54-56°C were afforded.

14. 40 mg of (+/-)-3β-hydroxy-2α-(3β[S]-hydroxy-1-octenyl)-5-oxo-1β-cyclopentaneheptanoic acid methyl ester, 5-cyclic ethylene acetal in 1 ml was saponificated with a solution of 45 mg of KOH in 2.5 ml of water at 0°C in nitrogen atmosphere. The mixture was allowed to warm to room temperature and stirred for 3 hours. After usual procedures of evaporating, extracting, washing, drying and evaporating, (+/-)-prostaglandin E_1, (+/-)-3β-hydroxy-2α-(3β[S]-hydroxy-1-octenyl)-5-oxo-1β-oxocyclopentaneheptanoic acid, 5-cyclic ethylene acetal, m.p. 82-84°C, was afforded.

15. A mixture of 37 mg of (+/-)-prostaglandin E_1 and 3 ml 1:1 acetic acid-water was stirred at 25°C for 3 hours. Saturated aqueous Na_2HPO_4 solution was added and the mixture extracted with 1:1 ethyl acetate-benzene. The organic layer was washed, evaporated to dryness affording the crystalline residue (+/-)-prostaglandin E_1, m.p. 111-113°C (recrystallized from ethyl acetate-benzene).

References

Wendler N.L. et al.; US Patent No. 3,870,747; Mar. 11, 1975; Assigned: Merck and Co., Inc., Rahway, N.J.

Nelson N.A.; US Patent No. 3,933,897; Jan. 20, 1976; Assigned: The Upjohn Company (Kalamazoo, MI)

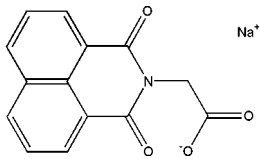
ALRESTATIN SODIUM

Therapeutic Function: Aldose reductase inhibitor

Chemical Name: 1H-Benz[de]isoquinoline-2(3H)-acetic acid, 1,3-dioxo-, sodium salt

Common Name: Alrestatin sodium

Structural Formula:



Chemical Abstracts Registry No.: 51876-97-2; 51411-04-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Alrestatin	BIOMOL	-	-

Raw Materials

1,8-Naphthalic acid anhydride
Glycine

Manufacturing Process

1,3-Dioxo-1H-benz[de]isoquinoline-2(3H)-acetic acid:

1,8-Naphthalic acid anhydride (110 g, 0.556 mole), glycine (48 g, 0.64 mole) and dimethylformamide (750 ml) are heated and stirred at reflux for 2 hr. The homogeneous dark solution is cooled to about 100°C and 750 ml of hot water is added slowly to the stirred solution. The reaction mixture is cooled and allowed to stand in a refrigerator for 16 hr. The precipitate is collected and recrystallized from ethanol, using decolorizing charcoal, to give the title compound, MP: 271°-272°C.

In practice it is usually used as sodium salt.

References

Sestanj K. et al.; US Patent No. 3,821,383; June 28, 1974; Assigned to A. Mc and Harrison Limited, Larent, Quebec, Canada

ALSACTIDE

Therapeutic Function: Adrenocorticotropin

Chemical Name: $\alpha^{1\text{-}17}$-Corticotropin, 1-β-alanine-17-(N-(4-aminobutyl)-L-lysinamide)-

Common Name: Alisactide ;Alsactide

Chemical Abstracts Registry No.: 34765-96-3

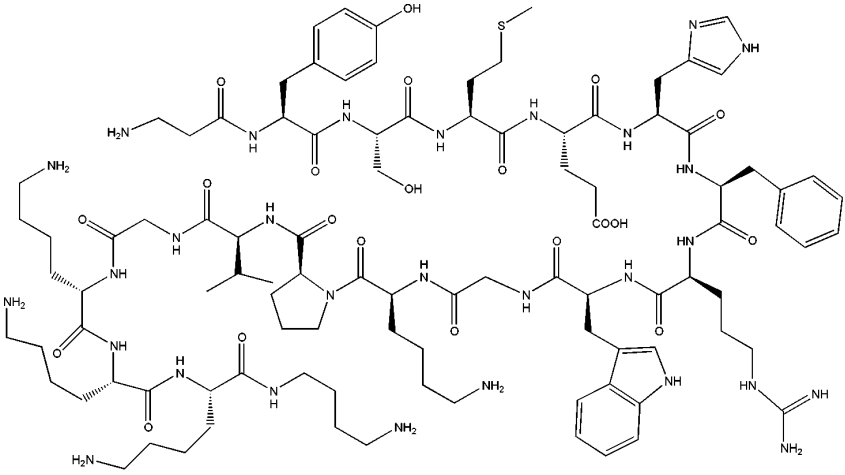
Trade Name	Manufacturer	Country	Year Introduced
Alsactide	ZYF Pharm Chemical	-	-

Raw Materials

Z-Lys(Boc) OTCP
Triethylamine
Palladium
N-Ethylmorpholine
Z-Lys(Boc)-NH-$(CH_2)_4$-NH-Boc
4-Toluenesulfonic acid
Z-Lys(Boc)-Pro-Val-Gly-Lys(Boc)-OH
1-Hydroxybenzotriazole

Trifluoroacetic acid
Dicyclohexylcarbodiimide
Thioglycolic acid
Boc-β-Ala-Tyr-Ser-Met-Glu-(OBut)-His-Phe-Arg-Trp-Gly-OH·4H_2O

Structural Formula:



Manufacturing Process

Abbreviations:

Boc - tert-butoxycarbonyl; TCP - 2,4,5-trichlorophenyl; Z - carbobenzyloxy.

(a) β-Ala-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-Gly-Lys-Lys-Lys-NH-$(CH_2)_4$-NH_2-acetate, aq.

Z-Lys(Boc)-NH-$(CH_2)_4$-NH-Boc: 7.0 g (31 mmols) of Boc-NH-$(CH_2)_4$-NH_2-HCl and 4.2 ml (30 mmols) of triethylamine in 100 ml of dimethylformamide are stirred for 20 hours together with 16.8 g (30 mmols) of Z-Lys(Boc) OTCP. The product is filtered off the triethylammonium chloride and the filtrate is evaporated to dryness in vacuo. The residue is dissolved in ethyl acetate, thoroughly shaken at 0°C with 2 N citric acid, 1 N bicarbonate and H_2O and dried over sodium sulfate. After distilling off the solvents, the residue is recrystallized two times from isopropanol/ether. Yield: 14.1 g (83%), M.P. 83°-85°C.

(b) H-Lys(Boc)-NH-$(CH_2)_4$-NH-Boc-tosylate: 11.4 g of the Z-compound prepared according to (a) are hydrogenated in the presence of Pd in 80 ml of methanol with, while adding methanolic toluene-sulfonic acid at pH 5. After the reaction is complete, the product is filtered to remove the catalyst, the methanol is distilled off in vacuo and the residue is triturated with ether. For purification purposes it is dissolved in warm isopropanol and precipitated with ether. Yield: 10.3 g (88%).

(c) Z-Lys(Boc)-Pro-Val-Gly-Lys(Boc)-Lys(Boc)-Lys(Boc)-NH-$(CH_2)_4$-NH-Boc: 10.9 g (10 mmols) of Z-Lys(Boc)-Pro-Val-Gly-Lys(Boc)-OH and 5.89 g (10 mmols) of Boc-NH-$(CH_2)_4$-NH_2-tosylate in 100 ml of dimethylformamide are combined with 12.8 ml (10 mmols) of N-ethylmorpholine and 2.7 g (20 mmols) of 1-hydroxybenzotriazole. 2.2 g of dicyclohexylcarbodiimide (11 mmols) are added at -10°C. The whole is then allowed to come to room temperature. The stirring is continued for 3 hours, the solvent is distilled off in vacuo. The residue is digested with 1 N bicarbonate and water and, after drying, recrystallized from acetonitrile. Yield: 10.6 g (74.2%). M.P. 150°-155°C (while foaming). $[\alpha]_D^{20}$: -24.0° (c=1 in dimethylformamide).

(d) H-Lys(Boc)-Pro-Val-Gly-Lys(Boc)-Lys(Boc)-Lys(Boc)-NH-$(CH_2)_4$-NH-Boc-tosylate-dihydrate: 15.1 g (10 mmols) of the Z-compound prepared according to (c) are catalytically hydrogenated in the presence of Pd in 300 ml of methanol, a pH of 5 being maintained by simultaneously adding methanolic toluene-sulfonic acid. After complete reaction, the methanol is distilled off and the residue is reprecipitated from pyridine/ ether and methanol/water. The oil, which first precipitates becomes solid after a short time. Yield: 12.1 g (77.5%).

(e) 1.65 g (1.1 mmols) of Boc-β-Ala-Tyr-Ser-Met-Glu-(OBut)-His-Phe-Arg-Trp-Gly-OH·$4H_2O$ and 1.56 g (1 mmol) of H-Lys(Boc)-Pro-Val-Gly-Lys(Boc)-Lys-(Boc)-Lys(Boc)-NH-$(CH_2)_4$-NH-Boc-tosylate-dihydrate are dissolved together with 540 mg (4 mmols) of 1-hydroxybenzotriazole in 30 ml of dimethylformamide. A solution of 1.25 g (6 mmols) of dicyclohexylcarbodiimide in 4 ml of dimethylformamide is prepared and 1/3 of this solution is added to the above solution. The whole is stirred for 1 hour, then another third is added and, after a further hour, the last third is fed in. After a further 2 to 3 hours of stirring, the reaction product is precipitated with ether. Yield: 3.1 g.

Without further purification, the compound is freed from the protective groups by standing for 1 hour in 80-90% trifluoroacetic acid containing some thioglycolic acid, and is subsequently precipitated by adding 150 ml of ether. Yield: 3.06 g of crude peptide-trifluoroacetate. After purification on carboxymethyl cellulose, 1.45 g of the chromatographically pure peptide are obtained in the form of acetate. $[\alpha]_D^{20}$:-68.6°-2° (c=0.5 in 1% acetic acid). Amino acid analysis:

$Ser_{0.86}Glu_{0.99}Pro_{0.97}Gly_{2.00}Val_{1.03}Met_{0.98}Tyr_{0.02}Phe_{1.00}\beta Ala_{1.01}Lys_{4.00}His_{1.02}Arg_{0.94}$.

References

Geiger R. et al.; US Patent No. 3,749,709; July 31, 1973; Assigned to Farbwerke Hoechst Aktiengesellschaft vormals Meister Lucius and Bruning, Frankfurt am, Main, Germany

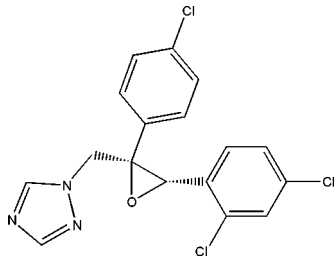
ALTECONAZOLE

Therapeutic Function: Antifungal

Chemical Name: (cis)-1-[[2-(4-Chlorophenyl)-3-(2,4-dichlorophenyl)oxiranyl] methyl]-1H-1,2,4-triazole

Common Name: Alteconazole

Structural Formula:



Chemical Abstracts Registry No.: 93479-96-0

Trade Name	Manufacturer	Country	Year Introduced
Alteconazole	Onbio Inc.	-	-

Raw Materials

Potassium t-butylate	2,4-Dichlorobenzyltriphenylphosphonium chloride
4-Chloroacetophenone	N-Bromosuccinimide
2,2'-Azoisobutyrodinitrile	3-Choroperoxybenzoic acid
1,2,4-Triazole	Sodium hydride

Manufacturing Process

63.6 g of potassium t-butylate in 300 ml of dry methanol were introduced into a solution of 229 g of 2,4-dichlorobenzyltriphenylphosphonium chloride in 800 ml of dry methanol at 10°C, and 77.2 g of 4-chloroacetophenone were added after half an hour. The reaction solution was refluxed for 3 hours, the precipitated salt was filtered off at room temperature, the filtrate was evaporated down under reduced pressure, the residue was digested with petroleum ether at from 50°C to 70°C to free it from triphenylphosphine oxide, and the solution was evaporated down under reduced pressure.

The residue was taken up in 1 liter of carbon tetrachloride, and the solution was refluxed with 81.7 g of N-bromosuccinimide and 4 g of 2,2'-azoisobutyrodinitrile. After the reaction was complete, the succinimide was filtered off, the filtrate was evaporated down under reduced pressure and the residue was recrystallized from methanol. 73.4 g (38.8%) of Z-1-(2,4-dichlorophenyl)-2-(4-chlorophenyl)-3-bromoprop-1-ene of melting point 128°C was obtained.

58.9 g of Z-1-(2,4-dichlorophenyl)-2-(4-chlorophenyl)-3-bromoprop-1-ene were refluxed with 52.3 g of 3-choroperoxybenzoic acid in 590 ml of chloroform. After the reaction was complete, the chloroform phase was

washed acid-free with aqueous sodium bicarbonate solution and water, dried over sodium sulfate and evaporated down under reduced pressure, and the residue was recrystallized from methanol to give two crystalline fractions:

41.3 g (70.2%) of 2-bromomethyl-2-(4-chlorophenyl)-3-(2,4-dichlorophenyl) oxirane (isomer A) of melting point 98-99°C, and, 12 g (20.4%) of 2-bromomethyl-2-(4-chlorophenyl)-3-(2,4-dichlorophenyl)oxirane (isomer B) of melting point 93-95°C.

20.9 g of 1,2,4-triazole and 4.4 g of sodium hydride (50% strength dispersion in mineral oil) were dispersed in 150 mL of N,N-dimethylformamide, and a solution of 39.2 g of 2-bromomethyl-2-(4-chlorophenyl)-3-(2,4-dichlorophenyl)oxirane (isomer A) and 16.6 g of potassium iodide in 150 ml of N,N-dimethylformamide was added at room temperature. After 8 hours, the reaction solution was worked up, and the product was recrystallized from diisopropyl ether. 31 g (81.9%) of 2-(1,2,4-triazol-1-ylmethyl)-2-(4-chlorophenyl)-3-(2,4-dichlorophenyl)oxirane (isomer A) - alteconazole was obtained. MP: 119°C.

References

Janssenet B. al.; US Patent No. 4,464,381; August 7, 1984; Assigned to BASF Aktiengesellschaft, Fed. Rep. of Germany

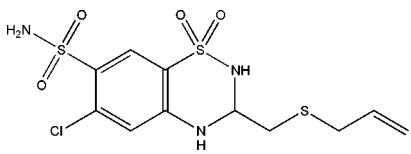
ALTHIAZIDE

Therapeutic Function: Diuretic, Antihypertensive

Chemical Name: 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-3,4-dihydro-3-((2-propenylthio)methyl)-, 1,1-dioxide

Common Name: Althiazide; Altizide

Structural Formula:



Chemical Abstracts Registry No.: 5588-16-9

Trade Name	Manufacturer	Country	Year Introduced
Althiazide	Solchem	-	-
Altizide	Bayer	-	-

Raw Materials

4-Amino-2-chloro-5-(methylsulfamyl)benzenesulfonamide
Dimethyl allylmercaptoacetal

Manufacturing Process

To 6.75 g (0.0225 mole) of 4-amino-2-chloro-5-(methylsulfamyl) benzenesulfonamide in 45 ml of dimethylformamide is added 4.86 g (0.03 mole) of dimethyl allylmercaptoacetal followed by 1.5 ml ethyl acetate saturated with hydrogen chloride gas. The solution is refluxed for 1.5 hours, cooled and added dropwise with stirring to ice/water. The resulting precipitate is filtered, dried and recrystallized from isopropanol. The recrystallization gave 4.0 g of 2-methyl-3-allylthiomethyl-6-chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide; M.P. 168.5-170°C.

References

Merck Index, Monograph number: 326, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
GB Patent No. 902,658; Aug. 9, 1962
McManus J.M. et al.; US Patent No. 3,102,882; Sept. 3, 1963; Assigned to Chas. Pfizer and Co., Inc., New York

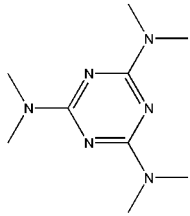
ALTRETAMINE

Therapeutic Function: Antitumor

Chemical Name: 2,4,6-Tris(dimethylamino)-1,3,5-triazine

Common Name: Hexamethylmelamine

Structural Formula:



Chemical Abstracts Registry No.: 645-05-6

Trade Name	Manufacturer	Country	Year Introduced
Hexastat	Roger Bellon	France	1979
Hexastat	Rhone Poulenc	Switz.	1981
Altretamine	Rhone Poulenc	W. Germany	1982

Raw Materials

Hexamethylolmelamine-Hexamethyl Ether
Hydrogen

Manufacturing Process

50 g of hexamethylolmelamine-hexamethyl ether in 950 cc methanol are hydrogenated, at 90°C to 100°C, in the presence of 2 g Raney nickel with 100 atmospheres excess pressure of hydrogen in a steel autoclave holding 2 L until the absorption of hydrogen is terminated. After the catalyst has been filtered off with suction, the methanol is distilled off. As a result, 23.1 g (86% of the theoretical) of crude hexamethylmelamine are formed having a melting point of 158°C to 162°C. After recrystallization from methanol, the pure product is obtained having a melting point of 168°C.

References

Merck Index 310
DFU 5 (10) 492, 635 (1980)
DOT 18 (4) 165 (1982)
I.N. p. 61
von Brachel, H. and Kindler, H.; US Patent 3,424,752; January 28, 1969; Assigned to Casella Farbwerke Mainkur AG

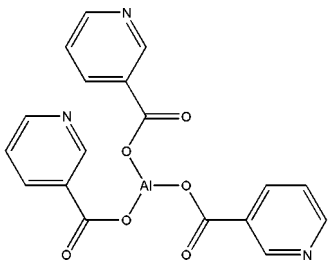
ALUMINUM NICOTINATE

Therapeutic Function: Vasodilator

Chemical Name: 3-Pyridinecarboxylic acid aluminum salt

Common Name: Tris(nicotinato)aluminum

Structural Formula:



Chemical Abstracts Registry No.: 1976-28-9

Trade Name	Manufacturer	Country	Year Introduced
Nicalex	Merrell Dow	Belgium	1960
Alunitine	Continental Pharma	US	-

Raw Materials

Nicotinic acid
Aluminum hydroxide

Manufacturing Process

Aluminum nicotinate is prepared by dissolving nicotinic acid in hot water and adding a slurry of aluminum hydroxide to it. A slight excess of aluminum hydroxide is used in order that the final product would be free of nicotinic acid. The precipitate is collected on a filter and dried. The final product contains a mixture of aluminum nicotinate and a small but acceptable amount of aluminum hydroxide.

References

Merck index 346
Kleeman and Engel p. 33
I.N.p.62
Miale, J.P.; US Patent 2,970,082; January 31, 196l; Assigned to Walker Laboratories, Inc.

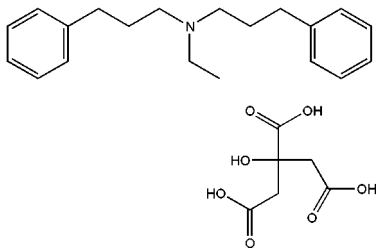
ALVERINE CITRATE

Therapeutic Function: Anticholinergic, Spasmolytic

Chemical Name: Benzenepropanamine, N-ethyl-N-(3-phenylpropyl)-, citrate

Common Name: Alverine citrate

Structural Formula:



Chemical Abstracts Registry No.: 5560-59-8; 150-59-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Alverine citrate	Kemikos	-	-
Alverine citrate	Norgine	-	-
Alverine citrate	Bristhar Laboratorios	-	-
Alvercol	Norgine	-	-

Trade Name	Manufacturer	Country	Year Introduced
Antispasmin	Balkanpharma - Dupnitza Co.	-	-
Spasmaverine	Bellon	-	-
Spasmonal	Norgine	-	-
Spasmonal	Ying-Yuan Chemical Pharmaceutical Co., Ltd.	-	-

Raw Materials

Ethylamine	3-Phenylpropylchloride
Hydrogen	Potassium hydroxide
Platinum	Barium sulfate

Manufacturing Process

2 Methods of producing of alverine:

1. 3-Phenylpropylchloride reacted with ethylamine in the presence potassium hydroxide and N-ethyl-3,3'-diphenyldipropylamine (alverine) was obtained.

2. 3-Phenylpropenal reacted with ethylamine in the presence hydrogen and Pt as catalyst and $BaSO_4$ and N-ethyl-3,3'-diphenyldipropylamine (alverine) was obtained.

In practice it is usually used as citrate.

References

Kleemann A., Engel J.; Pharmazeutische Wirkstoffe, GeorgThieme Verlag Stuttgart. New York, 1982

AMADINONE

Therapeutic Function: Progestin

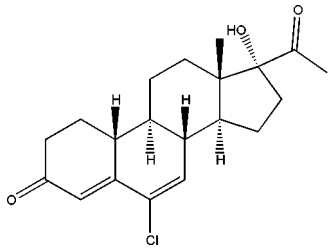
Chemical Name: 19-Norpregna-4,6-diene-3,20-dione, 6-chloro-17-hydroxy-

Common Name: Amadinone, 19-Norchlormadinone

Chemical Abstracts Registry No.: 30781-27-2

Trade Name	Manufacturer	Country	Year Introduced
Amadinone	ZYF Pharm Chemical	-	-

Structural Formula:



Raw Materials

$\delta^{(4)}$-3,20-Dioxo-6α,7α-oxido-17α-acetoxy-19-norpregnene
Hydrochloric acid
Methanesulfonyl chloride
Sodium acetate

Manufacturing Process

A solution of 250.0 mg of δ^4-3,20-dioxo-6α,7α-oxido-17α-acetoxy-19-norpregnene in 15 ml of 1 N hydrochloric acid in dioxan is kept for 1 h at 25°C, then poured into water and neutralized with sodium bicarbonate solution. The precipitated crude product is dissolved in a 5:1 mixture of ether and methylene chloride, washed with water until the washings run neutral, and the solution is dried and evaporated under vacuum to give the δ^4-3,20-dioxo-6-chloro-7α-hydroxy-17α-acetoxy-19-nor-pregnene.

The crude δ^4-3,20-dioxo-6-chloro-7α-hydroxy-17α-acetoxy-19-nor-pregnene is dissolved in 3 ml of pyridine, mixed at 5°-0°C with 0.3 ml of methanesulphonyl chloride while being stirred, and the mixture is kept for 2 days at 10°C. The reaction product is then poured into dilute sodium bicarbonate solution, dissolved in ether, and the ethereal solution is washed until the washings run neutral, dried and evaporated under vacuum and the δ^4-3,20-dioxo-6-chloro-7α-mesyloxy-17α-acetoxy-19-norpregnene is obtained.

The δ4-3,20-dioxo-6-chloro-7α-mesyloxy-17α-acetoxy-19-norpregnene is dissolved in 25 ml of dimethyl formamide, mixed with 4.5 g of anhydrous sodium acetate, and the whole is heated for 75 min at 85°C under nitrogen while being stirred. The cooled reaction mixture is diluted with water, extracted with a 5:1-mixture of ether and methylene chloride, and the organic layer is washed with 100 ml of water, dried and evaporated. The resulting crude product is dissolved in benzene and chromatographed on 15 times its own weight of alumina (activity II). The afore-mentioned solvent elates 105.0 mg of pure $\delta^{4,6}$-3,20-dioxo-6-chloro-17α-acetoxy-19-norpregnadiene, melting point 159°-161°C (recrystallized from methylene chloride:hexane).

The $\delta^{4,6}$-3,20-dioxo-6-chloro-17-hydroxy-19-norpregnadien, melting point 159°-161°C, may be produced by hydrolysis of $\delta^{4,6}$-3,20-dioxo-6-chloro-17α-acetoxy-19-norpregnadiene.

References

GB Patent No. 1,007,758; Dec. 29, 1961; Assigned: Ciba Limited, a body corporate organized according to the laws of Switzerland, of Basle, Switzerland

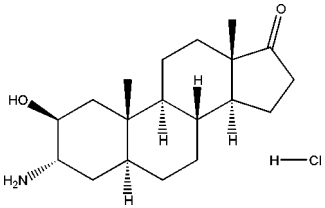
AMAFOLONE HYDROCHLORIDE

Therapeutic Function: Antiarrhythmic

Chemical Name: (2β,3α,5α)-3-Amino-2-hydroxyandrostan-17-one hydrochloride

Common Name: Amafolone hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 51740-76-2; 50588-47-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Amafolone hydrochloride	ZYF Pharm Chemical	-	-

Raw Materials

Perchloric acid	N-Bromoacetamide
Acetic acid	5α-Androst-2-en-17-one
Ammonia	Potassium hydroxide

Manufacturing Process

A solution of 70% perchloric acid (60 ml) in water (280 ml) was added to a stirred solution of 5α-androst-2-en-17-one (200.0 g) in ether (1.15 l) at 15°C followed by portionwise addition of N-bromacetamide (112.0 g) over 10 min. After stirring for 1 h the precipitated white crystalline solid was filtered off, washed neutral with ether and water and crystallised to give 2β-hydroxy-3α-bromo-5α-androstan-17-one (172.0 g). The ether layer of the filtrate was washed neutral, dried (Na_2SO_4) and concentrated to give a second crop (28.0 g). The two crops (200.0 g) were suspended in methanol (1 L), 10 N aqueous potassium hydroxide solution (100 ml) added and the mixture slowly distilled over 45 min. Addition of water precipitated the product as a white solid which

was filtered off, washed with water, dried and 88.0 g of 2β,3β-epoxy-5α-androstan-17-one were obtained (crystallisation from ether:light petrol).

A solution of the 2β,3β-epoxy-5α-androstan-17-one (30.0 g) in ethanol (130 ml), water (15 ml) and liquid ammonia was heated in an autoclave at 150°C for 6 h and the resultant crystalline suspension evaporated to dryness. Water (35 ml) and acetic acid (36 ml) were added and the solution kept at 90°C for 1 h, cooled and excess water added. The precipitated material was filtered off and the filtrate made alkaline with aqueous 10 N potassium hydroxide solution to precipitate a white solid which was filtered off, washed neutral with water, dissolved in methylene chloride, the solution dried (Na_2SO_4) concentrated and ether added to give 2β-hydroxy-3α-amino-5α-androstan-17-one (14.3 g), melting point l92°-195°C.

In practice it is usually used as hydrochloride.

References

Hewett C.L., Savage D.S.; US Patent No. 3,862,196; Jan. 21, 1975; Assigned: Akzona Incorporated, Asheville, N.C.

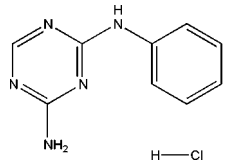
AMANOZINE HYDROCHLORIDE

Therapeutic Function: Diuretic

Chemical Name: N-Phenyl-1,3,5-triazine-2,4-diamine monohydrochloride

Common Name: Amanozine, Amenozine

Structural Formula:



Chemical Abstracts Registry No.: 6011-10-5; 537-17-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Amanozine	Onbio Inc.	-	-

Raw Materials

1-Phenylbiguanide hydrochloride
Sodium carbonate

Manufacturing Process

21.3 g (0.1 mole) of 1-phenylbiguanide hydrochloride were dissolved in hot water and the solution was added to 5.3 g (0.05 mole) sodium carbonate by stirring. On cooling 15 g of the needle crystals have fallen. They were heated to reflux with 80 ml of dry formic acid. Then 40-50 ml formic acid was distilled off. The residue was with water diluted, cooled with ice and the conc. alkali was added. The precipitate fallen. It was filtered off and recrystallized from 40-50% ethanol. The pure product 4-amino-2-anilino-1,3,5-triazine had MP: 232°-233°C.

Monochlorohydrate of it crystallized as long colorless needles melted at 258°-260°C.

References

Clauder O. et al.; Austrian Patent No. 168,063; April 10, 1959; Richter Gedeon Vegyeszeti R.T. in Budapest
Kleemann A., Engel J.; Pharmazeutische Wirkstoffe, GeorgThieme Verlag Stuttgart. New York, 1982

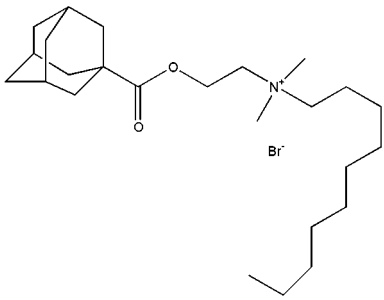
AMANTANIUM BROMIDE

Therapeutic Function: Antiseptic

Chemical Name: (2-(1-Tricyclo[3.3.1.13,7]decylcarbonyloxy)ethyl) decyldimethyl-ammonium bromide

Common Name: Amantanium bromide

Structural Formula:



Chemical Abstracts Registry No.: 58158-77-3

Trade Name	Manufacturer	Country	Year Introduced
Amantanium bromide	Onbio Inc.	-	-

Raw Materials

2-Dimethylaminoethanol	1-Adamantanecarboxylic acid chloride
1-Bromodecan	Sodium hydroxide

Manufacturing Process

A solution of 21.7 g (0.11 mole) 1-adamantanecarboxylic acid chloride in 100 ml ether was added to a solution of 19.4 g (0.22 mole) 2-dimethylaminoethanol in 200 ml ether. The reaction mixture was stirred overnight at room temperature. Then additional 15.0 g (0.17 mole) 2-dimethylaminoethanol was added and the reaction mixture again stirred overnight. The reaction mixture was poured into 300 ml water and treated with 20 ml of 10% NaOH solution. From the ether layer was recovered 23.0 g of 2-dimethylaminoethyl 1-adamantanecarboxylate as oil.

The 2-dimethylaminoethyl 1-adamantanecarboxylate was mixed with 1-bromodecan and allowed to stand for about 6 weeks. The resultant crystalline mass was washed with ether and dried to gave 2-(1'-adamantanecarbonyloxy)ethyldimethyldecylammonium bromide as white crystals, melting point 183°-184.5°C (two recrystallizations from ethyl acetate).

References

Bauman R.A.; US Patent No. 3,928,411; Dec. 23, 1975; Assigned: Colgate-Palmoliv Company, New York, N.Y.

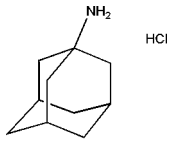
AMANTIDINE HYDROCHLORIDE

Therapeutic Function: Antiviral, Antiparkinsonian

Chemical Name: 1-Adamantanamine hydrochloride

Common Name: 1-Aminoadamantane hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 665-66-7

Raw Materials

Adamantane	Hydrocyanic acid
Sodium hydroxide	Hydrogen chloride

Trade Name	Manufacturer	Country	Year Introduced
Symmetrel	DuPont (Endo)	US	1966
Symmetrel	Geigy	W. Germany	1966
Symmetrel	Geigy	UK	1971
Mantadan	De Angeli	Italy	1971
Mantadix	Theraplix	France	1973
Symmetrel	Fujisawa	Japan	1975
Amantadin	Ratiopharm	W. Germany	-
Amantan	Byk Gulden	-	-
Amazolon	Sawai	Japan	-
Antadine	DuPont	Australia	-
Atarin	Medica	Finland	-
Contenton	SK Dauelsberg	W. Germany	-
Influenol	Santos	Spain	-
Paramantin	Orion	Finland	-
Paritrel	Trima	Israel	-
PK-Mertz	Mertz	W. Germany	-
Protexin	Landerlan	Spain	-
Solu-Contenton	SK and F	W. Germany	-
Trivaline	Farmex	France	-
Viregyt	EGYT	Hungary	-
Virofral	Duphar	Belgium	-
Virofral	Ferrosan	Denmark	-
Virosol	Phoenix	Argentina	-

Manufacturing Process

360 ml of 96% sulfuric acid and a solution of 13.6 grams (0.1 mol) of adamantane in 100 ml of n-hexane were emulsified in the apparatus described and provided with an inclined centrifugal stirrer. Then a mixture of 46 grams (1.7 mols) of liquid hydrocyanic acid and 29.6 grams (0.4 mol) of tertiary butanol was added dropwise within 1.5 hours at about 25°C.

After 30 minutes of postreaction, the product was poured on ice. The granular mass which precipitated [N-(adamantyl-1)formamide] was sucked off and washed with water. The raw product (37 grams) was then refluxed for 10 hours with a solution of 60 grams of NaOH in 600 ml of diethylene glycol.

After cooling, the solution was diluted with 1.5 liters of water and subjected to three extractions with ether. The amine was extracted from the ethereal solution with 2 N HCl and liberated therefrom by the addition of solid NaOH (while cooling). The alkaline solution was extracted with ether and the ethereal solution was dried with solid NaOH. Distillation resulted in 10.6 grams (70% of the theory) of 1-aminoadamantane which, after sublimation, melted at 180°C to 192°C (seal capillary). It is converted to the hydrochloride.

References

Merck Index 373
Kleeman and Engel p. 33

PDR p. 862
OCDS Vol. 2 p. 18 (1980)
DOT 3 (1) 6 (1967) and 7 (2) 44 (1971)
I.N. p. 63
REM p. 927
Haaf, W.; US Patent 3,152,180; October 6, 1964; Assigned to Studiengesellschaft Kohle GmbH, Germany

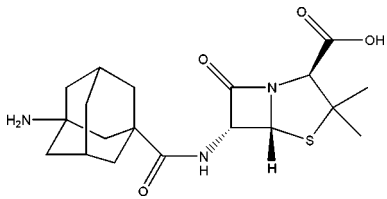
AMANTOCILLIN

Therapeutic Function: Antibiotic

Chemical Name: 4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-(((3-aminotricyclo[3.3.1.1^{3,7}]dec-1-yl)carbonyl)amino)-3,3-dimethyl-7-oxo-, (2S-(2α,5α,5β))-

Common Name: Amantocillin

Structural Formula:



Chemical Abstracts Registry No.: 10004-67-8

Trade Name	Manufacturer	Country	Year Introduced
Amantocillin	Onbio Inc.	-	-

Raw Materials

Sulfuric acid
Sodium hydroxide
Thionyl chloride
Triethylamine
3-Bromoadamantane-1-carboxylic acid
Acetic acid
6-Aminopenicillanic acid

Manufacturing Process

A mixture of 3-bromoadamantane-1-carboxylic acid (5.8 g), acetonitrile (45 ml) and concentrated sulphuric acid (9 ml) was refluxed for 20 h. After cooling, the mixture was poured into water (250 ml), and the resulting suspension concentrated in vacuo to remove most of the acetonitrile. Aqueous sodium hydroxide (33%) was added until the pH was 4.0 (about 24 ml). The precipitate was filtered off, washed with water, and dried to yield 4.4 g of the 3-acetaminoadamantane-1-carboxylic acid, melting point 254°-258°C (two recrystallizations from methanol-aceto nitrile).

A solution of 3-acetamino-adamantane-1-carboxylic acid (3.0 g) in 4 N sodium hydroxide (40 ml) was refluxed for 5 h. After cooling, the pH of the solution was adjusted to 7 with acetic acid. The crystalline precipitate was filtered off, washed with ethanol and dried to yield 2.20 g of the desired compound, melting point over 330°C. In order to purify the compound, 2.0 g of it was suspended in water (10 ml), 4 N NaOH (2 ml) was added, and the resulting solution filtered through a filter aid known under the registered trademark 'Dicalite'. The filtrate was adjusted to a pH of 6.5 with acetic acid. The resulting crystalline precipitate was filtered off, washed with a little water followed by alcohol, and dried to yield 1.55 g of pure 3-amino-adamantane-1-carboxylic acid.

3-Aminoadamantane-1-carboxylic acid (1.0 g) was refluxed with thionyl chloride (4.6 ml) for 1 h. Excess of thionyl chloride was removed in vacuo. The residue was dissolved in benzene (3 ml), and the resulting solution evaporated under reduced pressure to remove traces of thionyl chloride. This process was repeated to leave 1.3 g of a 3-thionyliminoadamantane-1-carboxylic acid chloride, almost colourless.

500.0 mg of 3-thionyliminoadamantane-1-carboxylic acid chloride were dissolved in dry acetone (8 ml), and the resulting solution was added during 20 min at room temperature with stirring, to a suspension of 6-aminopenicillanic acid (520.0 mg) in 50% aqueous acetone (20 ml), previously adjusted to a pH of 7.0 with triethylamine. During the process, a pH value of 7.0 was maintained by the addition of a 1 N solution of triethylamine in 50% aqueous acetone from an automatic titrator. At the end of the reaction, a clear solution was obtained. Acetone was removed in vacuo, and 70% of the theoretical amount of 3-amino-adamantyl-1-penicillin was formed.

The aqueous solution was concentrated in vacuo to a volume of 4 ml. Addition of acetone (40 ml) gave an oily precipitate which after decanting and addition of fresh acetone gave 900.0 mg of a semicrystalline solid which contained 50% of the theoretical amount of 3-aminoadamantyl-1-penicillin.

References

Godtfredsen W.O.; US Patent No. 3,564,049; Feb. 16, 1971; Assigned: Lovens Kemiske Fabrik Produktionsaktieselskab, Ballerup, Denmark, a firm

AMBAZONE

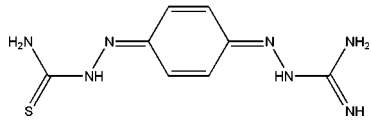
Therapeutic Function: Antiseptic

Chemical Name: Guanidine, ((4-oxo-2,5-cyclohexadien-1-ylidene)amino)-, thiosemicarbazone monohydrate

Common Name: Ambazone; Guanothiazone

Chemical Abstracts Registry No.: 6011-12-7; 539-21-9 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Ambazone	Generic	-	-
Ambazone	Terapia	-	-
Ambazone	East-Asia Pharmaceutical Chemical Co., Ltd.	-	-
Faringosept	Terapia	-	-
Faringosept	Interprindera	-	-
Iversal	Bayer	-	-
Primal	Bayer	-	-

Raw Materials

Quinone monoguanylhydrazone nitrate
Thiosemicarbazide
Nitric acid

Manufacturing Process

To a solution of 22.7 g of quinone monoguanylhydrazone nitrate in 250 ml water is added dropwise hot aqueous solution of 9.1 g thiosemicarbazide, then is added slowly a solution of 5 ml concentrated nitric acid in 10 ml of water. The mixture is stirred at 60°C for 1 hour. The product is dissolved in 1-1.2 L of water at 100°C. The solution is filtered and added to an aqueous ammonium solution. Blue residue of p-benzoquinone amidinohydrazone thiosemicarbazone is filtered and dried, melting point 188°C (decomp.).

References

Merck Index, Monograph number: 395, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Petersen S., Domagk G.; DE Patent No. 965,723; 1957-06-19; Assigned to Bayer AG

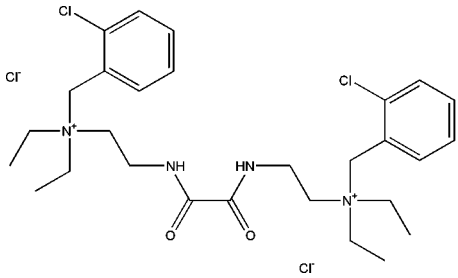
AMBENONIUM CHLORIDE

Therapeutic Function: Cholinesterase inhibitor

Chemical Name: N,N'-[(1,2-Dioxo-1,2-ethanediyl)bis(imino-2,1-ethanediyl)] bis[2-chloro-N,N-diethylbenzenemethanaminium] dichloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 115-79-7

Trade Name	Manufacturer	Country	Year Introduced
Mytelase CL	Winthrop	US	1956
Mytelase	Winthrop	W. Germany	-
Mytelase	Winthrop	France	1950
Mytelase	Winthrop	UK	1970
Mytelase	Nippon Shoji	Japan	-
Mysuran	Winthrop	-	-

Raw Materials

2-Diethylaminoethylamine
Ethyl oxalate
2-Chlorobenzyl chloride

Manufacturing Process

N,N'-Bis(2-Diethylaminoethyl)Oxamide: A solution of 150 grams (1.32 mol) of 2-diethylaminoethylamine in 250 ml of xylene was gradually added to a solution of 73.0 grams (0.5 mol) of ethyl oxalate in 250 ml of xylene, with external cooling. The mixture was then refluxed for eight hours, cooled and diluted with ether. The ether-xylene solution was extracted with 10% hydrochloric acid, and the hydrochloric acid extracts were in turn extracted with ether and then made alkaline with 35% sodium hydroxide solution. The organic material which separated was extracted with ether, and the ether solution was dried over anhydrous sodium sulfate and concentrated, giving 106.5 grams of N,N'-bis(2-diethylaminoethyl)oxamide, MP 40-42°C.

N,N'-Bis(2-Diethylaminoethyl)Oxamide Bis(2-Chlorobenzochloride): A solution of 7 grams (0.025 mol) of N,N'-bis(2-diethylaminoethyl)oxamide and 16.1 grams (0.1 mol) of 2-chlorobenzyl chloride in 100 ml of acetonitrile was refluxed for eleven hours. The solid which separated upon cooling was collected by filtration and recrystallized by dissolving it in ethanol and adding ether to cause the product to separate. After drying at about 60°C (1-3 mm) there was obtained 4.1 grams of N,N'-bis(2-diethylaminoethyl)oxamide bis(2-chlorobenzochloride), MP 196-199°C.

References

Merck Index 378
Kleeman and Engel p. 34
I.N. p. 64
REM p. 898
Kirchner, F.K.; US Patent 3,096,373; July 2, 1963; Assigned to Sterling Drug Inc.
Behr, L.C. and Schreiber, R.S.; US Patent 2,438,200; March 23, 1948; Assigned to E.I. du Pont de Nemours and Co.

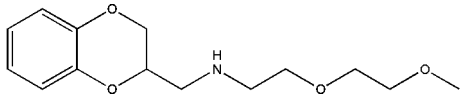
AMBENOXAN

Therapeutic Function: Muscle relaxant

Chemical Name: 2,3-Dihydro-N-[2-(2-methoxyethoxy)ethyl]-1,4-benzodioxine-2-methanamine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 2455-84-7

Trade Name	Manufacturer	Country	Year Introduced
Ambenoxan	ZYF Pharm Chemical	-	-

Raw Materials

2-Aminomethyl-1,4-benzodioxane
β-Methoxyethoxy ethyl chloride
Potassium carbonate

Manufacturing Process

2-Aminomethyl-1,4-benzodioxane (17 g) and β-methoxyethoxy ethyl chloride (7 g) were heated at 160°C for 2 hours. The reaction mixture was cooled and chloroform (30 ml) and a solution of potassium carbonate (7 g) in water (20 ml) added thereto.The chloroform layer was removed and the aqueous layer extracted twice with chloroform (10 ml each time). The chloroform extracts were combined and dehydrated over anhydrous sodium sulfate. Filtration, followed by distillation gave 2-(β-methoxyethoxyethyl)amino-methyl-1,4-benzodioxane (yield 7.7 g) as a pale yellow oil boiling at 180-186°C/11.5 mm.

The base was converted to a white hydrochloride having a melting point of

104-106°C by the addition of alcoholic hydrogen chloride to an ether solution of the base and isolation of the salt which separated.

References

Shapero M., Green P.N.; US Patent No. 3,308,136; Mar. 7, 1967; Assigned to Ward Blenkinsop and Company Limited, Middlesex, England, a British company

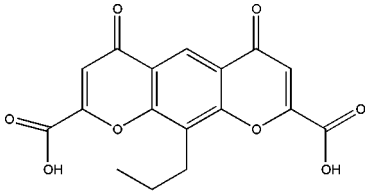
AMBICROMIL

Therapeutic Function: Antiallergic, Histamine H1 antagonist

Chemical Name: 4H,6H-Benzo[1,2-b:5,4-b']dipyran-2,8-dicarboxylic acid, 4,6-dioxo-10-propyl-

Common Name: Probicromil; Ambicromil

Structural Formula:



Chemical Abstracts Registry No.: 58805-38-2

Trade Name	Manufacturer	Country	Year Introduced
Probicromil	ZYF Pharm Chemical	-	-

Raw Materials

Benzyltrimethylammonium hydroxide
Dimethyl acetylenedicboxylate
Chlorosulfonic acid

Manufacturing Process

4,6-Dioxo-10-propyl-4H,6H-benzo[1,2-b:5,4-b']dipyran-2,8-carboxylic acid:

2 ml of benzyltrimethylammonium hydroxide was added to a solution of 18.3 g 2-propylresorcine and dimethyl acetylenedicboxylate in 500 ml of ethanol and the mixture obtained was heated for 20 hours at reflux. The solution was cooled, 30 g sodium hydroxide in 150 ml of water was added and all mass was heated for 2 hours at reflux. On cooling the reaction mixture was poured into 2 L of water and washed with ethyl acetate. The water layer was acidified with conc. hydrochloric acid and a precipitate fallen was collected, washed

with water, and dried in vacuum at 80°C to give 21 g cream-colored solid product.

21 g above product was in portion added to 200 ml of chlorosulfonic acid by ice cooling. The temperature of reaction was not higher 10°C. Then the reaction mixture was heated for 2.5 hours at 50°C. On cooling it was poured into 3 L of ice/water, the fallen precipitate was filtered off, washed with water and dried in vacuum. The solid product was heated with 100 ml of ethanol, an insoluble part was collected and boiled with 100 ml of ethyl acetate. Insoluble product was centrifuged and dried in vacuum at 60°C. Yield of title product hydrate 10.5 g. 4,6-Dioxo-10-propyl-4H,6H-benzo[1,2-b:5,4-b']dipyran-2,8-carboxylic acid melted at 310°-311°C (deg).

References

Cairns H. et al.; D.E. Patent No. 2,851,440; Nov. 11, 1978

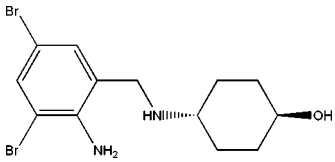
AMBROXOL

Therapeutic Function: Expectorant

Chemical Name: 4-[[(2-Amino-3,5-dibromophenyl)methyl]amino] cyclohexanol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 18683-91-5

Trade Name	Manufacturer	Country	Year Introduced
Mucosolvan	Thomae	W. Germany	1980
Mucosolvan	De Angeli	Italy	1981
Mucosolvon	Boehringer Ingelheim	Switz.	1982
Fluixol	Ripari-Gero	Italy	-
Fluibron	Chiesi	Italy	-
Muciclar	Piam	Italy	-

Raw Materials

N-(trans-p-Hydroxycyclohexyl)-(2-aminobenzyl)-amine
Bromine

Manufacturing Process

6.5 g of N-(trans-p-hydroxycyclohexyl)-(2-aminobenzyl)-amine were dissolved in a mixture of 80 cc of glacial acetic acid and 20 cc of water, and then 9.6 g of bromine were added dropwise at room temperature while stirring the solution. After all of the bromine had been added, the reaction mixture was stirred for two hours more and was then concentrated in a water aspirator vacuum. The residue was taken up in 2 N ammonia, the solution was extracted several times with chloroform, and the organic extract solutions were combined and evaporated. The residue, raw N-(trans-p-hydroxycyclohexyl)-(2-amino-3,5-dibromobenzyl)-amine, was purified with chloroform and ethyl acetate over silica gel in a chromatographic column, the purified product was dissolved in a mixture of ethanol and ether, and the solution was acidified with concentrated hydrochloric acid. The precipitate formed thereby was collected and recrystallized from ethanol and ether, yielding N-(trans-p-hydroxycyclohexyl)-(2-amino-3,5-dibromobenzyl)-amine hydrochloride, MP 233-234.5°C (decomposition).

References

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Kleeman and Engel p. 35
I.N. p. 64
Kack, J., Koss, F.W., Schraven, E. and Beisenherz, G.; US Patent 3,536,713; October 27, 1970; Assigned to Boehringer Ingelheim G.m.b.H.

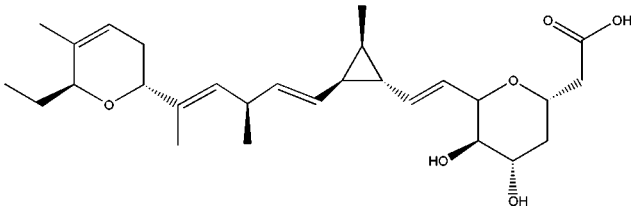
AMBRUTICIN

Therapeutic Function: Antifungal

Chemical Name: 2H-Pyran-2-acetic acid, 6-(2-(2-(5-(6-ethyl-3,6-dihydro-5-methyl-2H-pyran-2-yl)-3-methyl-1,4-hexadienyl)-3-methylcyclopropyl) ethenyl)tetrahydro-4,5-dihydroxy-

Common Name: Ambruticin; SMP-78

Structural Formula:



Chemical Abstracts Registry No.: 58857-02-6

Trade Name	Manufacturer	Country	Year Introduced
Ambruticin	Universitet Karlsruhe (TH)	-	-
Ambruticin	Kosan Biosciences Inc.	-	-

Raw Materials

Methyltriphenylphosphonium bromide
Tributyltin hydride
DMAP
(-)-Dimenthyl succinate
1,1-Bromochloroethane
Diborane-THF complex
Triphenylphosphine
Triphenylmethyl chloride
Diazomethane
Sulfuric acid
Glycosyl fluoride
Triethylamine
Doss-Martin's periodinane
Sodium hydride
Hydroquinone
Glyoxylic acid
2,4'-Dibromoacetophenone
(+)-α-Methylbenzylamine
trans-Propenyltrimethyltin
N,N-Diisopropylamine
Butyl lithium
4-Toluenesulfonyl fluoride
Lithium
Sodium
Ammonium chloride
Methyl 2,3-di-O-benzyl-α-D-glucopyranoside
t-Butyldiphenylsilyl chloride
Tetrabutylammonium fluoride
2,2,6,6-Tetramethylpiperidine
Potassium hydroxide
Periodinane
Diisobutylaluminum hydride
1,1'-Thiocarbonyldiimidazole
Sodium methoxide
Acetic anhydride
4-Toluenesulfonic acid
Diethylaminosulfur trifluoride
PDC
Aldehyde
Imidazole
Potassium fluoride
Oxalyl chloride
Methyl magnesium bromide
Acetic anhydride
Sodium hydrogen carbonate
Hydrogen hydrochloride
Lithium hydroxide
Tetrabromomethane
Tetramethylammonium acetate
Benzylchlorobis(triphenyl-phosphine)palladium (II)

Manufacturing Process

Preparation of methyl 2,3-di-O-benzyl-1,4-dideoxy-1α/1β-fluoro-D-glucoheptopyranuronate:

To a stirred solution of the methyl 2,3-di-O-benzyl-α-D-glucopyranoside (1.01 g, 2.70 mmol) in DMF (10 ml) was added imidazole (0.37 g, 5.40 mmol) followed by a solution of t-butyldiphenylsilyl chloride (0.89 g, 3.24 mmol) in DMF (3.5 ml) at 0°C. The resulting solution was stirred at room temperature for 2 h, cooled to 0°C, H_2O (1 ml) was added, and the mixture was stirred for 10 min. The resulting solution was poured into H_2O (100 ml) and extracted with Et_2O (3x100 ml). The organic layers were combined, washed with brine, dried over sodium sulfate and filtered. The solvent was removed in vacuum to give a colorless oil, which was purified by column chromatography over silica gel (hexane-Et_2O, 7:3) to afford 1.64 g (99%) of methyl 2,3-di-O-benzyl-6-O-t-butyldiphenylsilyl-α-D-glucopyranoside as a colorless viscous oil.

To a stirred solution of methyl 2,3-di-O-benzyl-6-O-t-butyldiphenylsilyl-α-D-glucopyranoside (0.617 g, 1.01 mmol) in toluene (5 ml) was added 1,1'-thiocarbonyldiimidazole (0.359 g, 2.01 mmol) at room temperature. The solution was heated at reflux. The reaction mixture was poured into 0.5 N HCl (50 ml) and extracted with CH_2Cl_2 (3x50 ml). The organic layers were combined, washed with sat. sodium bicarbonate solution followed by brine, dried over sodium sulfate and filtered. The solvent was removed in vacuum to give a crude yellow oil, which was purified by column chromatography over silica gel (hexane-EtOAc, 7:3) to afford 0.676 g (93%) of methyl 2,3-di-O-benzyl-6-O-t-butyldiphenylsilyl-4-O-imidazolyl-thiocarbonyl-α-D-glucopyranoside as a colorless viscous oil.

To a stirred solution of nBu_3SnH (0.24 g, 0.83 mmol) in toluene (4.2 ml) was added a solution of methyl 2,3-di-O-benzyl-6-O-t-butyldiphenylsilyl-4-O-imidazolyl-thiocarbonyl-α-D-glucopyranoside (0.30 g, 0.42 mmol) in toluene (2 ml) over 2 min at 100°C. The resulting solution was heated at reflux for 12 h. The solvent was removed in vacuum and the resulting crude oil was purified by column chromatography over silica gel (hexane-Et_2O, 9:1) to afford 0.20 g (83%) of the methyl 2,3-di-O-benzyl-6-O-t-butyldiphenylsilyl-4-deoxy-α-D-glucopyranoside as a colorless viscous oil.

To a stirred solution of the methyl 2,3-di-O-benzyl-6-O-t-butyldiphenylsilyl-4-deoxy-α-D-glucopyranoside (25.9 g, 43.4 mmol) in THF (400 ml) was added dropwise a 1 M solution of nBu_4NF 65.1 ml in THF over 30 min at room temperature. The resulting solution was stirred at room temperature for 18 h and then poured into H_2O (500 ml). The mixture was extracted with Et_2O (3x500 ml). The organic extracts were combined, washed with brine, dried over sodium sulfate and filtered. The solvent was removed in vacuum to give a colorless oil, which was purified by column chromatography over silica gel (hexane-EtOAc, 1:1) to afford 14.81 g (95%) of methyl 2,3-di-O-benzyl-4-deoxy-α-D-glucopyranoside as a colorless viscous oil.

To a stirred solution of methyl 2,3-di-O-benzyl-4-deoxy-α-D-glucopyranoside (6.12 g, 17.1 mmol) in DMF (69 ml) was added 21.81 g (58 mmol) of PDC at room temperature. The resulting red-brown viscous solution was stirred at room temperature for 20 h. The reaction mixture was diluted with Et_2O (100 ml) and stirred for 10 min. The clear yellow liquid was collected by decantation. The gummy brown residue was extracted with Et_2O (3x100 ml). The extracts were combined, and concentrated in vacuum to give a yellow viscous oil, which was purified by column chromatography over silica gel (CH_2Cl_2 -MeOH, 10:1) to give 5.60 g (88%) of methyl 2,3-di-O-benzyl-4-deoxy-α-D-glucopyranosiduronic acid as an amorphous powder.

To a stirred solution of the methyl 2,3-di-O-benzyl-4-deoxy-α-D-glucopyranosiduronic acid (1.73 g, 4.65 mmol) in CH_2Cl_2 (30 ml) was added oxalyl chloride (0.943 g, 0.65 ml, 7.43 mmol) followed by DMF (0.23 mmol) at room temperature. The resulting clear solution was stirred at room temperature for 2 h, and then concentrated in vacuo.

To a solution of the crude acyl chloride derivative in Et_2O (50 ml) was added a solution of diazomethane in Et_2O (30 ml) at 0°C over 20 min. The resulting clear yellow solution was stirred at room temperature for 30 min and then

evaporated in vacuo at under 20°C to give a crude yellow oil, which was purified by column chromatography over silica gel (hexane-Et_2O, 1:1) to afford 1.44 g (78%) of the corresponding diazoketone as a yellow viscous oil.

A solution of the diazoketone prepared above (1.39 g, 3.52 mmol) in MeOH (60 ml) was placed in a 100 ml pyrex test tube, and irradiated by a Hanovia 30620 type medium pressure UV arc under constant cooling by running H_2O for 48 h. The reaction mixture was concentrated in vacuo to give a yellow oil, which was purified by column chromatography over silica gel (hexane-Et_2O, 3:2) to afford 0.96 g (68%) of methyl (methyl 2,3-di-O-benzyl-4-deoxy-α-D-glucoheptopyranosiduronate as a colorless viscous oil.

To a stirred solution of the methyl (methyl 2,3-di-O-benzyl-4-deoxy-α-D-glucoheptopyranosiduronate (0.705 g, 1.76 mmol) in acetic anhydride (7 ml) was added 1 ml of a 10% solution of H_2SO_4 in acetic anhydride at -30°C. The resulting solution was stirred at -20°C for 10 min. The reaction mixture was poured into a sat. sodium bicarbonate solution (100 ml) and stirred well for 30 min at room temperature to destroy the excess of acetic anhydride. The resulting mixture was extracted with Et_2O (3x100 ml). The organic extracts were combined, washed with brine, dried over sodium sulfate and filtered. The solvent was removed in vacuum to give a colorless oil, which was purified by column chromatography over silica gel (hexane-Et_2O, 3:2) to afford 0.664 g (88%) of 82:18 mixture of methyl (acetyl 2,3-di-O-benzyl-4-deoxy-α/β-D-glucoheptopyranosiduronate).

To a freshly prepared solution of sodium methoxide (1.931 mmol) in MeOH (15 ml) was added a solution of methyl (acetyl 2,3-di-O-benzyl-4-deoxy-α/β-D-glucoheptopyranosiduronate) (413.0 mg, 0.966 mmol) in MeOH (5 ml) at 0°C. The resulting solution was stirred at 0°C for 10 min and then poured into H_2O (50 ml). The mixture was extracted with Et_2O (3x50 ml). The organic extracts were combined, washed with brine, dried over sodium sulfate and filtered. The solvent was removed in vacuum to give a residue, which was purified by column chromatography over silica gel (hexane-EtOAc, 3:2) to afford 360.0 mg (97%) of the mixture of methyl 2,3-di-O-benzyl-4-deoxy-α/β-D-glucoheptopyranuronate.

To a stirred solution of methyl 2,3-di-O-benzyl-4-deoxy-α/β-D-glucoheptopyranuronate (472.0 mg, 1.22 mmol) in CH_2Cl_2 (12 ml) was added diethylaminosulfur trifluoride (DAST) (590.0 mg, 3.66 mmol) at -30°C. The resulting colorless solution was stirred at 0°C for 20 min and then cooled again to -30°C. MeOH (1 ml) was added to the reaction mixture to destroy the excess of DAST. After stirring at 0°C for 10 min, the solution was poured into a sat. sodium bicarbonate solution (50 ml) and extracted with Et_2O (3x50 ml). The organic extracts were combined, washed with brine, dried over sodium sulfate and filtered. The solvent was removed in vacuum to give a colorless oil, which was purified by column chromatography over silica gel (hexane-Et_2O, 3:2) to afford 454.0 mg (96%) of 27:73 mixture of methyl 2,3-di-O-benzyl-1,4-dideoxy-1α/1β-fluoro-D-glucoheptopyranuronate.

Preparation of methyl (8E,10S,11S,12S)-2,3-di-O-benzyl-1,4-dideoxy-1β-[11-methyl-12-formylcyclopropylethenyl]-D-glucoheptopyranuronate.

A dry, 1.0 L, three-necked, round-bottomed flask containing a magnetic stirring bar, and a thermometer was charged with freshly distilled 2,2,6,6-tetramethylpiperidine (29.7 ml, 176 mmol) and dry THF (240 ml). The solution was cooled to 0°C and nBuLi 2.5 M in hexane, 70.4 ml, 176 mmol) was added dropwise over 45 min. Following the addition, the mixture was stirred for 20 min at 0°C, then cooled to -78°C. A solution of (-)-dimenthyl succinate (31.56 g, 80 mmol) in THF (80 ml) was added dropwise over 1 h. The resulting yellow solution of succinate dianion was stirred for 1 h. To the reaction mixture was added a solution of 1,1-bromochloroethane (10.1 g, 70.4 mmol) in THF (15 ml) over a 5 h-period. After the reaction mixture was stirred for 2.5 h, it was poured into ice-cooled 0.5 N HCl (320 ml) and the product extracted with Et_2O (3x300 ml). The combined organic phases were washed with brine (1x400 ml), dried over sodium sulfate, filtered, and concentrated in vacuum. The residue was chromatographed over silica gel (hexane-Et_2O 20:1) to give 13.23 g (45 %) of dimenthyl (1S,2S)-3-methylcyclopropane-1,2-dicarboxylate as colorless crystals, melting point 98°-99°C.

To a solution of the dimenthyl (1S,2S)-3-methylcyclopropane-1,2-dicarboxylate (2.5 g, 5.94 mmol) in THF (10 ml) was added a 10% KOH solution in 9:1(EtOH-H_2O (3.94 ml, 7.02 mmol) at room temperature. The reaction mixture was stirred at room temperature for 3.5 days, then the solvent was evaporated, diluted with H_2O, and extracted with Et_2O. The aqueous layer was acidified with a 10% HCl solution to pH ~ 3 and extracted several times with Et_2O. The combined organic layers were washed successively with H_2O, brine, and dried over sodium sulfate. Evaporation of the solvent in vacuum afforded 1.4 g (83%) of the menthyl (1S,2S,3S)-2-carboxy-3-methylcyclopropane-1-carboxylate as a clear oil.

To a solution of the menthyl (1S,2S,3S)-2-carboxy-3-methylcyclopropane-1-carboxylate (1.32 g, 4.68 mmol) in dry THF (40 ml) cooled to 0°C was added dropwise a 1.0 M solution of B_2H_6-THF complex (5.62 ml, 5.62 mmol) over a 20 min-period. The reaction mixture was allowed to warm to room temperature and stirred for 8 h, followed by the addition of a second equivalent of B_2H_6-THF complex (5.617 ml, 5.617 mmol). When all the starting material had disappeared, the reaction mixture was carefully quenched at room temperature by a dropwise addition of 1:1, H_2O-AcOH (1 ml) with stirring until no more gas evolution occurred. The reaction mixture was concentrated at room temperature, and the slurry was diluted with EtOAc (80 ml) and washed with H_2O (30 ml). The aqueous phase was extracted with EtOAc (3x80 ml). The combined organic layers were washed with a sat. sodium bicarbonate solution, brine, and then dried over sodium sulfate. Solvent removal and purification of the residue by chromatography (hexane-EtOAc, 8:2) gave 1.25 g (100%) of menthyl (1S,2S,3S)-2-hydroxymethyl-3-methylcyclopropane-1-carboxylate as a white solid, melting point 85°-86°C.

A solution of the menthyl (1S,2S,3S)-2-hydroxymethyl-3-methylcyclopropane-1-carboxylate (0.536 g, 2 mmol) in CH_2Cl_2 (10 ml) was added to a suspension of periodinane (1.017 g, 2.4 mmol) in CH_2Cl_2 (10 ml) with stirring. The reaction mixture was stirred at room temperature for 1.5 h, followed by the addition of a second equivalent of the periodinane reagent. When all the starting material had disappeared, the reaction mixture was filtered through

Celite, and the filter cake was washed with CH_2Cl_2. The solvent was evaporated in vacuum, and the residue was chromatographed over silica gel (hexane-EtOAc, 95:5) to give 0.51 g (96%) of menthyl (1S,2S,3S)-2-formyl-3-methylcyclopropane-1-carboxylate as a white crystalline solid, melting point 66°-67°C.

A solution of triphenylphosphine (1.42 g, 5.41 mmol) in CH_2Cl_2 (15 ml) was cooled to 0°C and treated with CBr_4 (0.896 g, 2.70 mmol). A solution of menthyl (1S,2S,3S)-2-formyl-3-methylcyclopropane-1-carboxylate (0.360 g, 1.35 mmol) in CH_2Cl_2 (10 ml) was then added dropwise. The yellow solution was stirred at 0°C for 30 min. The solvent was evaporated in vacuum, and the residue was chromatographed over silica gel (hexane-EtOAc, 96:4) to give 0.56 g (98%) of menthyl (1S,2S,3S)-2-(2,2-dibromovinyl)-3-methylcyclopropane-1-carboxylate as a white solid, melting point 75°-76°C.

To a stirred solution of the menthyl (1S,2S,3S)-2-(2,2-dibromovinyl)-3-methylcyclopropane-1-carboxylate (3.96 g, 9.37 mmol) in toluene (50 ml) was added a 1 M solution of diisobutylaluminum hydride (DIBALH) (28.1 ml, 28.1 mmol) in hexane at -78°C. The resulting solution was stirred at -78°C for 10 min and then at 0°C for 30 min. The reaction mixture was poured into 0.2 N HCl (200 ml) and extracted with Et_2O (3x200 ml). The organic extracts were combined, washed with brine, dried over sodium sulfate and filtered. The solvent was removed in vacuum to give a colorless crude oil, which was purified by column chromatography over silica gel (hexane-Et_2O, 1:1) to afford 2.29 g (90%) of the corresponding cyclopropylcarbinol as a colorless oil.

To a stirred solution of the cyclopropylcarbinol obtained above (2.33 g, 8.64 mmol) in DMF (35 ml) was added triphenylmethyl chloride (9.64 g, 34.6 mmol) followed by Et_3N (9.63 ml, 69.1 mmol) and DMAP (0.21 g, 1.73 mmol) at room temperature. The resulting mixture was stirred at room temperature for 72 h, poured into an aqueous ammonium chloride solution (100 ml), and then extracted with Et_2O (3x200 ml). The organic layer was combined, washed with brine, dried over sodium sulfate and filtered. The solvent was removed in vacuum to give a colorless oil, which was purified by column chromatography over silica gel (hexane-CH_2Cl_2, 8:1) to afford 3.98 g (90%) of the (1S,2S,3S)-2-(2,2-dibromovinyl)-3-methyl-1-triphenylmethoxymethylcyclopropane as a colorless viscous oil.

To a stirred solution of the (1S,2S,3S)-2-(2,2-dibromovinyl)-3-methyl-1-triphenylmethoxymethyl-cyclopropane (128.6 mg, 0.251 mmol) in THF (5 ml) was added dropwise a 1.42 M solution of nBuLi (0.35 ml, 0.50 mmol) in hexane at -78°C. After stirring at -78°C for 10 min, the solution was poured into H_2O (30 ml) and extracted with Et_2O (3x30 ml). The organic extracts were combined, washed with brine, dried over sodium sulfate and filtered. The solvent was removed in vacuum to give a colorless residue, which was purified by column chromatography over silica gel (hexane-Et_2O, 20:1) to afford 81.4 mg (92%) of (1S,2S,3S)-3-ethynyl-2-methylcyclopropylmethyl triphenylmethyl ether as a colorless viscous oil.

To a stirred solution of the (1S,2S,3S)-3-ethynyl-2-methylcyclopropylmethyl triphenylmethyl ether (333.0 mg, 0.945 mmol) in hexane (3 ml) was added a

1.0 M solution of DIBALH (0.95 ml, 0.95 mmol) in hexane at 40°C. The resulting solution was stirred at 50°C for 2 h. After cooling to room temperature, the reaction mixture was diluted with toluene (4 ml). To this in situ-generated vinylalane solution was added a solution of methyl 2,3-di-O-benzyl-1,4-dideoxy-1α/1β-fluoro-D-glucoheptopyranuronate (anomeric mixture, α:β=27:73, 282.0 mg, 0.727 mmol) in toluene (1 ml) at -20°C. The resulting colorless solution was stirred at -20°C for 10 min then at room temperature for 30 min. The reaction mixture was poured into 0.2 N HCl (20 ml) and extracted with Et_2O (3x30 ml). The organic extracts were combined, washed with brine, dried over sodium sulfate and filtered. The solvent was removed in vacuum to give a colorless crude residue, which was purified by column chromatography over silica gel (hexane-CH_2Cl_2-EtOAc, 20:20:1) to afford 0.256 g (49%) of methyl (8E,10S,11S,12S)-2,3-di-O-benzyl-1,4-dideoxy-1β-[11-methyl-12-triphenylmethoxymethylcyciopropylethenyl]-D-glucoheptopyranuronate and 0.150 g (28%) of methyl (8E,10S,11S,12S)-2,3-di-O-(benzyl-1,4-dideoxy-1α-[11-methyl-12-triphenylmethoxymethylcyclopropylethenyl]-D-glucoheptopyranuronate as colorless oils.

To a stirred solution of methyl (8E,10S,11S,12S)-2,3-di-O-benzyl-1,4-dideoxy-1β-[11-methyl-12-triphenylmethoxymethylcyclopropylethenyl]-D-glucoheptopyranuronate (173.0 mg, 0.24 mmol) in CH_2Cl_2 (2 ml) was added a solution of p-toluenesulfonic acid (9.0 mg, 0.048 mmol) in MeOH (2 ml) at room temperature. The resulting solution was stirred at room temperature for 2 h and then poured into a sat. sodium bicarbonate solution (20 ml). This mixture was extracted with Et_2O (3 x 30 ml). The organic extracts were combined, washed with brine, dried over sodium sulfate and filtered. The solvent was removed in vacuum to give a colorless residue, which was purified by preparative thin layer chromatography (hexane-EtOAc, 1:1) to afford 106.0 mg (92%) of the methyl (8E,10S,11S,12S)-2,3-di-O-benzyl-1,4-dideoxy-1β-[11-methyl-12-hydroxymethylcyclopropylethenyl]-D-glucoheptopyranuronate as a colorless oil.

To a stirred solution of the methyl (8E,10S,11S,12S)-2,3-di-O-benzyl-1,4-dideoxy-1β-[11-methyl-12-hydroxymethylcyclopropylethenyl]-D-glucoheptopyranuronate (96.2 mg, 0.20 mmol) in CH_2Cl_2 (5 ml) was added Doss-Martin's periodinane (127.0 mg, 0.30 mmol) at room temperature. The resulting reaction mixture was stirred at room temperature for 30 min and then diluted with Et_2O (20 ml). This mixture was poured into a sat. sodium bicarbonate solution (10 ml) containing sodium thiosulfate (0.5 g). The organic layer was separated and the aqueous layer was washed with Et_2O (2x20 ml). The organic extracts were combined, washed with brine, dried over sodium sulfate and filtered. The solvent was removed in vacuum to give a crude residue, which was purified by preparative thin layer chromatography (hexane-EtOAc, 3:1) to afford 86.5 mg (90%) of methyl (8E,10S,11S,12S)-2,3-di-O-benzyl-1,4-dideoxy-1β-[11-methyl-12-formylcyclopropylethenyl]-D-glucoheptopyranuronate as a colorless oil.

Preparation of (+)-6-ethyl-5-methyl-2-(4-sulfotolyl-1,3-dimethyl-but-1-ene)-yl-3,6-dihydro-2H-pyran:

Sodium hydride (16.0 g, 0.4 mol, as a 60% dispersion in mineral oil) in a 1.0 L three-necked flask was washed with hexane (3x50 ml) to remove the

mineral oil. The flask was then equipped with rubber stoppers, a reflux condenser, and a mechanical stirrer. The system was alternatively evacuated and filled with nitrogen; DMSO (140 ml) was introduced rapidly, and the mixture was heated at 75°-80°C for 60 min, or until the evolution of hydrogen ceased. The resulting black-greenish solution of methylsulfinyl carbanion was cooled in an ice-H_2O bath, and methyltriphenylphosphonium bromide (142.8 g, 0.4 mol) in warm DMSO (320 ml) was added at 15°-20°C. The resulting solution was allowed to warm to it and stirred for 10 min, then at 30°-32°C for 10 min or until a red-brownish color developed. The reaction mixture was cooled to 15°C and the aldehyde (43.34 g, 0.44 mol) was added dropwise (through a cannula), keeping the temperature between 15°-20°C. The reaction mixture was stirred at room temperature for 25 min, then at 30°-32°C for 20 min. The reaction was immediately distilled in the presence of a cat. amount of hydroquinone under reduced pressure to give 32.0 g (75%) of 3-methyl-1,3-hexadiene collected in a solid carbon dioxide trap, boiling point 35°-37°C/59 mm Hg.

Freshly distilled 3-methyl-1,3-hexadiene (15.6 g, 0.162 mol) was placed into a Carius tube containing a cat. amount of hydroquinone, glyoxylic acid monohydrate (22.45 g, 0.244 mol), and $CHCl_3$ (80 ml). The tube was sealed and heated at 115°-120°C for 12 h. The reaction mixture was cooled to 0°C and diluted with H_2O (30 ml), the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3x60 ml). The combined organic extracts were washed with H_2O (1x100 ml), brine (1x100 ml), and dried over sodium sulfate. Complete removal of solvent afforded 22.5 g (81%) of a 4:1 mixture of (cis:trans) 6-ethyl-5-methyl-3,6-dihydro-2H-pyran-2-carboxylic acid as a reddish viscous oil, which was used directly in the next step without further purification.

A mixture of potassium fluoride (33.83 g, 0.582 mol), 2,4'-dibromoacetophenone (80.93 g, 0.291 mol), and DMF (350 ml) was stirred at room temperature for 5 min. A solution of 4:1 mixture of (cis:trans) acids (45.0 g, 0.265 mol) in DMF (50 ml) was then added to the reaction mixture and the whole stirred at room temperature for 3 h, then at 100°C for 30 min. The reaction mixture was cooled to room temperature and diluted with H_2O (200 ml). The aqueous solution was extracted with Et_2O (4x400 ml). The combined ethereal extracts were washed with H_2O (3x400 ml) and dried over sodium sulfate. After the solvent was partially removed in vacuo, a precipitate was formed. The slurry was the filtered to give 51.0 g (53%) of p-bromophenacyl ester of 6-ethyl-5-methyl-3,6-dihydro-2H-pyran-2-carboxylic acids as a white solid material, melting point 137°-138°C.

To a solution of the p-bromophenacyl ester of 6-ethyl-5-methyl-3,6-dihydro-2H-pyran-2-carboxylic acids (46.0 g, 0.125 mol) in glacial AcOH (650 ml) was slowly added zinc (dust, 49.31 g, 0.754 mol) in a 60 min-period at room temperature. The reaction mixture was stirred at room temperature for 8 h, then filtered on Celite, and the zinc residue washed with AcOH (200 ml), then THF (200 ml). Most of the solvent was evaporated and the crude reaction mixture diluted with Et_2O and washed with H_2O (2x150 ml). The organic layer was treated with a diluted NaOH solution to pH ~ 10. The aqueous phase was washed with Et_2O several times, then acidified with a 1.0 N HCl solution to pH ~ 4, and extracted with Et_2O. The combined organic extracts were

successively washed with H_2O, brine, and dried over sodium sulfate. After evaporation of the solvent, 19.23 g (90%) of pure (+)-6-ethyl-5-methyl-3,6-dihydro-2H-pyran-2-carboxylic acid was obtained as a yellowish solid, melting point 61°-63°C. This acid was used in the next step without further purification.

To a solution of (+)-6-ethyl-5-methyl-3,6-dihydro-2H-pyran-2-carboxylic acid (21.0 g, 0.123 mol) in MeOH (125 ml) was added (+)-α-methylbenzylamine (14.97 g, 0.123 mol) with stirring. The solvent was partially evaporated in vacuo and Et_2O (100 ml) was added. The solvents were partially evaporated and more Et_2O was added. The process was repeated until crystallization occurred. The reaction mixture was cooled to 0°C and filtered to give 19.0 g of the salt. The recrystallization process was repeated four more times or until the optical rotation of the corresponding acid was constant. After five recrystallizations, 6.0 g of the corresponding salt were obtained. This salt was then acidified with a 1.0 N HCl solution to pH ~ 4 and extracted with Et_2O several times. The organic phase was successively treated with H_2O, brine, and then dried over sodium sulfate. Evaporation of the solvent in vacuo gave 3.4 g (32%, from the racemic acid) of the optically pure acid (+)-6-ethyl-5-methyl-3,6-dihydro-2H-pyran-2-carboxylic acid as a clear viscous oil.

To a stirred solution of the (+)-6-ethyl-5-methyl-3,6-dihydro-2H-pyran-2-carboxylic acid (3.0 g, 17.65 mmol) in CH_2Cl_2 (60 ml), and DMF (0.12 ml) at 0°C was added oxalyl chloride (1.82 ml, 21.18 mmol) over a 30 min-period. The reaction mixture was stirred at 0°C for 1 h, then at room temperature for 2 h. The solvent was evaporated in vacuum, and the residue was used directly in the next reaction without further purification. In a 50 ml, two-necked, round-bottomed flask equipped with a Teflon-covered magnetic stirring bar, a drierite filled trap, and a thermometer was placed the crude acid chloride in HMPA (16 ml). Freshly prepared trans-propenyltrimethyltin (4.34 g, 21.18 mmol) was then added followed by the addition of benzylchlorobis(triphenylphosphine)palladium (II) (13.6 mg, 0.02 mmol). The yellow solution was heated at 65°-70°C with stirring under an air atmosphere for 3 h. The reaction mixture was cooled to room temperature and H_2O (15 ml) was added. The mixture was extracted with Et_2O (3x60 ml). The ethereal solutions were combined and washed with H_2O, brine, dried over sodium sulfate, and the solvent removed in vacuum. The residue was purified by chromotography over silica gel (hexane-EtOAc, 98:2) to give 3.1 g (90%) of (+)-6-ethyl-5-methyl-2-(but-2-ene-1-one)-yl-3,6-dihydro-2H-pyran as a colorless volatile oil.

A solution of the α,β-(+)-6-ethyl-5-methyl-2-(but-2-ene-1-one)-yl-3,6-dihydro-2H-pyran (3.02 g, 15.44 mmol) in THF (80 ml) was cooled to 0°C and MeMgBr (3.1 M solution in Et_2O, 6.5 ml, 20.1 mmol) was added dropwise over a 30 min-period. After the addition, the reaction mixture was stirred at 0°C for 2 h under argon. The reaction mixture was quenched at 0°C by addition of a sat. ammonium chloride solution (14 ml), then H_2O (14 ml). The mixture was extracted with Et_2O (3x70 ml). The ethereal solutions were combined and washed with brine (1x50 ml), dried over sodium sulfate and the solvent removed by evaporation. The residue was purified by chromatography over silica gel (hexane-EtOAc, 98:2) to give 3.0 g (92 %) of the (+)-6-ethyl-5-methyl-2-(1-methyl-1-hydroxy-2-buten)-yl-3,6-dihydro-2H-pyran-as a clear

volatile liquid.

Acetic anhydride (3.02 ml, 31.96 mmol) was added to a stirred solution of (+)-6-ethyl-5-methyl-2-(1-methyl-1-hydroxy-2-buten)-yl-3,6-dihydro-2H-pyran (3.36 g, 15.98 mmol), Et_3N (4.46 ml), and DMAP (0.39 g, 3.2 mmol) in CH_2Cl_2 (15 ml) at room temperature. The solution was stirred at room temperature for 3 days in a sealed tube. Excess of anhydride was quenched by the addition of MeOH. Evaporation of the solvents gave a reddish-oily residue, which was suspended in Et_2O and successively treated with 1.0 N HCl, aqueous sodium hydrogen carbonate, and sodium chloride sat. solution. The organic layer was dried over sodium sulfate and evaporated in vacuum. Purification of the residue by chromatography over silica gel (hexane-EtOAc, 98:2) gave 2.9 g (72%) of the acetic acid (+)-6-ethyl-5-methyl-2-(1-methyl-1-hydroxy-2-buten)-yl-3,6-dihydro-2H-pyran ester as a colorless oil.

To a stirred solution of dry N,N-diisopropylamine (1.1 ml, 7.85 mmol) in THF (10 ml) cooled to 0°C was added nBuLi (2.5 M in hexanes, 3.14 ml, 7.85 mmol) over several min. After the solution was stirred for 10 min following the addition, the reaction mixture was cooled to -78°C, and an additional 1 ml of THF was added. The acetic acid (+)-6-ethyl-5-methyl-2-(1-methyl-1-hydroxy-2-buten)-yl-3,6-dihydro-2H-pyran ester (1.65 g, 6.54 mmol) in THF (7 ml) was slowly added over a 40 min-period at -78°- (-70)°C. After the reaction was stirred for 5 min, TBSCl (1.18 g) in THF-HMPA (1:1,6 ml) was added in one portion. The cooling bath was then removed, and the reaction mixture was allowed to warm to 0°C and stirred for 1 h, then at room temperature for an additional 1 h, and finally 1.5 h at 65°C. The yellow solution was cooled to room temperature and diluted with THF (60 ml), then treated with a 10% HCl aqueous solution (16 ml). The reaction mixture was stirred at room temperature for 3 h The solvent was evaporated and the residue diluted with Et_2O and treated with a 1.0 N KOH aqueous solution; the organic phase was discarded, and the aqueous solution was washed with Et_2O. The basic solution was acidified with 10% HCl and the product isolated by ether extraction. This afforded 1.0 g (61%) of a 12:1 mixture of (+)-6-ethyl-5-methyl-2-(3-methyl-hex-4-enoic acid)-3,6-dihydro-2H-pyran as a colorless oil. This mixture was carried through the next reaction without further purification.

A solution of (+)-6-ethyl-5-methyl-2-(3-methyl-hex-4-enoic acid)-3,6-dihydro-2H-pyran (1.0 g, 3% mmol) in Et_2O (20 ml) was treated with an excess of diazomethane. The solvent was then evaporated, and the two isomers were cleanly separated by chromatography over silica gel (hexane-EtOAc, 98:2) to give 0.97 g (92%) of the methyl (+)-6-ethyl-5-methyl-2-(3-methyl-hex-4-enoic acid)-3,6-dihydro-2H-pyran ester as a clear liquid.

A solution of N,N-diisopropylamine (0.24 ml, 1.7 mmol) in THF (3 ml) was treated with nBuLi (2.5 M in hexane, 0.68 ml, 1.7 mmol) at 0°C, under a nitrogen atmosphere. After 20 min at 0°C, the solution was cooled to -78°C, and a solution of the methyl (+)-6-ethyl-5-methyl-2-(3-methyl-hex-4-enoic acid)-3,6-dihydro-2H-pyran ester (266.0 mg, 1 mmol) in THF (3 ml) was slowly added. After 1 h at -78°C, p-toluenesulfonyl fluoride (348.0 mg, 2.0 mmol) in THF (2 ml) was added all at once. The reaction mixture was allowed to warm to room temperature and stirred for 24 h, then cooled to 0°C, quenched by careful addition of a sat. ammonium chloride solution, and

extracted with EtOAc several times. The combined organic extracts were washed with H_2O and brine, dried over sodium sulfate, and concentrated in vacuum. The residue was chromatographed over silica gel (hexane-EtOAc, 9:1) to give 180.0 mg (43% isolated yield) of methyl (+)-6-ethyl-5-methyl-2-(2-sulfonyl-benzene-3-methyl-hex-4-enoic acid)-3,6-dihydro-2H-pyran ester, melting point 129°-131°C as a mixture of diastereomers. This diastereomeric mixture was used directly in the next step without further purification.

To a stirred solution of methyl (+)-6-ethyl-5-methyl-2-(2-sulfonyl-benzene-3-methyl-hex-4-enoic acid)-3,6-dihydro-2H-pyran ester (130.0 mg, 0.31 mmol) in HMPA (2 ml) was added $(Me)_4N^+$ -OAc (370.0 mg, 2.78 mmol) and the mixture was heated at 96°-100°C for 17 h. The reaction mixture was cooled and diluted with EtOAc, washed with H_2O several times, brine, dried over magnesium sulfate, and the solvent removed in vacuum. The residue was purified by chromatography over silica gel (hexane-EtOAc 9:1) to give 0.08 g (71%) of (+)-6-ethyl-5-methyl-2-(4-sulfotolyl-1,3-dimethyl-but-1-ene)-yl-3,6-dihydro-2H-pyran as a clear liquid.

Preparation of (+)-Ambruticin:

To a stirred solution of (+)-6-ethyl-5-methyl-2-(4-sulfotolyl-1,3-dimethyl-but-1-ene)-yl-3,6-dihydro-2H-pyran (54.4 mg, 0.15(mmol) in dry Et_2O (1 ml) cooled to 0°C was added dropwise a solution of nBuLi (1.5 M in hexane, 0.18 mmol). The yellow solution was stirred at 0°C for 10 min, then at -42°C for 15 min. Dry hexane (0.5 ml) was added, and a solution of the methyl (8E,10S,11S,12S)-2,3-di-O-benzyl-1,4-dideoxy-1β-[11-methyl-12-formylcyclopropylethenyl]-D-glucoheptopyranuronate (60.0 mg, 0.125 mmol) in Et_2O (0.5 ml) was added dropwise. The reaction mixture was stirred at -42°C for 2 h, then quenched with ammonium chloride, and extracted with EtOAc several times. The combined organic extracts were washed with brine, dried over sodium sulfate, and the solvent removed in vacuum. The residue was chromatographed over silica gel (hexane-EtOAc, 8:2) to give 53.7 mg (51%) of a mixture of diastereomers. The mixture was used in the next reaction without further purification.

To a stirred solution of this mixture (10.0 mg, 0.012 mmol) in a mixture of MeOH-THF 1:1 (0.8 ml) cooled to -35°C was added an excess of Na(Hg) 6% (300.0 mg) in one portion. The reaction mixture was stirred at -35°C for 3.5 h, then diluted with Et_2O and filtered through Celite; the cake was washed several times with Et_2O. To the ether solution was added a sat. solution of ammonium chloride and then 1.0 N HCl solution until pH - 4. The aqueous phase was extracted several times with EtOAc, and the combined organic phase was washed with H_2O, brine, dried over sodium sulfate, and concentrated in vacuum. The residue was chromatographed over silica gel (hexane-EtOAc, 9:1) to give 13(E)-tetraene (methyl 5α,6β-dibenzyloxypolyangioate) as the main product, in 63% overall yield, as a clear colorless liquid. Careful chromatography of this E/Z mixture eluted with CH_2Cl_2/hexane/Et_2O (10:10:1) produced pure 13(E) product.

To a stirred solution of 13(E) methyl 5α,6β-dibenzyloxypolyangioate (7.0 mg, 0.0105 mmol) in THF (1.5 ml) was added a solution of LiOH (1.3 mg, 0.0525 mmol) in H_2O (0.5 ml) at room temperature. The resulting solution was

stirred at room temperature for 18 h and then poured into 0.2 N HCl (10 ml). This mixture was extracted with Et_2O (3x20 ml). The organic extracts were combined, washed with brine, dried over sodium sulfate and filtered. The solvent was removed in vacuum to give 7.0 mg of crude 5α,6β-dibenzyloxypolyangioic acid as a colorless oil. This crude acid was used in next debenzylation step without further purification.

To a stirred solution of the crude 5α,6β-dibenzyloxypolyangioic acid (7.0 mg, 0.0105 mmol) in liquid ammonia (10 ml, distilled from sodium) and EtOH (2 ml) at -78°C was added 0.7 mg (0.105 mmol) of lithium wire. The resulting mixture was stirred at -78°C for 30 min. Ammonium chloride (20.0 mg) was added to this mixture to quench the excess lithium and stirred for 30 min at -78°C. To the resulting mixture was added CH_2Cl_2 (10 ml), stirred for 1 h at room temperature, then poured into 0.2 N HCl (10 ml), and extracted with $CHCl_3$ (3x20 ml). The organic extracts were combined, washed with brine, dried over sodium sulfate and filtered. The solvent was removed in vacuum to give a colorless oil, which was purified by preparative thin layer chromatography (EtOAc-i-PrOH-H_2O, 85:10:5) to afford 3.2 mg (63% from 5 L) of ambruticin as an amorphous powder.

References

Kende A.S. et al.; Total synthesis of natural (+)-ambruticin; Tetrahedron Vol. 49, N 36, pp. 8015-8038, 1993

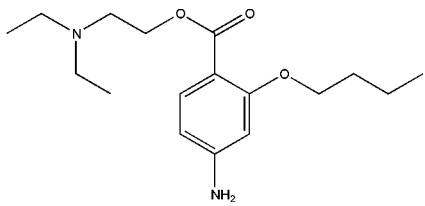
AMBUCAINE

Therapeutic Function: Local anesthetic

Chemical Name: Benzoic acid, 4-amino-2-butoxy-, 2-(diethylamino)ethyl ester

Common Name: Ambucaine; Ambutoxate; 2-Butoxyprocaine

Structural Formula:



Chemical Abstracts Registry No.: 119-29-9

Trade Name	Manufacturer	Country	Year Introduced
Ambucaine	ZYF Pharm Chemical	-	-
Ambucaine	Onbio Inc.	-	-

Raw Materials

Potassium carbonate
Sodium carbonate
Hydrochloric acid
Hydrogen
Ammonia
4-Nitro-2-hydroxybenzoic acid
n-Butylbenzenesulfonate
Nickel Raney
Diethylaminoethyl chloride

Manufacturing Process

A stired mixture of 4-nitro-2-hydroxybenzoic acid, anhydrous potassium carbonate and n-butyl benzenesulfonate in xylene was refluxed under a continuous water separator for about 19 h. The insoluble potassium salts were filtered off and washed with hot dry toluene. The combined filtrate and washings were distilled under reduced pressure to remove the solvents, thereby leaving a residual oil which solidified on cooling. The solid yields of greater than 95% of n-butyl 4-nitro-2-n-butoxybenzoate (recrystallized from methanol).

The n-butyl 4-nitro-2-n-butoxybenzoate obtained was dissolved in 50% aqueous ethanol. To this solution was added 2 - 3 molecular equivalents of sodium carbonate, and the resulting mixture, was stirred under reflux for about 16 h. After the ethanol has been distilled off under reduced pressure, the remaining aqueous solution was diluted with water and made acidic with concentrated hydrochloric acid. The precipitated yellow solid was filtered, washed with water, dried in a vacuum oven at 90°C and recrystallized from ethyl acetate. There was thus obtained a 4-nitro-2-n-butoxy-benzoic acid (95.5% yield), melting point 120.9°-122.8°C (corr.).

A mixture of 4-nitro-2-n-butoxybenzoic acid, anhydrous potassium carbonate and 400 ml of dry toluene was refluxed and stirred under a continuous water separator. When the evolution of water had ceased (3 h), the water separator was removed and there was added diethylaminoethyl chloride. The mixture was then refluxed with stirring for about 20 h, filtered while hot, and the solvent was removed from the filtrate by distilling in vacuo. The residual oil was dissolved in dilute hydrochloric acid, the solution was decolorized with activated carbon and the base was liberated by the addition of excess ammonia. The base was extracted with ethyl acetate, the solution was dried, and the ethyl acetate was removed by distilling in vacuo, yielding 2-diethylaminoethyl 4-nitro-2-n-butoxybenzoate as a pale yellow oil.

The 2-diethylaminoethyl 4-nitro-2-n-butoxybenzoate in ethanol is hydrogenated using 50 lbs. pressure of hydrogen at 25°C in the presence of Raney nickel (alternatively platinum oxide monohydrate). After the rapid exothermic reaction, the catalyst is filtered off and the filtrate evaporated to dryness to give the 2-diethylaminoethyl 4-amino-2-n-butoxybenzoate.

References

Clinton R.O., Laskowski S.C.; US Patent No. 2,689,248; Sept. 14, 1954; Assigned: Sterling Drug Inc., New York, N.Y., a corporation of Delaware

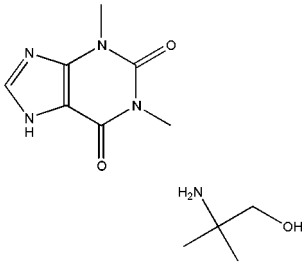
AMBUPHYLLINE

Therapeutic Function: Diuretic, Smooth muscle relaxant

Chemical Name: 3,7-Dihydro-1,3-dimethyl-1H-purine-2,6-dione compound with 2-amino-2-methyl-1-propanol (1:1)

Common Name: Theophylline aminoisobutanol; Bufylline

Structural Formula:



Chemical Abstracts Registry No.: 5634-34-4

Trade Name	Manufacturer	Country	Year Introduced
Butaphyllamine	Merrell Dow	US	1944
Buthoid	Merrell Dow	US	-

Raw Materials

Theophylline
2-Amino-2-methyl-1-propanol

Manufacturing Process

Equimolecular proportions of theophylline and 2-amino-2-methyl-1-propanol are dissolved in water and the water is evaporated until crystallization is almost complete. The crystals are filtered off and dried. The product has a melting point of 254-256°C, softening at 245°C. It has a water solubility of about 55%. It may be compounded in the form of tablets, for oral administration, or may be prepared in solution for distribution in ampoules. For the manufacture of solutions for packaging in ampoules, it is more convenient to simply dissolve the theophylline and the butanolamine in water, without going through the intermediate step of separating the crystalline salt.

References

Merck Index 385
I.N. p. 64
Shelton, R.S.; US Patent 2,404,319; July 16, 1946; Assigned to The Wm. S. Merrell Co.

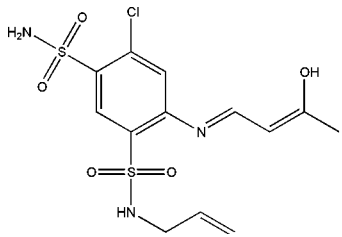
AMBUSIDE

Therapeutic Function: Diuretic, Antihypertensive

Chemical Name: N'-Allyl-4-chloro-6-[(3-hydroxy-2-butenylidene)amino]-m-benzenedisulfonamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 3754-19-6

Trade Name	Manufacturer	Country	Year Introduced
Hydrion	Robert and Carriere	France	1970

Raw Materials

2-Allylsulfamyl-5-chloro-4-sulfamylaniline
Acetaldehyde dimethylacetal

Manufacturing Process

Preparation of 2-Allylsulfamyl-4-Sulfamyl-5-Chloro-N-(3-Hydroxy-2-Butenylidene)Aniline or Ambuside: 2-allylsulfamyl-5-chloro-4-sulfamylanilinemonohydrate (6.9 grams, 0.020 mol) was dissolved in 14 ml acetylacetaldehyde dimethylacetal at room temperature and the viscous solution was filtered. Addition of 6 drops of 10:1 H_2O/concentrated HCl, and stirring for 20 hours gave a heavy suspension. Dilution with 150 ml of ethanol, collection of the solid, washing twice with 40 ml portions of ethanol, and drying gave 6.2 grams (78%) of product, MP 204-206°C.

References

Merck Index 386
Kleeman and Engel p. 35
OCDS Vol.2 p. 116 (1980)
I.N. p. 64
Robertson, J.E.; US Patent 3,188,329; June 8, 1955; Assigned to Colgate-Palmolive Co.

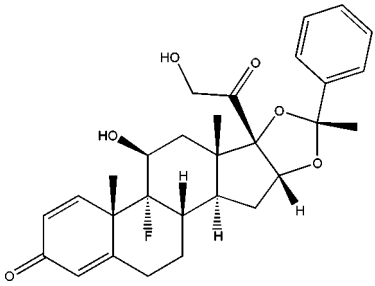
AMCINAFIDE

Therapeutic Function: Antiinflammatory, Antiallergic

Chemical Name: 9-Fluoro-11,21-dihydroxy-16,17-[(1-phenylethylidene) bis(oxy)]pregna-1,4-diene-3,20-dione

Common Name: Amcinafide

Structural Formula:



Chemical Abstracts Registry No.: 7332-27-6

Trade Name	Manufacturer	Country	Year Introduced
Amcinafide	Onbio Inc.	-	-

Raw Materials

Triamcinolone
Perchloric acid
Acetophenone

Manufacturing Process

1 ml 72% perchloric acid was added to a suspension of 4 g triamcinolone in 100 ml of fresh distilled acetophenone and the mixture was stirred at a room temperature before all triamcinolone solved (for about 2 hours). The solution was neutralized with help of 8 ml of 1.1 N sodium hydroxide and sufficient quantity of sodium bicarbonate. Then chloroform and water were added. Organic layer was separated and concentrated in vacuum. The residue was recrystallized from acetone-hexane and thoroughly washed from acetophenone with hexane. Triamcinolone acetophenide (amicinafide) was prepared. It had MP: 281°-283°C (decomp.);α_D^{23} = +23°. (c = 0.98 in $CHCl_3$).

References

Fried J.; D. E. Patent No. 1,099,529; August 6, 1958; Olin Mathieson Chemical Corporation New York, N.Y. (USA)

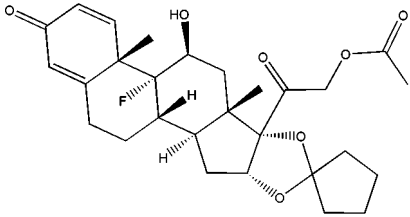
AMCINONIDE

Therapeutic Function: Topical corticosteroid, Antiinflammatory

Chemical Name: 16α,17α-Cyclopentylidenedioxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione-21-acetate

Common Name: Amcinopol

Structural Formula:



Chemical Abstracts Registry No.: 51022-69-6

Trade Name	Manufacturer	Country	Year Introduced
Cyclocort	Lederle	US	1979
Amcinonid	Cyanamid	W. Germany	1981
Visderm	Lederle	Japan	1982
Penticort	Lederle	France	-
Mycoderm	Lederle	-	-

Raw Materials

16α,17α-Cyclopentylidenedioxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione
Acetic anhydride

Manufacturing Process

An 11.1 g (24.1 mmol) portion of the compound 16α,17α-cyclopentylidenedioxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione is placed in a 250 ml round-bottom flask. A 100 ml portion of pyridine is added and the mixture is stirred to a complete solution. A 5.5 ml (54.6 mmol) portion of acetic anhydride is added dropwise and the mixture is stirred for 2% hours. An 11 ml portion of methanol is added and the mixture is stirred an additional hour. This mixture is concentrated under reduced pressure to about 10 to 15 ml and then poured slowly into a mixture of ice, water and dilute hydrochloric acid. This mixture is stirred and the solid which forms is collected by filtration, washed with water to a neutral pH and air dried yielding 11.5 g. This solid is taken up in hot acetone, treated with activated charcoal and filtered while hot through diatomaceous earth. The filtrate is concentrated on a steam bath while adding n-hexane to the point of incipient crystallization. This mixture is allowed to cool to room temperature. The solid which forms is

collected by filtration, washed with acetone-n-hexane (1:14) and air dried yielding 7.0 g of the desired product.

References

Merck Index 389
DFU 3 (5) 337 (1978)
Kleeman and Engel p. 36
PDR p. 1007
DOT 16 (10) 322 (1980)
I.N. p. 65
REM p.972
Schultz, W., Sieger, G.M. and Krieger, C.; British Patent 1,442,925; July 14, 1976; Assigned to American Cyanamid Company.

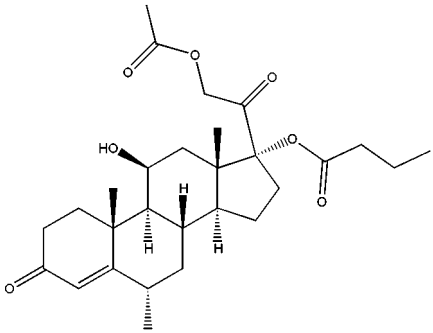
AMEBUCORT

Therapeutic Function: Antiinflammatory, Antiallergic

Chemical Name: 21-Acetoxy-17-butyryloxy-11β-hydroxy-6α-methyl-4-pregnene-3,20-dione

Common Name: Amebucort

Structural Formula:



Chemical Abstracts Registry No.: 83625-35-8

Trade Name	Manufacturer	Country	Year Introduced
Amebucort	ZYF Pharm Chemical	-	-

Raw Materials

17,21-Dihydroxy-6α-methyl-4-pregnene-3,20-dione
Pyridinium tosylate
Trimethyl orthoformate

Sweetwort slant with Curvularia lunata (NRRL 2380)
Glucose
Germination culture
Butyric anhydride
Sulfuric acid

Manufacturing Process

(a) 100 g of 17,21-dihydroxy-6α-methyl-4-pregnene-3,20-dione and 10 g of pyridinium tosylate are dissolved in 700 ml of dimethylformamide at room temperature and under agitation, and the clear solution is diluted with 3.5 L of toluene. The solution is then warmed up in a glycerin bath and, at a temperature of 120°C, 1.2 L of toluene is distilled off to remove traces of water. Under agitation, 240 ml of trimethyl orthoformate is gradually poured into the hot reaction solution; the latter is reacted for 30 min and thereafter additional toluene and other readily volatile reaction components are removed by 1 hour of distillation. The mixture is combined with 120 ml of pyridine, cooled to 60°C, and concentrated under vacuum at a bath temperature of 70°C. The mixture is then diluted with 400 ml of dimethylformamide, and the solution is poured under agitation into 10 L of water, thus obtaining the product in the form of a yellowish-white, crystalline precipitate. The mixture is stirred for another 2 hours, vacuum-filtered, washed with water, and dried for 24 hours at 40°C in a vacuum over phosphorus pentoxide, thus obtaining 111.6 g of 17,21-(1-methoxyethylidenedioxy)-6α-methyl-4-pregnene-3,20-dione, melting point 85-87°C.

(b) A 7-14 day old sweetwort slant with Curvularia lunata (NRRL 2380) is freed of the supernatant with 3 ml of physiological sodium chloride solution, and this supernatant is used to inoculate a 2-liter Erlenmeyer flask containing 500 ml of a nutrient solution of 2% glucose and 2% cornsteep, sterilized for 30 min at 120°C in an autoclave and adjusted to pH 6.5. After 60 hours of shaking on a rotary shaker at 30°C, 250 ml of this germination culture is used to inoculate the preliminary fermentor. A 20-liter prefermentor charged with 15 L of a nutrient medium of the same composition as the germination medium and sterilized at 121°C and 1 bar gauge pressure is inoculated with 250 ml of germination culture. With the addition of silicone SH as the defrother, germination is now conducted up to 29°C and 0.6 bar pressure under aeration (15 L/min) and agitation (220 rpm) for 24 hours. The main fermentor is inoculated with 1.5 L of this prefermentor culture. A 20-liter main fermentor, filled with 13.5 L of a sterilized nutrient medium made up of 3% cornsteep liquor and 0.7% glucose, adjusted to pH 5.5, is inoculated with 1.5 L of prefermentor culture. After an incubation phase of 12 hours under prefermentation conditions, a sterile-filtered solution of 12.18 g of 17,21-(1-methoxyethylidenedioxy)-6α-methyl-4-pregnene-3,20-dione in 130 ml of dimethylformamide is added thereto and the mixture is further agitated and aerated. 4 hours after addition of the substrate, the pH value of the culture broth is set at pH 4.5 and held at this value. The pH 0.2 by automatic control with 16% sodium hydroxide solution and 20% sulfuric acid until the end of the fermentation. After a contact period of 51 hours, the microbiological conversion is complete. The content of the fermentor is then treated in a continuous centrifuge, and the culture filtrate as well as the centrifuged fungal mycelium are extracted separately with methyl isobutyl ketone. The extracts are combined and first concentrated in a forced-circulation evaporator to 1 liter at 40°C under vacuum, and then entirely evaporated to dryness in a 2-

liter round flask on a rotary evaporator under vacuum at a bath temperature of 40°C. The remaining oily residue is combined with 400 ml of hexane and decanted after vigorous shaking. Subsequently, the residue is once again combined with 400 ml of hexane and agitated at room temperature for 2 hours. The now completely crystallized residue is vacuum-filtered, washed with 100 ml of hexane, and dried for 4 hours at 60°C in a vacuum. Yield: 9.9 g of 17-acetoxy-11β,21-dihydroxy-6α-methyl-4-pregnene-3,20-dione which, after recrystallization from acetone-diisopropyl ether, melts at 192-194°C.

A solution of 1.0 g of 17-acetoxy-11β,21-dihydroxy-6α-methyl-4-pregnene-3,20-dione in 20 ml of pyridine is combined with 3 ml of butyric anhydride and stirred at room temperature for 2 hours. The reaction solution is then allowed to flow into 150 ml of cooled 8% sulfuric acid and agitated for another 5 hours; the product, initially precipitated in oily form, becomes completely crystallized. The product is vacuum-filtered, washed with water, and dried for 6 hours at 80°C in a vacuum. For purifying purposes, the crude product is recrystallized from acetone-diisopropyl ether, thus obtaining 940 mg of 17-acetoxy-21-butyryloxy-11β-hydroxy-6α-methyl-4-pregnene-3,20-dione, melting point 98-120°C.

References

Annen K., Petzoldt K., Laurent H., Wiechert R., Hofmeister H.; US Patent No. 4,912,098; March 27, 1990; Assigned to Schering Aktiengesellschaft (Berlin and Bergkamen, DE)

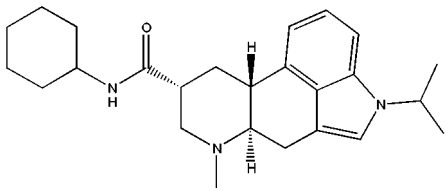
AMESERGIDE

Therapeutic Function: Serotonin antagonist

Chemical Name: Ergoline-8-carboxamide, N-cyclohexyl-6-methyl-1-(1-methylethyl)-, (8β)-

Common Name: Amesergide

Structural Formula:



Chemical Abstracts Registry No.: 121588-75-8

Trade Name	Manufacturer	Country	Year Introduced
Amesergide	Onbio Inc.	-	-
LY 237733	Lilly	-	-

Raw Materials

(8β)-1-Isopropyl-6-methylergoline-8-carboxylie acid
Potassium carbonate
Isobutyl chloroformate
Cyclohexylamine
Ammonium hydroxide

Manufacturing Process

To a 250 ml three-neck round bottom flask was added 10.0 g (32.01 mmol) of (8β)-1-isopropyl-6-methylergoline-8-carboxylie acid, 4.43 g (32.1 mmol) of potassium carbonate and 200 ml of N,N-dimethylformamide. The mixture was refluxed and 25 ml of a distillate was collected. The remaining solution was cooled in an ice bath, and then with an acetonitrile/carbon dioxide bath which lowered the temperature of the reaction mixture to about -45°C this mixture was added 4.59 g (33.62 mmol) of isobutyl chloroformate dropwise. The resulting mixture was stirred for approximately 5 min and 3.49 g (35.21 mmol) of cyclohexylamine was added. The reaction mixture was allowed to warm to room temperature and stirred for approximately 19 h. To the mixture was added 500 ml of ice water containing 25 ml of concentrated ammonium hydroxide. The mixture was cooled and the precipitated solid was collected by vacuum filtration. The resulting solid was washed with water and dried in vacuo to provide 10.13 g (yield 76.8%) of the (8β)-N-cyclohexyl-1-isopropyl-6-methylergoline-8-carboxamide having a purity of 92.3%.

The resulting solid was combined with three other lots of the desired compound previously synthesized to provide a total weight of 33.6 g. This material was dissolved in 1200 ml of hot methanol and the resulting solution was filtered. The filtrate was allowed to cool to room temperature and 600 ml of water was added dropwise. The mixture was cooled in the freezer and the precipitated crystals were collected by vacuum filtration. The crystals were washed with methanol and dried in vacuo to provide 26.95 g of the desired compound having a purity of 96.5% as determined by HPLC. The dried solid was dissolved in 1100 ml of hot methanol, and the resulting solution was filtered hot and allowed to cool. To this mixture was added 600 ml of water and again the precipitated solid was collected by vacuum filtration. The solid was washed with water and dried in vacuo to provide 25.82 g of the (8β)-N-cyclohexyl-1-isopropyl-6-methylergoline-8-carboxamide, melting point 250°C. The assayed material indicated 98.7% purity.

References

Foreman M.M. et al.; European Patent Application 0,296,748; June 6, 1988; Hudson, Christopher Mark et al Erl Wood Manor Windlesham Surrey GU20 6PH (GB)

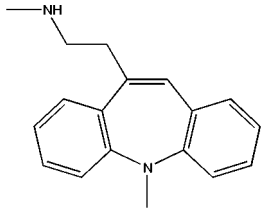
AMEZEPINE

Therapeutic Function: Antidepressant

Chemical Name: 5H-Dibenz[b,f]azepine, 5-methyl-10-(2-methylamino) ethyl)-

Common Name: Amezepine

Structural Formula:



Chemical Abstracts Registry No.: 60575-32-8

Trade Name	Manufacturer	Country	Year Introduced
Amezepine	ZYF Pharm Chemical	-	-
Amezepine	Onbio Inc.	-	-

Raw Materials

Potassium	9-Methoxycarbony-10-methylacridinium methosulphate
Sodium hydroxide	Potassium borohydride
Fumaric acid	Lithium aluminum hydride
Hydrochloric acid	Phosphorus pentoxide
Caustic potash	1-Dimethylamino-2-chloroethane hydrochloride

Manufacturing Process

78.0 g 9-methoxycarbony-10-methylacridinium methosulphate salt (obtained according to a process analogous to that described by Rauhut et al. [J. Org. Chem.,(30, 3587 (1965)], 800 ml ethanol and 40 ml distilled water are mixed; then 80.0 g potassium borohydride are added over the course of 45 min, at room temperature. The mixture is agitated for 30 min, poure into a water-ice mixture, agitated for 2 h, and extracted with ether; the extract is dried by vacuum distillation. 51.0 g 9-methoxycarbonyl-10-methylacridan, melting point 106°C (recrystallized from isopropyl ether) are obtained.

250.0 g 1-dimethylamino-2-chloroethane hydrochloride and 250 ml water are mixed and cooled; 250 ml sodium hydroxide solution are added at a temperature below 10°C; the mixture is agitated for 15 min at 5°C and extracted with ether. The ethereal phases are washed with water and dried over magnesium sulfate; the ether is distilled off and the residue is redistilled. 130.0 g 1-dimethylamino-2-chloroethane, boiling point 106°-108°C, are obtained.

36.5 g 9-methoxycarbonyl-10-methylacridan and 1 L of toluene are mixed; 50 ml toluene are distilled off and the mixture is cooled. 5.56 g potassium are

added at a temperature below +10°C; the mixture is agitated for 2 h at room temperature, refluxed for 30 min, and cooled.

A solution of 52.5 ml 1-dimethylamino-2-chloroethane in 200 ml toluene is added at a temperature below 20°C; the mixture is refluxed for 20 h and cooled, and 100 ml t-butanol are added. The mixture is agitated for 1 h at room temperature, 35 ml ethanol are added, and the mixture is again agitated for 30 min at room temperature. It is then extracted with 2 N hydrochloric acid; the acidic phases are washed with ether, made alkaline by the addition of sodium hydroxide solution, and extracted with ether; the ethereal phases are washed with water, dried over magnesium sulphate and then distilled to dryness under a vacuum. The residue is dissolved in 100 ml methanol; 300 ml of a saturated solution of fumaric acid in methanol are added; the methanol is distilled off and replaced by ethyl acetate. Crystallization is allowed to commence and the mixture is cooled with ice for 30 min and suction-filtered; the precipitate is washed with water and dried. 37.0 g 9-(2-dimethylaminoethyl)-9-methoxycarbonyl-10-methylacridan fumarate are obtained, melting point 176°C (recrystallized from methanol-ethyl acetate).

50.0 g of the 9-(2-dimethylaminoethyl)-9-methoxycarbonyl-10-methylacridan fumarate are suspended in 500 ml water; the suspension is cooled and 30 ml sodium hydroxide solution are added. The mixture is extracted with dichloromethane and the organic phases are washed with water, dried over magnesium sulphate and then distilled to dryness under a vacuum 36.0 g 9-(2-dimethylaminoethyl)-9-methoxycarbonyl-10-methylacridan are obtained.

400 ml tetrahydrofuran are cooled and 20.0 g lithium aluminum hydride are added over the course of 15 min, followed by a solution of 36.0 g 9-(2-dimethylaminoethyl)-9-methoxycarbonyl-10-methylacridan in 400 ml tetrahydrofuran added over the course of 30 min. The mixture is refluxed for 2 h and cooled, and 200 ml tetrahydrofuran containing 20% water are added at a temperature below 0°C. The mixture is filtered, washed with dichloromethane, and distilled to dryness under a vacuum; the residue is dissolved in dichloromethane and the organic phases are washed with water, dried over magnesium sulfate, and concentrated, ethyl acetate being added to replace the dichloromethane. Crystallization is allowed to commence and the mixture is cooled with ice for 1 h, suction-filtered, washed with water, and dried.

24.5 g 9-(2-dimethylaminoethyl)-9-hydroxymethyl-10-methylacridan, melting point 150°C (recrystallized from dichloromethane - ethyl acetate) are obtained. On concentration of the mother liquors, a second yield of 1.6 g of product is obtained (total yield: 79%).

A mixture of 24.5 g 9-(2-dimethylaminoethyl)-9-hydroxymethyl-10-(methylacridan) 1 L of m-xylene and 125.0 g phosphorus pentoxide are refluxed for 3 h; the reacture mixture is cooled, poured on to ice, agitated for 15 min, alkaline by the addition of sodium hydroxide solution, and extracted with ethyl acetate; the organic phases are washed with water, dried over magnesium sulfate, and dried by vacuum distillation. The residue is dissolved in ether, filtered, and concentrated to a small volume; pentane is added with distillation to remove the ether. The mixture is filtered and concentrated to about 100 ml; crystallization is allowed to commence and the mixture is

cooled with ice for 1 h and suction-filtered; the precipitate is washed with water and dried in vacua. After chromatographing on magnesium silicate, eluting with ether 16.0 g 5-methyl-10-(2-dimethylaminoethyl)-5H-dibenz[b,f]azepine, melting point 78°C (recrystallized from pentane) are obtained (yield: 70%).

32.5 ml benzene and 5 ml ethyl chloroformate are mixed; a solution of 6.5 g 5-methyl-10-(2-dimethylaminoethyl)-5H-dibenz[b,f] azepine in 32.5 ml benzene are added; the mixture is refluxed for 5 h and cooled; ethyl acetate is added and the mixture is agitated in the presence of N-hydrochloric acid; the organic phase is decanted off, washed with water, dried over magnesium sulfate, and distilled to dryness under a vacuum; 5.0 g 5-methyl-10-[2-(N-ethoxycarbonyl-N-methylamino)ethyl]-5H-dibenz[b,f]azepine are obtained. (Yield: 64%).

5.0 g caustic potash in 50 ml n-butanol is added to 5.0 g 5-methyl-10-[2-(N-ethoxycarbonyl-N-methylamino)ethyl]-5H-dibenz[b,f]azepine; the mixture is agitated and refluxed for 20 h, and the butanol is distilled off in vacua; the residue is taken up with water, the mixture is extracted with ethyl acetate, and the organic phases are washed with water and dried over magnesium sulfate, and then distilled to dryness under vacuum; the residue is dissolved in 10 ml ether and the solution is chromatographed on magnesium silicate, eluting with ether, and distilled to dryness under a vacuum; 3.5 g crude 5-methyl-10-(2-methylamino-ethyl)-5H-dibenz[b,f] azepine are obtained.

References

GB Patent No. 1,316,361; May 9, 1973; Assigned: ROUSSEL UCLAF, a French Body Corporate of 35 Boulevard des Invalidies, Paris 7e, France

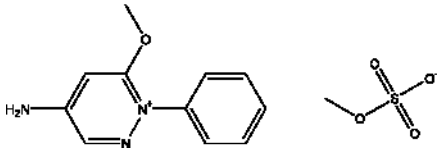
AMEZINIUM METHYL SULFATE

Therapeutic Function: Antihypotensive

Chemical Name: 4-Amino-6-methoxy-1-phenylpyridazinium methyl sulfate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 30578-37-1

Trade Name	Manufacturer	Country	Year Introduced
Regulton	Nordmark	W. Germany	1981
Regulton	Knoll	Switz.	1983

Raw Materials

1-Phenyl-4-aminopyridazone
Dimethyl sulfate

Manufacturing Process

18.7 parts of 1-phenyl-4-aminopyridazone-(6) and 19 parts of dimethyl sulfate in 400 parts of xylene are kept at 120°C for one hour while mixing well. The reaction mixture is suction filtered, 28 parts (89.5% of the theory) of 1-phenyl-4-amino-6-methoxypyridazinium methosulfate is obtained having a melting point of 173°C to 174°C after recrystallization from acetonitrile. The perchlorate has a melting point of 179°C to 182°C.

References

Merck Index 395
DFU 5 (4) 207 (1980)
DOT 18 (7) 317 (1982)
I.N. p. 66
Reicheneder. F. and Kropp, R.; US Patent 3,631,038; December 28, 1971; Assigned to Badische Anilin und Soda-Fabrik A.G.

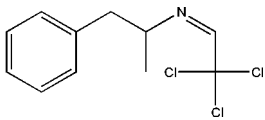
AMFECLORAL

Therapeutic Function: Anorexic

Chemical Name: 1-Phenyl-N-(2,2,2-trichlorethylidene)-2-propylamine

Common Name: Amfecloral; Amphecloral

Structural Formula:



Chemical Abstracts Registry No.: 5581-35-1

Trade Name	Manufacturer	Country	Year Introduced
Amphecloral	ZYF Pharm Chemical	-	-

Raw Materials

d-Amphetamine
Chloral hydrate

Manufacturing Process

Molar equivalents of d-amphetamine base and chloral hydrate were dissolved

in benzene and the solution was heated to distill off benzene and water, azeotropically. Two molar equivalents of water were separated in this manner. The remainder of the benzene was distilled off, leaving a liquid residue which was then fractionally distilled to yield the clear, colorless liquid condensation product, N-[2-(1-phenylpropyl)]-2,2,2-trichloroethylidenimine, which boiled at 95°C/0.5 mm and had an index of refraction, n_D^{20} of 1.530 and a specific optical rotation of +49.9(+/-)0.3° [in dioxane].

Following the above procedure but using dl-amphetamine, the DL-form of N-[2-(1-phenyl-propyl)]-2,2,2-trichloroethylidemmine was also prepared. It had the same boiling point and index of refraction as the (-)-form above but its specific optical rotation was zero.

References

Ch. J. Cavallito; US Patent No. 2,923,661; Feb. 2, 1960; Assigned to Irwin, Neigler and Co., Decatur, III.; a corporation of Illinoi

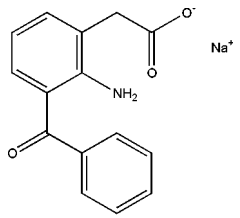
AMFENAC SODIUM

Therapeutic Function: Antiinflammatory

Chemical Name: 2-Amino-3-benzoylbenzeneacetic acid sodium salt

Common Name: Amfenac sodium, Fenamate

Structural Formula:



Chemical Abstracts Registry No.: 61618-27-7; 51579-82-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Amfenac sodium	Yungjin Pharmacetical Co. Ltd.	-	-
Fenazox	Chemos GmbH	-	-

Raw Materials

Hydrochloric acid
Acetic acid
Sodium hydroxide
Ethyl 2-acetamido-3-benzoylphenylacetate
2-Acetamido-3-benzoylphenylacetic acid

Manufacturing Process

7-Benzoylindolin-2-one:

Method A. A mixture of 2.5 g (0.0077 mole) of ethyl 2-acetamido-3-benzoylphenylacetate in 50 ml of 3 N hydrochloric acid was refluxed for one hour. The reaction mixture was filtered and the filtrate was poured into a mixture of ice and water. The precipitate was collected and recrystallized from acetone; yield of 7-benzoylindolin-2-one 1 g (55%); melting point 154°C.

Method B. A solution of 1.3 g (0.0044 mole) of 2-acetamido-3-benzoylphenylacetic acid in 15 ml of 3 N hydrochloric acid and 15 ml of acetic acid was refluxed for three hours. The cooled solution was poured into ice water and the 7-benzoylindolin-2-one which precipitated was collected and dried.

2-Amino-3-benzoylphenylacetic acid:

A mixture of 1.0 g (0.004 mole) of 7-benzoylindolin-2-one was added to 30 ml of 3 N sodium hydroxide and the basic solution was refluxed for 45 min under nitrogen. The mixture was filtered and the filtrate was neutralized with glacial acetic acid. The precipitate was filtered off, washed with water and dried. The 2-amino-3-benzoylbenzeneacetic acid melted at 122°C (dec.). The yield was 0.8 g (72%).

References

Welstead, Jr., William J., Moran H. W.; US Patent No. 4,045,576; August 30, 1977; Assigned to A. H. Robins Company, Incorporated (Richmond, VA)

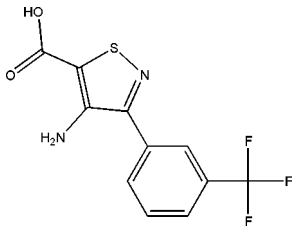
AMFLUTIZOLE

Therapeutic Function: Uricosuric

Chemical Name: 5-Isothiazolecarboxylic acid, 4-amino-3-(3-(trifluoromethyl) phenyl)-

Common Name: Amflutizole

Structural Formula:



Chemical Abstracts Registry No.: 82114-19-0

Trade Name	Manufacturer	Country	Year Introduced
LY 141894	Eli Lilly	-	-
Amflutizole	Onbio Inc.	-	-

Raw Materials

3-Trifluoromethyl-α-(p-toluenesulfonyloxyimino)benzylcyanide
Methyl thioglycolate
Triethylamine
Potassium hydroxide

Manufacturing Process

To a stirred solution of 3-trifluoromethyl-α-(p-toluenesulfonyloxyimino) benzylcyanide in methanol containing methyl thioglycolate was added dropwise over a 30 min period triethylamine. The reaction mixture was stirred at room temperature for 4 h following complete addition, and then was cooled to 0°C and filtered. The precipitate which was collected was recrystallized from hexane and ethyl acetate to provide methyl 3-(3-trifluoromethylphenyl)-4-amino-5-isothiazolecarboxylate, melting point 94°-95°C.

A solution of methyl 3-(3-trifluoromethylphenyl)-4-amino-5-isothiazolecarboxylate and potassium hydroxide in methanol was heated at reflux for 6 h. The reaction mixture was then poured into ice containing 12 N aqueous hydrochloric acid. The free acid precipitated from the acidic solution, and after all of the ice had melted, the aqueous acidic mixture was filtered. The precipitate was crystallized from ethanol and water to provide 3-(3-trifluoromethylphenyl)-4-amino-5-isothiazolecarboxylic acid, melting point 179°-180°C. Yield 80%.

References

Beck J.R. et al.; US Patent No. 4,346,094; August 24, 1982; Assigned: Eli Lilly and Company, Indianapolis, Ind.

AMICARBALIDE ISETHIONATE

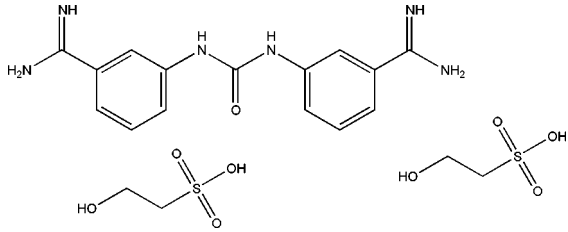
Therapeutic Function: Antiprotozoal

Chemical Name: 3,3'-(Carbonyldiimino)bis[benzenecarboximidamide] isethionate (1:2)

Common Name: Amicarbalide isethionate; Diampron

Chemical Abstracts Registry No.: 3671-72-5; 3459-96-9 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Diampron	May and Baker	-	-
Amicarbalide isethionate	Onbio Inc.	-	-

Raw Materials

Phosgene
Hydrogen chloride
Saturated anhydrous ethanolic ammonia
m-Aminobenzonitrile

Manufacturing Process

m-Aminobenzonitrile (50 g) in anhydrous pyridine (200 ml) was treated with a solution of phosgene (15 ml) in anhydrous toluene (100 ml) over 10 min with mechanical stirring. The red solution was heated for 0.5 hour on the steam bath, cooled, and added to water (2 litres). The pale grey precipitate was filtered off, washed with ether, and crystallised from methanol (250 ml). N,N^1-Di(m-cyanophenyl)urea separated as grey prisms, melting point 205-206°C.

A suspension of N,N^1-di(m-cyanophenyl)urea (42 g) in anhydrous chloroform (420 ml), containing anhydrous ethanol (70 ml), was saturated with anhydrous hydrogen chloride at 0-5°C. After setting aside for 2 hours, a clear solution was obtained, which began to crystallise. After a week, the crystals were filtered off, washed well with anhydrous ether, and dried over calcium chloride. The iminoether hydrochloride so obtained (72 g) was added to saturated anhydrous ethanolic ammonia (720 ml), and the suspension heated at 55-60°C for 6 hours. After cooling to 20°C the crystals were filtered off, and recrystallized from 2 N hydrochloric add (300 ml). 3,3^1-Diamidinodiphenylurea dihydrochloride monohydrate separated as white prisms, melting point 286°C (decomp.).

In practice it is usually used as isethonate salt.

References

GB Patent No. 888,965; Feb. 7, 1962; Assigned to May and Baker Limited, a British Copmpany, of Dagenham, Essex

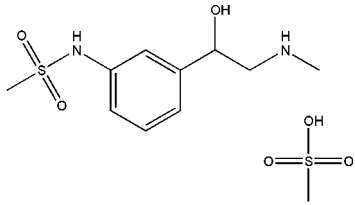
AMIDEPHRINE MESYLATE

Therapeutic Function: Vasoconstrictorá Nasal decongestant

Chemical Name: N-(3-(1-Hydroxy-2-(methylamino)ethyl)phenyl) methanesulfonamide monomethanesulfonate

Common Name: Amidefrine mesilateæ Amidephrine mesylate

Structural Formula:



Chemical Abstracts Registry No.: 1421-68-7; 3354-67-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Amidefrine mesylate	Pharm. Chemical Shanghai Lansheng Corporation	-	-

Raw Materials

N-Benzylmethylamine
Methanesulfonic acid
Hydrogen
3-(2-Bromoacetyl)methanesulfonanilide
Palladium on carbon
Sodium hydroxide

Manufacturing Process

A solution of N-benzylmethylamine 7.27 g (0.06 mole) in 25 ml of acetonitrile is added dropwise during 10 min to a solution of 8.76 g (0.03 mole) of 3-(2-bromoacetyl)methanesulfonanilide (M.P. 118-121°C) in 100 ml of acetonitrile. External cooling is employed to maintain a reaction temperature of 10°C during the addition. The cooling bath is then removed and the solution stirred for an additional 20 min. Concentration of the reaction mixture yields a yellow oil which is dissolved in 300 ml of ether and washed with water to remove byproduct N-benzylmethylamine hydrobromide. The ethereal solution is dried over magnesium sulfate and the solvent distilled leaving a viscous oil. The oil is purified by dissolving in ether (250 ml), and filtering the ether solution through diatomaceous earth to remove insoluble colored impurities. The treated ether solution is diluted with 100 ml of acetonitrile. Treatment of the ether-acetonitrile solution with an ether solution of methanesulfonic acid yields 3-(2-benzylmethylaminoacetyl)methanesulfonanilide methanesulfonate as a white precipitate which is collected and washed with 100 ml of 1:1 acetonitrile-ether and dried. It weighs 9.0 g (70%), and exhibits M.P. 197.5-201°C. It is recrystallized from 96% ethanol, yielding 8.0 g (62.3%) of the 3-(2-benzylmethylaminoacetyl)methanesulfonanilide methanesulfonate as a crystalline product, M.P. 206-209°C.

A solution of 31.8 g (0.74 mole) of 3-(2-benzylmethylaminoacetyl) methanesulfonanilide methanesulfonate in 700 ml of absolute ethanol is reduced in an atmospheric hydrogenation unit (2 to 5 p.s.i. g positive pressure) during 24 hours with a 10% palladium catalyst prepared from 320 mg of palladium chloride and 2.0 g of pulverized charcoal. After absorption of the calculated amount of hydrogen, the catalyst is filtered, the filtrate concentrated to about 100 ml, mixed with about 500 ml of ether, resulting in precipitation of a white solid weighing 24.3 g (96%), M.P. 201-203.5°C. Two recrystallizations from ethanol (35 ml/g of solid) yield the analytically pure 3-(2-methylamino-1-hydroxyethyl)methanesulfonanilide methanesulfonate, 19.6 g (75%), M.P. 207-209°C.

3-(2-Methylamino-1-hydroxyethyl)methanesulfonanilide methanesulfonate, 17.0 g (0.05 mole) is dissolved in 50 ml of 1 N sodium hydroxide, yielding a yellow solution having pH 8. The water is removed from the solution by evaporation in vacuo and the residue is treated with several portions of ethanol which are evaporated to remove last traces of moisture. The bulk of the sodium methanesulfonate byproduct is then removed from the residue by dissolving the product in 350 ml of hot absolute ethanol and clarifying by filtration through a diatomaceous earth filter aid. The ethanolic filtrate is evaporated to dryness. Last traces of sodium methanesulfonate are then removed by washing the residue with 15 ml of cold water and then with two 15 ml portions of 1:1 cold water-isopropanol, and finally with ether, yielding 7.7 g of 3-(2-methylamino-1-hydroxyethyl)methanesulfonanilide as a white solid, M.P. 159-161°C.

In practice it is usually used as monomethanesulfonate salt.

References

Merck Index, Monograph number: 418, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Larsen A.A., Uloth R.H.; US Patent No. 3,341,584; Sept. 12, 1967; Assigned to Mead Johnson and Co., Evansville, Ind., Indiana

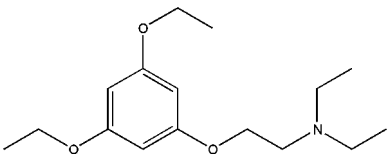
AMIFLOVERINE

Therapeutic Function: Spasmolytic

Chemical Name: 2-(3,5-Diethoxyphenoxy)-N,N-diethylethanamine

Common Name: Amifloverine

Structural Formula:



Chemical Abstracts Registry No.: 54063-24-0

Trade Name	Manufacturer	Country	Year Introduced
Amifloverine	ZYF Pharm Chemical	-	-
Amifloverine	Onbio Inc.	-	-

Raw Materials

Sodium
1-Chloro-2-diethylaminoethane hydrochloride
3,5-Dimethoxyphenol

Manufacturing Process

4.6 g of sodium was reacted with 125 ml of ethanol and, when the sodium had disappeared, 15.4 g of 3,5-dimethoxyphenol in 50 ml of absolute ethanol was added, followed by 17.2 g of 1-chloro-2-diethylaminoethane hydrochloride in suspension in 25 ml of ethanol. The mixture was refluxed for 6 hours. Then the precipitated sodium chloride was separated and the alcoholic solution was concentrated. The residue was taken up in 50 ml of ether and etheral hydrogen chloride was slowly added under reduced pressure. The mixture was filtered after cooling in ice and was dried under reduce pressure over potassium carbonate. For purification, the product (2-(3,5-diethoxyphenoxy)-N,N-diethylethanamine) was recrystallized from 200 ml of boiling isopropanol using vegetable carbon black. 16.4 g (yield 56.7%) of white crystals melting at 127°C was obtained.

References

Lafon L.; US Patent No. 3,740,397; June 19, 1973; Assigned to Societe Orsymonde, Paris, France

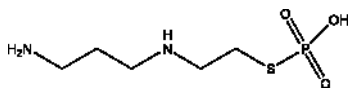
AMIFOSTINE

Therapeutic Function: Radioprotective, Chemoprotectant, Mucolytic

Chemical Name: 2-[(3-Aminopropyl)amino]ethanethiol dihydrogen phosphate (ester)

Common Name: Amifostine; Ethiofos; Fosteamine

Structural Formula:



Chemical Abstracts Registry No.: 20537-88-6

Trade Name	Manufacturer	Country	Year Introduced
Ethyol	MedImmune, Inc.	-	-
Amifostine	Haorui Pharma-Chem Inc.	-	-
Ethyol	Schering-Plough	-	-

Raw Materials

2-(3-Aminopropylamino)ethanol
Hydrobromic acid
Trisodium phosphorothioate

Manufacturing Process

A solution of 2-(3-aminopropylamino)ethanol (25.0 g, 0.212 mole) in 48 % hydrobromic acid (200 ml) was distilled until 35 ml of distillate had been collected. The solution was refluxed and, periodically, more distillate was collected. The total volume of distillate removed in 7 distillation periods was 160 ml, or 80 % of the original volume of 48% hydrobromic acid, and the time of continuous boiling was approximately 48 hours. The residual solution was then evaporated to dryness under reduced pressure with the aid of several added portions of methanol. The crystalline residue was thoroughly triturated with acetone, collected, and washed on the funnel with acetone. After the product had been pressed as dry as possible on the funnel, it was dissolved in a slight excess of boiling methanol and the solution was filtered. Addition of acetone to the filtrate precipitated pure N-(2-bromoethyl)-1,3-propanediamine dihydrobromide as colorless crystals, which were dried in vacuum over phosphorus pentoxide: yield 58.0 g (80%), melting point 205-206°C. Trisodium phosphorothioate (6.93 g, 38.5 mmoles) was gradually added in small portions with vigorous stirring to water (38 ml) cooled externally by means of a water bath (15°-20°C). To the resulting suspension was added N-(2-bromoethyl)-1,3-propanediamine dihydrobromide (13.3 g, 38.8 mmoles). After a few minutes, complete solution occurred, and N,N-dimethylformamide (19 ml) was added with continued external cooling at 15°-20°C. After the solution had been stirred at about 20°C for 90 min, it was poured into methanol (250 ml), and the mixture was refrigerated at 4°C overnight. The white precipitate that formed was collected and pressed as dry as possible on the funnel. The solid was dissolved in water (40 ml), and the solution was filtered. Addition of methanol (250 ml) reprecipitated the product. After the mixture had been refrigerated about 1 hour, the product was collected and washed on the funnel, first with methanol and finally with ether. The white solid was dried in vacuo at room temperature, then exposed to ambient conditions of the laboratory for 5 hours, and bottled under nitrogen and stored in a freezer. The yield of S-2-(3-aminopropylamino)ethyl dihydrogen phosphorothioate monohydrate, melting point (from methanol) 160-161°C, dec., was 8.15 g (91%).

References

Piper J.R., Johnston Th. P.; US Patent No. 3,892,824, July 1, 1975; Assigned to Southern Research Institute, Birmingem, Ala.

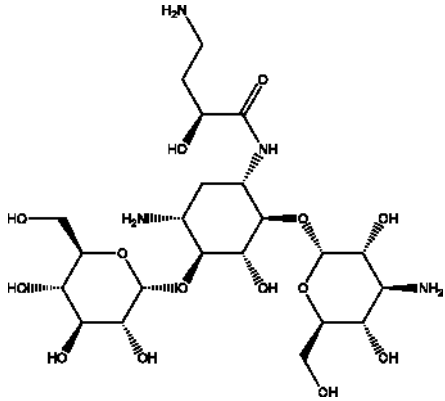
AMIKACIN

Therapeutic Function: Antibacterial

Chemical Name: (S)-O-3-Amino-3-deoxy-α-D-glucopyranosyl-(1-6)-O-[6-amino-6-deoxy-α-D-glucopyranosyl-(1-4)]-N^1-(4-amino-2-hydroxy-1-oxobutyl)-2-deoxy-D-streptamine

Common Name: 1-N-[L(-)-4-Amino-2-hydroxybutyryl]kanamycin A

Structural Formula:



Chemical Abstracts Registry No.: 37517-28-5; 39831-55-5 (Sulfate)

Trade Name	Manufacturer	Country	Year Introduced
Amikin	Bristol	US	1976
Amiklin	Bristol	France	1976
Biklin	Gruenenthal	W. Germany	1976
Amikin	Bristol	UK	1976
Biklin	Bristol Banyu	Japan	1977
BB-K8	Bristol	Italy	1978
Amiglyde-V	Bristol	-	-
Amisin	Faro	Turkey	-
Biklin	Frika	Austria	-
Briclin	Mead Johnson	-	-
Kaminax	Ausonia	Italy	-
Likacin	Lisapharma	Italy	-
Novamin	Bristol	-	-
Amikacin	Banyu	Japan	-

Raw Materials

N-Hydroxysuccinimide
Sulfuric acid
L-(-)-γ-Amino-α-hydroxybutyric acid
6'-Monobenzyloxy-carbonyl-kanamycin A

Sodium hydroxide	Carbobenzoxy chloride
Hydrogen	Palladium on carbon

Manufacturing Process

Preparation of L-(-)-γ-benzyloxycarbonylamino-α-hydroxybutyric acid: L-(-)-γ-amino-α-hydroxybutyric acid (7.4 g, 0.062 mol) was added to a solution of 5.2 grams (0.13 mol) of sodium hydroxide in 50 ml of water. To the stirred solution was added dropwise at 0-5°C over a period of 0.5 hour, 11.7 grams (0.068 mol) of carbobenzoxy chloride and the mixture was stirred for another hour at the same temperature. The reaction mixture was washed with 50 ml of ether, adjusted to pH 2 with dilute hydrochloric acid and extracted with four 80 ml portions of ether. The ethereal extracts were combined, washed with a small amount of saturated sodium chloride solution, dried with anhydrous sodium sulfate and filtered. The filtrate was evaporated in vacuum and the resulting residue was crystallized from benzene to give 11.6 grams (74%) of colorless plates; MP 78.5°C to 79.5°C.

Preparation of N-Hydroxysuccinimide Ester of L-(-)-γ-Benzyloxycarbonylamino-α-hydroxybutyric acid: A solution of 10.6 grams (0.042 mol) of L-(-)-γ-benzyloxycarbonylamino-α-hydroxybutyric acid and 4.8 grams (0.042 mol) of N-hydroxysuccinimide in 200 ml of ethyl acetate was cooled to 0°C and then 8.6 grams (0.042 mol) of dicyclohexylcarbodiimide was added. The mixture was kept overnight in a refrigerator. The dicyclohexylurea which separated was filtered off and the filtrate was concentrated to about 50 ml under reduced pressure to give colorless crystals of L-(-)-γ-benzyloxycarbonylamino-α-hydroxybutyric acid which were collected by filtration; 6.4 grams, MP 121-122.5°C. The filtrate was evaporated to dryness in vacuum and the crystalline residue was washed with 20 ml of a benzene-n-hexane mixture to give an additional amount of L-(-)-γ-benzyloxycarbonylamino-α-hydroxybutyric acid. The total yield was 13.4 grams (92%).

Preparation of 1-[L-(-)-γ-Benzyloxycarbonylamino-α-Hydroxybutyryl]-6'-Carbobenzoxykanamycin A: A solution of 1.6 grams (4.6 mmol) of L-(-)-γ-benzyloxycarbonylamino-α-hydroxybutyric acid in 40 ml of ethylene glycol dimethyl ether (DME) was added dropwise to a stirred solution of 2.6 grams (4.2 mmol) of 6'-monobenzyloxycarbonylkanamycin A in 40 ml of 50% aqueous ethylene glycol dimethyl ether and the mixture was stirred overnight. The reaction mixture was evaporated under reduced pressure to give a brown residue 1-[L-(-)-γ-benzyloxycarbonylarnino-α-hydroxybutyryl]-6'-carbobenzoxykanamycin A which was used for the next reaction without further purification.

Preparation of 1-[L-(-)-γ-Amino-α-Hydroxybutyryl] Kanamycin A: The crude product 1-[L-(-)-γ-benzyloxycarbonylamino-α-hydroxybutyryl]-6'-carbobenzoxykanamycin A was dissolved in 40 ml of 50% aqueous dioxane and a small amount of insoluble material was removed by filtration. To the filtrate was added 0.8 ml of glacial acetic acid and 1 gram of 10% palladium-on-charcoal and the mixture was hydrogenated at room temperature for 24 hours in a Parr hydrogenation apparatus. The reaction mixture was filtered to remove the palladium catalyst and the filtrate was evaporated to dryness in vacuum.

The residue was dissolved in 30 ml of water and chromatographed on a

column of CG-50 ion exchange resin (NH_4^+ type, 50 cm x 1.8 cm). The column was washed with 200 ml of water and then eluted with 800 ml of 0.1 N NH_4OH, 500 ml of 0.2 N NH_4OH and finally 500 ml of 0.5 N NH_4OH. Ten milliliter fractions were collected and fractions 146 to 154 contained 552 mg (22%. based on carbobenzoxykanamycin A, 6'-monobenzyloxycarbonylkanamycin A) of the product which was designated BB-K8 lot 2. MP 187°C (dec). Relative potency against *B. subtilis* (agar plate) = 560 mcg/mg (standard: kanamycin A free base).

A solution of 250 mg of BB-K8 lot 2 in 10 ml of water was subjected to chromatography on a column of CG-50 (NH_4^+ type, 30 cm x 0.9 cm). The column was washed with 50 ml of water and then eluted with 0.2 N NH_4OH. Ten milliliter fractions were collected. Fractions 50 to 63 were combined and evaporated to dryness under reduced pressure to give 98 mg of the pure product base.

Preparation of the Monosulfate Salt of 1-[L-(-)-γ-Amino-α-Hydroxybutyryl] Kanamycin A: One mol of 1-[L-(-)-γ-amino-α-hydroxybutyryl] kanamycin A is dissolved in 1 to 3 liters of water. The solution is filtered to remove any undissolved solids. To the chilled and stirred solution is added one mol of sulfuric acid dissolved in 500 ml of water. The mixture is allowed to stir for 30 minutes, following which cold ethanol is added to the mixture till precipitation occurs. The solids are collected by filtration and are determined to be the desired monosulfate salt.

References

Merck Index 405
Kleeman and Engel p. 38
PDR p. 692
DOT 12 (5) 202 (1976)
I.N. p. 68
REM p. 1180
Kawaguchi, H., Naito, T. and Nakagawa, S.; US Patent 3,781,268; December 25, 1973; Assigned to Bristol-Myers Company
Schreiber, R.H. and Kell, J.G.,; US Patent 3,974,137; August 10, 1976; Assigned to Bristol-Myers Company

AMILORIDE HYDROCHLORIDE

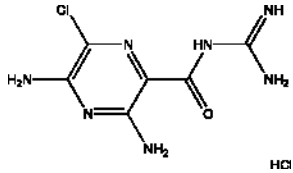
Therapeutic Function: Diuretic

Chemical Name: 3,5-Diamino-N-(aminoiminomethyl)-6-chloropyrazine carboxamide hydrochloride

Common Name: Guanamprazine; Amipramidin; Amipramizide

Chemical Abstracts Registry No.: 2016-88-8; 2609-46-3 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Midamor	Merck	UK	1971
Modamide	Merck	France	1973
Arumil	Sharp and Dohme	W. Germany	1975
Midamor	Merck	US	1981
Colectril	Merck	US	-
Moducren	DohmeGhibret	France	-
Moduretic	Merck	-	-
Nilurid	Merck	-	-
Pandiuren	Sintyal	Argentina	-
Puritrid	Leiras	Finland	-

Raw Materials

Sulfuryl chloride	Methyl-3-aminopyrazinoate
Ammonia	Sodium
Guanidine	Hydrogen chloride

Manufacturing Process

Step A: Preparation of methyl 3-amino-5,6-dichloropyrazinoare: Methyl 3-aminopyrazinoate (765 g, 5 mols) is suspended in 5 liters of dry benzene. While stirring under anhydrous conditions sulfuryl chloride (1.99 liters, 3.318 g, 24.58 mols) is added over a period of 30 minutes and stirring is continued for 1 hour. During this period, the temperature rises to about 50°C and then begins to drop. The mixture is heated cautiously to reflux (60°C), refluxed for 5 hours and then stirred overnight at room temperature. The excess sulfuryl chloride is distilled off at atmospheric pressure (distillation is stopped when vapor temperature reaches 78%). The dark red mixture is chilled to 6°C. The crystals are filtered off, washed by displacement with two 100 ml portions of cold (8°C) benzene, then washed with 300 ml petroleum ether and dried in vacuum at room temperature, yielding 888 g (80%) of methyl 3-amino-5,6-dichloropyrazinoate in the form of red crystals, MP 228-230°C. The crude product is dissolved in 56 liters of boiling acetonitrile and passed through a heated (70-80°C) column of decolorizing charcoal (444 g). The column is washed with 25 liters of hot acetonitrile, the combined eluate concentrated in vacuum to about 6 liters and chilled to 5°C. The crystals that form are filtered, washed three times with cold acetonitrile, and air dried to constant weight, yielding 724 g (82% recovery, 66% overall) of methyl 3-amino-5,6-dichloropyrazinoate in the form of yellow crystals, MP 230-234°C. After additional recrystallizations from acetonitrile the product melts at 233-234°C.

Step B: Preparation of methyl-3,5diamino-6-chloropyrazinoete: In a 2-liter, 3-

necked flask fitted with a a mechanical stirrer, thermometer and gas inlet tube is placed dry dimethyl sulfoxide (1 liter). Methyl 3-amino-5,6-dichloropyrazinoate (100 g, 0.45 mol) is added and the mixture stirred and heated at 65°C on a steam bath until solution is effected. A stream of dry ammonia gas is admitted to the solution with continuous stirring, over a period of 45 minutes while the temperature is maintained at 65-70°C. The solution is cooled to about 10°C with continuous stirring and ammonia gas is admitted for an additional 1 1/4 hours. The yellow reaction mixture is poured, with stirring, into cold water (2 liters) and the light yellow solid that separates is removed by filtration, thoroughly washed with water, and dried in a vacuum desiccator to give 82.5 g (91%) of methyl 3,5-diamino-6-chloropyrazinoate, MP 210-212°C. Recrystallization from acetonitrile gives material melting at 212-213°C.

Step C: Preparation of the base: A 300 ml one-necked, round-bottomed flask, equipped with a water-cooled condenser, calcium chloride tube and magnetic stirrer is charged with anhydrous methanol (150 ml) and sodium metal (5.75 g, 0.25 g atom). When the reaction is complete, the solution is treated with dry guanidine hydrochloride (26.3 g, 0.275 mol) and stirred for 10 minutes. The sodium chloride that forms is removed by filtration. The solution is concentrated in vacuum to a volume of 30 ml and the residue treated with the product of Step B, heated one minute on a steam bath and kept at 25°C for 1 hour. The product is filtered, washed well with water, dissolved in dilute hydrochloric acid and the free base precipitated by addition of sodium hydroxide to give the amiloride product base, a solid which melts at 240.5-241.5°C.

To produce the hydrochloride, the base is suspended in water (70 ml) and treated with sufficient 6 N hydrochloric acid to dissolve the free base. The solution is filtered and treated with concentrated hydrochloric acid (5 ml). The hydrochloride salt (22 g, 97%) separates and is recrystallized from water (50 ml) containing concentrated hydrochloric acid (3 ml).

References

Merck Index 406
Kleeman and Engel p.40
PDR p. 1199
OCDS Vol. 1 p. 278 (1977)
DOT 19 (3) 172 (1983)
I.N. p. 69
REM p. 941
Cragoe, E.J., Jr.; US Patent 3,313,813; April 11,1967; Assigned to Merck and Co., Inc.

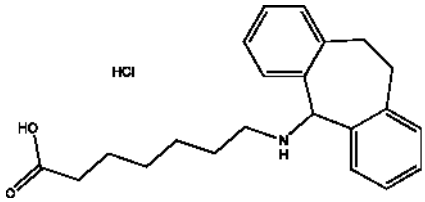
AMINEPTINE HYDROCHLORIDE

Therapeutic Function: Central stimulant

Chemical Name: 7-[10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl-amino]heptanoic acid hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 57574-09-1 (Base); 30272-08-3 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Survector	Eutherapie	France	1978
Survector	Servier	Italy	1982
Maneon	Poli	Italy	1982

Raw Materials

5-Chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene
Ethyl 7-aminoheptanoate

Manufacturing Process

6.5 g of 5-chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene in 60 ml of nitromethane and 10.8 g of ethyl 7-aminoheptanoate in 12ml of nitromethane were mixed at ambient temperature. The reaction was slightly exothermic. The reaction mixture was left to stand overnight and the solvent was evaporated in vacuum. The residue was taken up in normal hydrochloric acid and the resulting precipitate was filtered off.

10.5 g of crude ethyl 7-[dibenzo(a,d)cycloheptadiene-5-yl]aminoheptanoate hydrochloride were obtained, of which a sample recrystallized from benzene gave a pure product melting instantaneously at 166°C to 168°C.

The hydrochloride of the crude ester obtained above was added to 25 ml of 2 N hydrochloric acid. The whole was kept under reflux for 2 hours. The material dissolved and a new hydrochloride then reprecipitated. After cooling, the hydrochloride of the crude acid was filtered off, washed with iced water and then recrystallized from distilled water. 5.7 g of 7-[dibenzo(a,d)cycloheptadienb-yl] aminoheptanoic acid hydrochloride were obtained, melting instantaneously at 226°C to 230°C.

References

Merck Index 409
Kleeman and Engel p. 40
DOT 19 (10) 547 (1983)

I.N. p. 69
Melen, C., Danree, B. and Poignant, J.C.; US Patent 3,758,528; September 11, 1973; Assigned to Societe en nom Collectif Science Union et Cie; Societe Francaise de Recherche Medicale
Melen, C., Danree, B. and Poignant, J.C.; US Patent 3,821,249; June 28, 1974; Assigned to Societe en nom Collectif Science Union et Cie; Societe Francaise de Recherche Medicale

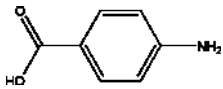
AMINOBENZOIC ACID

Therapeutic Function: Sunscreen agent, Antirickettsial

Chemical Name: p-Aminobenzoic acid

Common Name: Vitamin H; Vitamin B_x; PABA

Structural Formula:



Chemical Abstracts Registry No.: 150-13-0

Trade Name	Manufacturer	Country	Year Introduced
Pabalate	Robins	US	1949
Hachemina	Medea	Spain	-
Pabafilm	Owen	US	-
Pabagel	Owen	US	-
Pabanol	Elder	US	-
Potaba	Westwood	US	-
Pre-Sun	Westwood	US	-
Sunbrella	Dorsey	US	-

Raw Materials

Xylene
Ammonium sulfate
Sodium hypochlorite

Manufacturing Process

The following example illustrates in detail the preparation of amino benzoic acids from the hot reaction product obtained by the oxidation of a xylene and containing a mixture of salt, amide salt and diamide of a phthalic acid.

800 cc of hot aqueous oxidation product, obtained from the oxidation of p-xylene with ammonium sulfate, hydrogen sulfide and water are boiled and

agitated for 4 hours to remove carbon dioxide, hydrogen sulfide and ammonia, sufficient water being added to maintain a constant volume. The mixture is filtered to remove a precipitate containing elemental sulfur. 12 grams of activated charcoal are added to the filtrate and the mixture held at a temperature of 180°F for 20 minutes. Filtration through diatomaceous earth removes color bodies formed during the oxidation process and yields a pale yellow filtrate. The filtrate is acidified with sulfuric acid to a pH of 3 or less to precipitate approximately 49 grams of white solid, comprising a mixture of terephthalic acid and amides of terephthalic acid, which are removed by filtration. This solid is then washed with water at 200°F and redissolved in 200 cc of water containing 28.6 grams of sodium hydroxide.

A mixture of sodium hypochlorite and sodium hydroxide is prepared by adding 27.5 grams of chlorine to a vessel equipped with cooling means and containing a solution of 50 grams of sodium hydroxide in 375 cc of water, thereafter adding sufficient water to produce 500 cc of solution. 190 cc of this cold solution are slowly added to the acid-amide solution previously prepared so as to keep the temperature of the mixture below 55°F. The mixture is stirred for 15 minutes and then heated rapidly to 200°F and maintained at that temperature for one hour. 2 grams of sodium thiosulfate are added to consume excess sodium hypochlorite. The solution is acidified to a pH of 3 or less and filtered hot. The filter cake, comprising about 26.9 grams of terephthalic acid, is then suspended in 300 cc of dilute sulfuric acid of pH about 2, heated to 200°F and filtered hot.

The filtrates are combined, cooled, and extracted with three successive 200 cc portions of ether. The pH of the filtrate is then raised to 3.5 with sodium hydroxide and the filtrate extracted with six successive 200 cc portions of ether to yield the balance of the product. The crude p-aminobenzoic acid product is recovered by evaporation of ether and is suspended in hot benzene, cooled and filtered to remove benzoic and toluic acids together with small amounts of impurities soluble in the filtrate. Recrystallization of the product from 200 cc of water yields 14.5 grams of light tan needles of p-aminobenzoic acid having an acid number of 411 (theoretical value 409).

Aminobenzoic acid can be then purified and decolorized by a process described in US Patent 2,735,865.

References

Merck Index 423
PDR pp.926, 1894
I.N. p.1012
REM p.787
Toland, W.G. and Heaton, C.D.; US Patent 2,878,281; March 17, 1959; Assigned to California Research Corporation
Spiegler, L.; US Patent 2,947,781; August 2, 1960; Assigned to E.I. Du Pont de Nemours and Company
Lyding, A.R.; US Patent 2,735,865; February 21, 1956; Assigned to Heyden Chemical Corporation

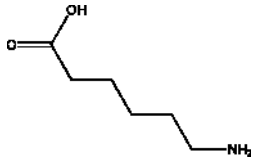
AMINOCAPROIC ACID

Therapeutic Function: Antifibrinolytic

Chemical Name: 6-Aminohexanoic acid

Common Name: Epsilcapramin

Structural Formula:



Chemical Abstracts Registry No.: 60-32-2

Trade Name	Manufacturer	Country	Year Introduced
Epsilon	Roche	W. Germany	1962
Epsilon-Aminoca	Roche	W. Germany	1962
Capramol	Choay	France	1963
Amicar	Lederle	US	1964
Epsikapron	Kabi Vitrum	UK	1967
Acikaprin	Polfa	Poland	-
Amicar	Lederle	US	-
Capracid	Kabi Vitrum	Sweden	-
Capracid	Bonomelli-Hommel	Italy	-
Capralense	Choay	France	-
Capramol	Intalfarmaco	Italy	-
Caprolisin	Malexi	Italy	-
EACA	Kasi Vitrum	Sweden	-
Ekaprol	Difrex	Australia	-
Epsilon	Star	Finland	-
Hemocaprol	Delagrange	France	-
Capusumine	Nichiiko	Japan	-
Hemotin	Hokuriku	Japan	-
Ipsilon	Daiichi	Japan	-
Resplamin	Kyorin	Japan	-

Raw Materials

Caprolactam
Water

Manufacturing Process

5 kg of caprolactam were heated with 40 liters of water in a pressure vessel

at 250°C for a period of four hours. These quantities of reactants correspond to a water:lactam molecular ratio of 50:1. After cooling, the small quantity of the nonsoluble substance that is formed is filtered off, and the filtrate is evaporated as far as possible. The resulting concentrate is mixed with three times its volume of strong alcohol, thereby causing the desired product, epsilon-aminocaproic acid (6-aminohexanoic acid), to crystallize out. After separating the crystalline product thus obtained, a further quantity of epsilon-aminocaproic acid can be obtained from the mother liquid if desired.

References

Merck Index 433
Kleeman and Engel p. 41
PDR pp. 872, 997
I.N. p. 13
REM p. 831
Koch, T.; US Patent 2,453,234; November 9, 1948; Assigned to American Enka Corporation

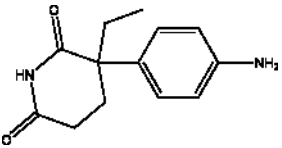
AMINOGLUTETHIMIDE

Therapeutic Function: Cytostatic

Chemical Name: 3-(4-Aminophenyl)-3-ethyl-2,6-piperidinedione

Common Name: α-(p-Aminophenyl)-α-ethylglutarimide

Structural Formula:



Chemical Abstracts Registry No.: 124-84-8

Trade Name	Manufacturer	Country	Year Introduced
Ellipten	Ciba	US	1960
Cytadren	Ciba Geigy	US	1980
Orimeten	Ciba Geigy	Switz.	1981
Orimeten	Ciba Geigy	UK	1982

Raw Materials

α-Phenyl-α-ethyl glutarimide
Nitric acid
Hydrogen

Manufacturing Process

The α-(p-nitrophenyl)-α-ethyl-glutarimide starting material can be prepared as follows: 217 g of α-phenyl-α-ethyl-glutarimide are dissolved in 800 g of concentrated sulfuric acid with subsequent cooling to about -10°C and nitration is carried out at -10°C to +10°C by slow addition of a mixed acid consisting of 110 g of concentrated sulfuric acid and 110 g of 63% nitric acid. The nitration solution is stirred into ice, the separated nitro compound taken up in methylene or ethylene chloride, the solution washed with water and sodium carbonate solution until neutral and the solvent evaporated under vacuum. The residue is crystallized from methanol or ethyl acetate, whereby a yellowish crystal powder of MP 128-136°C is obtained in a yield of about 85% which consists for the most part of α-(p-nitrophenyl)-α-ethyl-glutarimide. By recrystallization from methanol the pure p-nitrophenyl compound is obtained of MP 137-139°C. From the residues of the mother liquors a small quantity of the isomeric α-(o-nitrophenyl)-α-ethyl-glutarimide of MP 170-172°C can be obtained.

26.2 g of α-(p-nitrophenyl)-α-ethyl-glutarimide of MP 137-139°C dissolved in ethyl acetate, are reduced in the presence of nickel with hydrogen in a shaking flask at 50-70°C until the absorption of hydrogen falls off. The catalyst is then filtered off with suction and the solution concentrated and cooled, as a result of which colorless crystals of MP 146-149°C are obtained. Recrystallization from methanol gives pure α-(p-aminophenyl)-α-ethyl-glutarimide of MP 149-150°C (yield 97%).

Instead of ethyl acetate another solvent can be used in the above reduction, such as methanol or ethanol.

The hydrochloride of MP 223-225°C is obtained by dissolving the base with alcohol and the corresponding quantity of hydrochloric acid gas in the hot with subsequent cooling of the solution. Colorless crystals are formed of MP 223-225°C, which are easily soluble in water.

References

Merck Index 443
PDR p. 794
OCDS Vol. 1 p.257 (1977)
I.N. p. 71
REM p. 1143
Hoffmann, K. and Urech, E.; US Patent 2,848,455; August 19, 1958; Assigned to Ciba Pharmaceutical Products, Inc.

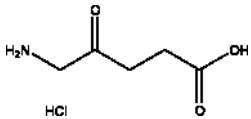
AMINOLEVULINIC ACID HYDROCHLORIDE

Therapeutic Function: Photosensitizer

Chemical Name: Pentanoic acid, 5-amino-4-oxo-, hydrochloride

Common Name: Aminolevulinic acid hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 5451-09-2; 106-60-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Levulan Kerastick	DUSA Pharmaceuticals Inc.	-	-

Raw Materials

N-Furfurylphthalimide
Rose Bengal
Palladium on carbon

Manufacturing Process

1) Oxidation Step

2.27 g (10.0 mmol) of N-furfurylphthalimide was charged into a three-necked glass flask equipped with an oxygen feed tube, a thermometer, and a reflux condenser, and dissolved in 100 ml of anhydrous pyridine. After the addition of 7.0 mg of Rose Bengal, oxygen gas was fed at a rate of 20 ml/min at 10°-20°C under irradiation by light. A 27 W white fluorescent lamp was used as a light source and the radiation was performed from the outside of the flask. After 7 hours, the irradiation was terminated and the pyridine was evaporated under reduced pressure to obtain 2.47 g of a light brown, semi-crystalline product.

2) Reduction Step (Hydrogenation)

2.00 g of the semi-crystalline solid obtained in (1) was dissolved in 40 ml of methanol and stirred at 50°C in a hydrogen atmosphere under atmospheric pressure in the presence of 200 mg of 5% palladium-on-carbon catalyst.

After five hours, the reaction was terminated and the mixture was allowed to cool to room temperature. The catalyst was removed by filtration and methanol was evaporated to obtain 2.11 g of white crystals.

The crystals were identified to be 5-phthalimidolevulinic acid by NMR analysis. The yield was 97%.

3) Hydrolysis Step

100 ml of 6 N hydrochloric acid was added to 2.11 g of the white crystals (2), and the mixture was heated under reflux for 5 hours.

After evaporating the hydrochloric acid under reduced pressure, a brown solid product was obtained and dissolved in ethanol. Acetone was added to the solution and the crystals produced were collected by filtration to obtain 0.689 g of 5-aminolevulinic acid hydrochloride. The yield based on N-furfurylphthalimide was 51%.

NMR spectrum data conformed to 5-aminolevulinic acid hydrochloride

References

Takeya H. et al.; US Patent No. 5,380,935; Jan. 10, 1995; Assigned Cosmo Research Institute; Cosmo Oil Co., Ltd., both of Tokyo, Japan

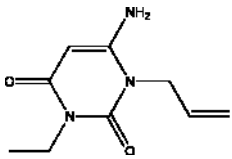
AMINOMETRADINE

Therapeutic Function: Diuretic

Chemical Name: 6-Amino-3-ethyl-1-(2-propenyl)-2,4(1H,3H)-pyrimidinedione

Common Name: Aminometramide

Structural Formula:



Chemical Abstracts Registry No.: 642-44-4

Trade Name	Manufacturer	Country	Year Introduced
Mincard	Searle	US	1954
Mictine	Searle	-	-

Raw Materials

Monoallyl urea
Sodium hydroxide
Cyanoacetic acid
Diethyl sulfate

Manufacturing Process

85 parts of monoallylurea are dissolved in 105 parts of acetic anhydride, and 85 parts of cyanoacetic acid are added gradually and the mixture is maintained at 65°C for 2.5 hours. The mixture is distilled at 20 mm until a syrup remains. 50 parts of water are added to this syrup and distillation is resumed. The resulting syrup is dissolved in 96% ethanol at 60°C, stirred with charcoal and filtered. One to one and one-half volumes of ether are added to the filtrate at 40°C. Upon cooling the N-cyanoacetyl-N'-allylurea precipitates.

It is collected on a filter and washed with ether. The white crystals melt at about 142-143°C. The N-cyanoacetyl-N'-allylurea is dissolved by warming with 10% sodium hydroxide. Sufficient 70% sodium hydroxide is added to raise the pH to 10. The solution is maintained at 60°C for five minutes. After cooling the crystals are collected on a filter and recrystallized from water. 1-Allyl-6-amino-1,2,3,4-tetrahydro-2,4-pyrimidinedione is obtained in the form of white crystals melting at 270-272°C.

334 parts of 1-allyl-6-amino-1,2,3,4-tetrahydro-2,4-pyrirnidinedione are dissolved in a solution of 88 parts of sodium hydroxide in 1,100 parts of water. While this mixture is stirred rapidly at 50°C, 430 parts of diethyl sulfate are added in the course of 30 minutes. Stirring is continued at 50-55°C for one hour longer, and an alkaline reaction is maintained by occasional additions of small portions of 20% aqueous sodium hydroxide solution, about 300 parts in all being required. On cooling, the 1-allyl-3-ethyl-6-amino-1,2,3,4-tetrahydro-2,4-pyrimidinedione separates as the monohydrate; it is filtered off, washed with cold water, and recrystallized from water containing a small amount of sodium hydroxide to hold in solution any unreacted 1-allyl-6-amino-1,2,3,4-tetrahydro-2,4-pyrimidinedione. The air dried product thus obtained contains 1 mol of crystal water and melts over a wide range with dehydration at 75-115°C. After dehydration by treatment with anhydrous ether, the anhydrous 1-allyl-3-ethyl-6-amino-1,2,3,4-tetrahydro-2,4-pyrimidinedione melts sharply at about 143-144°C.

References

Merck Index 455
OCDS Vol. 1 p. 265 (1977)
I.N. p. 72
Papesch, V. and Schroeder, E.F.; US Patent 2,650,922; September 1, 1953; Assigned to G.D. Searle and Co.

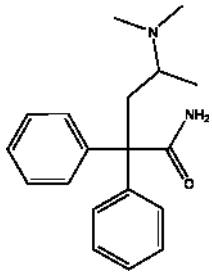
AMINOPENTAMIDE

Therapeutic Function: Anticholinergic

Chemical Name: 4-(Dimethylamino)-2,2-diphenylvaleramide

Common Name: Dimevamide

Structural Formula:



Chemical Abstracts Registry No.: 60-46-8

Trade Name	Manufacturer	Country	Year Introduced
Centrine	Bristol	US	1953

Raw Materials

α,α-Diphenyl-γ-dimethylaminovaleronitrile
Hydroxylamine hydrochloride

Manufacturing Process

A mixture of 14 g (0.05 mol) of α,α-diphenyl-γ-dimethylaminovaleronitrile, 16 g (0.2 mol) of sodium acetate, 14 g (0.2 mol) of hydroxylamine hydrochloride and 75 ml of ethyl alcohol was refluxed 18 hours. The mixture was cooled, poured into water and neutralized with ammonium hydroxide. The heavy white precipitate solidified on standing. The material was filtered and recrystallized from isopropanol. After three recrystallizations the aminopentamide product melted at 177° to 179°C.

The product is often used as the acid sulfate which is produced as follows: 252.0 g (0.85 mol) of α,α-diphenyl-γ-dimethylaminovaleronitrile was dissolved in one liter of isopropanol, and 70 ml of concentrated sulfuric acid was added as rapidly as possible. The mixture was heated until clear, then filtered and diluted with 1,500 ml of anhydrous ethyl acetate. The solution was cooled and filtered, and the white crystalline product was dried in vacuum over P_2O_5.

References

Merck Index 463
I.N. p. 342
Specter, M.E.; US Patent 2,647,926; August 4, 1953; Assigned to Bristol Laboratories, Inc.

AMINOPHYLLINE

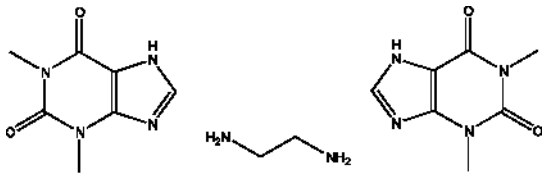
Therapeutic Function: Diuretic, Cardiac stimulant, Smooth muscle relaxant, Vasodilator

Chemical Name: 1H-Purine-2,6-dione, 3,7-dihydro-1,3-dimethyl-, compd. with 1,2-ethanediamine (2:1)

Common Name: Aminophelline; Teofyllamin; Theophyllin-Athylendiamin; Theophylline; Theophyl(l)amin; Ethylenediamine

Chemical Abstracts Registry No.: 317-34-0

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Memcophylline	Memphis Co.	-	-
Memcophylline IV	Memphis Co.	-	-
Aminophyl	Neon Laboratories Ltd.	-	-
Aminophylline	Wellcome	-	-
Aminophylline	AroKor Holdings Inc.	-	-
Aminophylline	West-ward Pharmaceutical Corp.	-	-
Aminophylline, Anhydrous	Spectrum Chemicals and Laboratory Products, Inc.	-	-
Afonilum	Knoll	-	-
Aminodur	Berlex	-	-
Cardophylin	Rhone Poulenc	-	-
Euphyllina	Byk Gulden	-	-
Pecram	Novartis	-	-
Phyllocontin	Purdue Frederick	-	-
Phyllotemp	Mundipharma	-	-
Planphylline	Asta	-	-
Pulmovet	Solvay	-	-
Tefamin	Recordati	-	-
Ventax	Yamanouchi Europe	-	-
Diffumal 24	Malesci Instituto Pharmabiologico	-	-
Durofilin	Zdravle	-	-
Retafyl	Orion Pharma International	-	-
Slow-Bid	Rhone-Poulenc Rorer	-	-
Spophyllin Retard	Slovakofarma	-	-
Theo	Amoun	-	-
Theostat	Pierre Fabre Medicament	-	-
Teotard	Krka	-	-
Uni-Dur	Schering-Plough	-	-
Aminocardol	Wander	-	-
Aminofilin	Srbolek	-	-

Trade Name	Manufacturer	Country	Year Introduced
Aminofilina	Ariston	-	-
Aminofilina	Biochimico	-	-
Aminofilina	IMA	-	-
Aminofilina	Sandoz	-	-
Aminofilina	Uniao Quimica Farm.	-	-
Aminofilina	Vital Brazil	-	-
Aminofilina	Azevedos	-	-
Aminofilina	C.P. Higiene	-	-
Aminofilina	Apteka im.T.Kosciusz	-	-
Theophyllaminum	Leiras	-	-
Theodrox	Suomen Astra	-	-
Theodrox	3 M Riker	-	-

Raw Materials

Theophylline
Ethylenediamine hydrate

Manufacturing Process

A mixture of 198 g (1 mol) theophylline and 60-78 g (0.75-1 mol) ethylenediamine hydrate in 300 g of water was stirred at 50°C and then the mixture was concentrated in vacuo. The product (aminophylline) was separeted by suction filtration. Aminophylline was used as an aqueous solution.

References

Byk H., DE Patent No. 223,695, June 30, 1910; Assigned to Chemische Werke

AMINOPROMAZINE FUMARATE

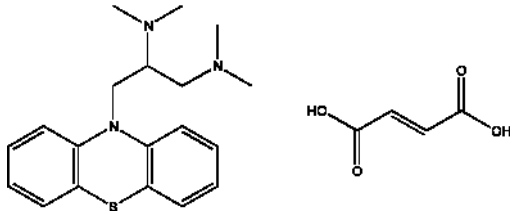
Therapeutic Function: Spasmolytic

Chemical Name: 10-(2,3-Bis(dimethylamino)propyl)phenothiazine fumarate (2:1)

Common Name: Aminopromazine fumarate; Proquamezine fumarate; Tetrameprozine

Chemical Abstracts Registry No.: 3688-62-8;58-37-7 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Jenotone	Coopers	-	-
Jenotone	Schering-Plough	-	-
Lispamol	Specia	-	-
Lorusil	Biochemie	-	-
Myspamol	May and Baker	-	-
Sedofarmolo	Centralvet	-	-

Raw Materials

Phenothiazine
Sodium amide
1,3-Bis(dimethylamino)-2-chloropropane

Manufacturing Process

Phenothiazine (20 g) is heated under reflux for 1 hour with sodium amide (5 g) in xylene (80 ml). A solution of 1,3-bis(dimethylamino)-2-chloropropane (27 g) (prepared by a method analogous to that described in Ingold and Rothstein J.C.S. 1931, 1676) in xylene (30 ml) is then added over 2 hours. Heating is continued for a further 1 hour and then the mixture is taken up in water (270 ml) and hydrochloric acid (d=1.19; 20 ml). The decanted acid layer is treated with caustic soda (d 1.33; 25 ml) and the base is extracted with ether (2 x 50 ml) which is then dried over potassium carbonate. On distillation there is obtained at 218-220°C/0.6 mm Hg a mixture (20 g) containing a major proportion of 10-[2,3-bis(dimethylamino)-1-propyl]phenothiazine and a minor proportion of 10-[1,3-bis(dimethylamino)-1-propyl]phenothiazine.

A mixture of bases (11 g) obtained is dissolved in isopropanol (25 ml). Ether (25 ml) containing dry hydrogen chloride (2 g) is added, the mixture is left to crystallise overnight in a refrigerator and the product is filtered off, washed and dried. There is thus obtained a salt (2.5 g), M.P. 244°C, which is 10-[1,3-bis(dimethylamino)-1-propyl]phenothiazine hydrochloride.

On evaporation of the mother liquors from the above hydrochloride a residue is obtained from which is isolated its isomer, 10-[2,3-bis(dimethylamino)-1-propyl]phenothiazine, the base crystallising from ethanol and melting at 58°C. The structure of these two isomers has been confirmed by comparison of their infra-red adsorption spectra with those of related products of known structure.

In practice it is usually used as fumarate.

References

Merck Index, Monograph number: 487, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
GB Patent No. 800,635; Nov.4,1955; Assigned to Socciete des Usines Chimiques Rhone-Poulenc, a French body corporate

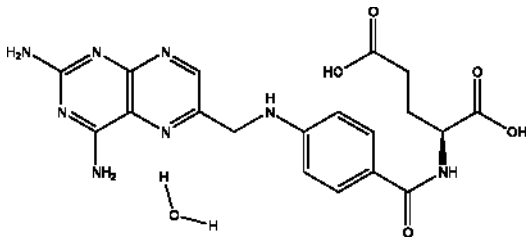
AMINOPTERIN HYDRATE

Therapeutic Function: Antineoplastic

Chemical Name: L-Glutamic acid, N-(4-(((2,4-diamino-6-pteridinyl)methyl) amino)benzoyl)-, hydrate

Common Name: 4-Amino-4-deoxyfolic acid; 4-Aminofolsäure; 4-Amino-PGA; Aminopterin; 4-Aminopteroylglutamic acid; 4-Aminopteroylglutaminsäure; Antifolic acid; Antifolsäure

Structural Formula:



Chemical Abstracts Registry No.: 54-62-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Aminopterin	Sigma Chemical Company	-	-

Raw Materials

1,3-Dihydroxyacetone
Bromine
Cysteine hydrochloride hydrate
Triphenylphosphine
Barium chloride dihydrate
N-(4-Aminobenzoyl)-L-glutamic acid
2,4,5,6-Tetraaminopyrimidine sulfate hydrate

Manufacturing Process

2,4,5,6-Tetraaminopyrimidine·H_2SO_4·H_2O (75.0 g, 0.293 mole) was added to a stirred solution of $BaCl_2$·$2H_2O$ (71.5 g, 0.293 mole) in H_2O (1.45 L) at 85-90°C. The mixture was stirred rapidly at about 90°C for 15 min, cooled to 40°C, and filtered from $BaSO_4$, which was washed thoroughly on a funnel with

H_2O. The clear, yellow filtrate was then diluted further with H_2O to give a volume of 4.35 L. This solution of the tetraaminopyrimidine·2HCl was then added to a solution of NaOAc (4.35 L of 4 N) in which 1,3-dihydroxyacetone (79.3 g, 0.88 mole) and cysteine·HCl·H_2O (51.5 g, 0.293 mole) had just been dissolved. The resulting solution was stirred mechanically at room temperature while a slow stream of air was continuously passed through it for 26 hours. (Yellow-orange solid began separating after 2 hours). The mixture was then kept in a refrigerator for 16 hours before the solid was collected, washed successively with cold H_2O, EtOH, and Et_2O before it was dried to constant weight in vacuo over P_2O_5 at 25°C. [The crude product mixture (47 g) was weighed in order to obtain an estimate of the volume of 48% HBr required to form hydrobromide salts]. A mechanically stirred mixture of the dried solid and EtOH (6.05 L) was heated to 70°C, and a solution of 48% HBr (28 ml) in EtOH (490 ml) was added in a thin stream while the mixture was maintained at 70-75°C. The mixture was then refluxed for about 5 min with rapid stirring while nearly all of the solid dissolved. The hot solution was treated with Norit and filtered through a Celite mat. The clear yellow filtrate was kept in a refrigerator overnight while a first crop of orange colored solid separated. The collected solid was washed with EtOH, then dried in vacuo (56°C over P_2O_5) to give 17.2 g of product. The filtrate was concentrated by evaporation (rotary evaporator) to about 2 L and then refrigerated to give a second crop of 10.2 g, which was dried as before; total yield of crude 2,4-diamino-6-pteridinemethanol hydrobromide 27.4 g (34%). The PMR spectrum of this material in CF_3CO_2D showed it to contain a barely detectable amount of methyl-substituted 2,4-diaminopteridine·HBr.

Bromine (59.6 g, 0.373 mole) was added dropwise over a 30 min to a stirred solution of triphenylphosphine (97.7 g, 0.373 mole) in anhydrous dimethylacetamide (486 ml) kept at 10°C (ice bath) and protected from atmospheric moisture. (Bromine remaining in the funnel was rinsed with 10 ml of dimethylacetamide). A smooth suspension containing finely divided, crystalline triphenylphosphine dibromide resulted. The 2,4-diamino-6-pteridinemethanol·HBr (25.4 g, 0.093 mole) described above was added in one portion through a powder funnel (with the aid of 10 ml dimethylacetamide). The ice bath was removed, and the stirred mixture was allowed to warm to 20-25°C. After about 1 hour, complete solution had occurred. The solution, which gradually developed a dark red color, was kept at 20-25°C for 1 hour longer and was then chilled (ice bath) before it was treated with EtOH (72 ml). After overnight refrigeration, the solvents were removed by evaporation in vacuo. The dark, semisolid residue was stirred with two 300 ml of C_6H_6 (to remove triphenylphosphine oxide), and each portion was removed from the C_6H_6 insoluble product by decantation. The solid that remained was dissolved with stirring in glacial AcOH (660 ml) which had been preheated to 80°C. The mixture was kept in a bath at 80°C until solution was complete. Tan crystalline solid separated as the dark solution was allowed to cool. Overnight refrigeration caused the AcOH to partially freeze. When it had thawed, the solid was collected, washed with chilled AcOH followed by Et_2O, and dried in vacuo (over P2O5 and NaOH pellets) at successive temperatures of 25°C, 56°C, and 110°C. (The higher temperature was necessary for complete removal of AcOH). The yield was 15.3 g (49%). (Some runs afforded 60% yield). This sample was further purified by reprecipitation from MeOH solution (Norit) by addition of Et_2O followed by drying in vacuo (25°C, P_2O_5), yield 13.0 g (42%) of 2,4-diamino-6-(bromomethyl)pteridine hydrobromide as

a pale yellow solid.

A mixture of 2,4-diamino-6-(bromomethyl)pteridine hydrobromide (168 mg, 0.500 mmole) and N-(4-aminobenzoyl)-L-glutamic acid (400 mg, 1.50 mmoles) in dimethylacetamide (2 ml) was stirred at 25°C under N_2 in a stoppered flask protected from light. Solution occurred after 2 hours. After 18 hours, the orange solution was mixed with H_2O (15 ml) with stirring to give a finely divided, yellow precipitate. The mixture was centrifuged, and the supernatant removed by decantation. The yellow solid was stirred with four 15 ml portions of H_2O, each of which was removed by decantation after centrifugation. The solid was then suspended in EtOH (15-20 ml), collected by filtration, washed with Et_2O, and dried in vacuo (25°C, P_2O_5) to give hydrated N-[4-[[(2,4-diamino-6-pteridinyl)methyl]amino]benzoyl]-L-glutamic acid (Aminopterin) hydrate (4:7) in 68% yield (160 mg). Examination by TLC revealed one UV-absorbing spot and no fluorescence at any point.

References

Merck Index, Monograph number: 493, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.

James R.P., Montgomery J.A.; US Patent No. 4,079,056; Mar. 14; Assigned to The Unites States of America, Departament of Health, Education and Welfare, Washington

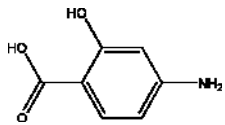
AMINOSALICYLIC ACID

Therapeutic Function: Antitubercular

Chemical Name: 4-Amino-2-hydroxybenzoic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 65-49-6

Trade Name	Manufacturer	Country	Year Introduced
Pamisyl	Parke Davis	US	1948
Parasal	Panray	US	1950
Rexipas	Squibb	US	1954
Aminacyl	Wander	UK	-
B-Pas	Salvoxyl-Wander	France	-
Enseals	Lilly	US	-
Nemasol	I.C.N.	Canada	-

Trade Name	Manufacturer	Country	Year Introduced
Neopasalate	Mallinckrodt Inc.	US	-
Panacyl	Pharma Rheinpreussen	W. Germany	-
Paramisan	Smith and Nephew	UK	-
Para-Pas	Gold Leaf	US	-
Pas	Sumitomo	Japan	-
Pasido	Ferrosan	Sweden	-
Propasa	Merck Sharp and Dohme	-	-
Rezipas	Squibb	US	-
Sanpas	Sanyo	Japan	-
Sta-Pas	Debat	France	-
Tebacin Acid	Consol. Midland	US	-

Raw Materials

Sodium-p-aminosalicylate
m-Aminophenol
Ammonium carbonate

Manufacturing Process

As described in US Patent 427,564, aminosalicylic acid may be prepared from m-aminophenol by heating with ammonium carbonate in solution under pressure.

Alternatively, aminosalicylic acid may be made from sodium p-aminosalicylate as described in US Patent 2,844,625 as follows: 196 grams of commercial sodium para-aminosalicylate (18.5% H_2O) was dissolved in 196 ml of water and 150 ml of isopropanol. 6 grams of sodium bisulfite was dissolved in the solution and the solution filtered. While stirring and keeping the temperature between 25-31°C, seven grams of 85% formic acid and 27.5 grams of 95% sulfuric acid in 150 ml of water was added during 1 ½ hours. The mixture was stripped 1 hour longer, cooled to 23°C and filtered. The filter cake was washed with 100 cubic centimeters of water, further washed with 100 cc of 25% isopropanol and 100 cc of water, and vacuum dried to constant weight at 45-50°C. Weight of p-aminosalicylic acid was 76.5 grams (92.7% yield) exhibiting a bulk density of 47 cc/oz.

References

Merck Index 485
Kleeman and Engel p. 43
I.N. p. 74
REM p. 1213
Gnehm, R.and Schmid, J.; US Patent 427,564; May 13, 1890
Centolella, A.P.; US Patent 2,844,625; July 22, 1958; Assigned to Miles Laboratories, Inc.
Doub, L.; US Patent 2,540,104; February 6, 1951; Assigned to Parke Davis and Co.

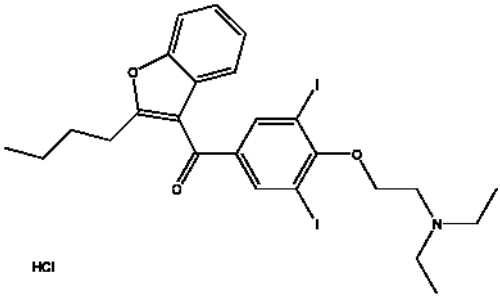
AMIODARONE HYDROCHLORIDE

Therapeutic Function: Coronary vasodilator

Chemical Name: (2-Butyl-3-benzofuranyl)[4-(2-diethylamino)ethoxyl-3,5-diiodophenyl]methanone hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 1951-25-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Cordarone	Labaz	France	1971
Cordarone	Sigma Tau	Italy	1980
Cordarone X	Labaz	UK	1981
Cordarone	Labaz	Switz.	1982
Cordarexne	Labaz	W. Germany	-
Amiodacore	C.T.S.	Israel	-
Atlansil	Roemmers	Argentina	-
Miodarone	Biosintetica	Brazil	-
Procor	Unipharm	Israel	-
Ritmocardyl	Bago	Argentina	-
Trangorex	Labaz	-	-
Uro-Septra	Biosintetica	Brazil	-

Raw Materials

2-n-Butyl-3-(3,5-diiodo-4-hydroxybenzoyl)benzofuran
Sodium methoxide
β-Diethylaminoethyl chloride

Manufacturing Process

135 grams of 2-n-butyl-3-(3,5-diiodo-4-hydroxybenzoyl)benzofuran dissolved in 600 cc of ethyl carbonate were treated with 5.7 grams of sodium in the form of sodium methoxide in methanol. Then, β-diethylaminoethyl chloride which had been obtained from 51.6 grams of the hydrochloride in ethyl

carbonate was introduced into a suspension of the sodium salt. The mixture was heated to a temperature of approximately 90°C which was maintained for approximately 2 hours. The mixture was cooled and allowed to stand overnight during which time the sodium chloride settled down.

The toluene solution containing diethylaminoethyl ether was extracted with increasingly diluted aqueous hydrochloric acid solutions while stirring. Extraction was continued until the alkalized solution produced no further precipitate. The combined aqueous solutions were washed with ether and then made strongly alkaline with aqueous sodium hydroxide. Extraction with ether was carried out three times. The organic layers were washed with water and then dried over anhydrous potassium carbonate. In order to produce the hydrochloride, the carbonate was filtered off and then the hydrochloride was precipitated from the ether solution with an ethereal hydrochloric acid solution. After the solution had been allowed to stand for a few hours, decantation was carried out and the syrupy hydrochloride residue was taken up in 500 cc of boiling acetone. The salt crystallized out by cooling. The substance was allowed to stand overnight at 0°C, and centrifuged, washed with ethyl acetate and then with ether and dried. 130 grams of 2-n-butyl-3-(3,5-diiodo-4-β-N-diethylaminoethoxybenzoyl)benzofuran hydrochloride in the form of a crystalline powder which melts at 156°C were obtained.

References

Merck Index 491
Kleeman and Engel p. 43
DOT 5 (4) 123 (1969)
I.N. p. 75
Tondeur, R. and Binon, F.; US Patent 3,248,401; April 26, 1966; Assigned to Societe Beige de I'Azote et des Produits Chimiques du Marly, SA, Belgium

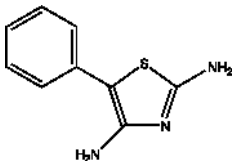
AMIPHENAZOLE

Therapeutic Function: Respiratory stimulant, Barbiturate antagonist, Morphine antagonist

Chemical Name: Thiazole, 2,4-diamino-5-phenyl-

Common Name: Amifenazole; Amiphenazole

Structural Formula:



Chemical Abstracts Registry No.: 490-55-1

Trade Name	Manufacturer	Country	Year Introduced
Aamphisol	RJR	-	-

Raw Materials

Thiourea
α-Bromophenylacetonitrile

Manufacturing Process

Thiourea reacted with α-bromophenylacetonitrile and as a result of this reaction 2-(cyanophenylmethyl)isothiourea was obtained.

By cyclisation of the 2-(cyanophenylmethyl)isothiourea 2,4-diamino-5-phenylthiazole (amiphenazol) was produced.

References

Kleemann A., Engel J.; Pharmazeutische Wirkstoffe, GeorgThieme Verlag Stuttgart. New York, 1982

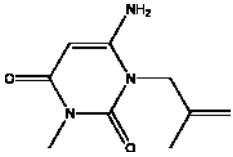
AMISOMETRADINE

Therapeutic Function: Diuretic

Chemical Name: 6-Amino-3-methyl-1-(2-methyl-2-propenyl)-2,4(1H,3H)-pyrimidinedione

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 550-28-7

Trade Name	Manufacturer	Country	Year Introduced
Rolicton	Searle	US	1956

Raw Materials

Methallylamine
Cyanoacetic acid
Methyl isocyanate
Sodium hydroxide

Manufacturing Process

Preparation of the ethyl analog is as follows (methyl isocyanate is used in amisometradine manufacture).

To a cooled and stirred solution of 142 parts of methallylamine in 900 parts of benzene, 156 parts of ethyl isocyanate are added dropwise. Upon concentration in vacuum N-ethyl-N'-methallylurea is obtained.

260 parts of this urea derivative are dissolved in 500 parts of acetic anhydride and treated with 157 parts of cyanoacetic acid at 60°C and heated at that temperature for 2 hours. The solution is then concentrated in vacuum to a syrup. 100 parts of water are added and the vacuum distillation is repeated. The remaining syrup contains a mixture of N-cyanoacetyl-N-ethyl-N'-methallylurea and a small quantity of N-cyanoacetyl-N-methallyl-N'-ethylurea.

This syrup is treated with sufficient 20% sodium hydroxide solution to raise the pH to 10. A violent reaction occurs. The reaction mixture is diluted with 50 parts of water, stirred, cooled and filtered. The material collected on the filter is recrystallized from 10% ethanol to yield a mixture of 1-methallyl-3-ethyl-6-amino-1,2,3,4-tetrahydro-2,4-pyrimidinedione and 1-ethyl-3-methallyl-6-amino-1,2,3,4-tetrahydro-2,4-pyrimidinedione melting at about 157-159°C.

References

Merck Index 493
OCDS Vol. 1 p. 266
I.N. p. 76
Papesch, V. and Schroeder, E.F.; US Patent 2,729,669; January 3, 1956; Assigned to G.D. Searle and Co.

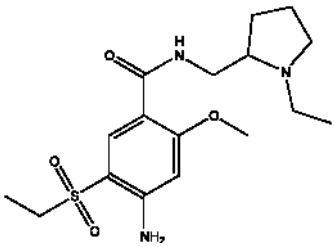
AMISULPRIDE

Therapeutic Function: Antipsychotic

Chemical Name: Benzamide, 4-amino-N-((1-ethyl-2-pyrrolidinyl)methyl)-5-(ethylsulfonyl)-2-methoxy-

Common Name: Aminosultopride; Amisulpride

Structural Formula:



Chemical Abstracts Registry No.: 71675-85-9

Trade Name	Manufacturer	Country	Year Introduced
Solian	Lorex-Synthelabo	-	-
Amitrex	Synthelabo	-	-
Socian	Sanofi-Synthelabo GmbH	-	-

Raw Materials

2-Methoxy-4-amino-5-mercaptobenzoic acid
Caustic soda
Ethyl sulfate

Manufacturing Process

2-Methoxy-4-amino-5-ethylthiobenzoic acid:

159 g of 2-methoxy-4-amino-5-mercaptobenzoic acid, 355 ml of water and 160 ml of caustic soda solution are placed in a flask fitted with a condenser. The mixture is heated until the solid dissolves, then 123 g of ethyl sulfate is added. The mixture is heated to reflux, treated with 10 ml of 30% caustic soda solution, then heated to reflux for 1 hour. After cooling, 800 ml of water is added and the solution is filtered. The precipitate obtained by adding 100 ml of concentrated hydrochloric acid in the presence of ether is drained, washed with water and dried. 162 g of 2-methoxy-4-amino-5-ethylthiobenzoic acid is obtained (yield=88%).

2-Methoxy-4-amino-5-ethylsulfonylbenzoic acid:

123 g of 2-methoxy-4-amino-5-ethylthiobenzoic acid is dissolved hot in 542 ml of acetic acid. The solution obtained is cooled to 35°C, then 185 ml of hydrogen peroxide is added in small quantities while the temperature is raised to 80°C. The temperature is lowered to 40°C and the mixture is kept at that temperature for some hours and then cooled to 10°C. The precipitate formed is drained, washed with acetic acid and dried, then dissolved in 600 ml of water and 100 ml of 20% ammonia. The precipitate formed by adding 70 ml of concentrated hydrochloric acid is cooled, drained, washed with water and dried. 61.5 g of 2-methoxy-4-amino-5-ethylsulfonylbenzoic acid is obtained (yield 42%, M.P. 95-100°C).

4-Amino-N-[(1-ethyl-2-pyrrolidinyl)methyl]-5-(ethylsulfonyl)-2-methoxybenzamide:

81 g of 2-methoxy-4-amino-5-ethylsulphonylbenzoic acid and 297 ml of acetone are placed in a flask fitted with an agitator, a thermometer and a dropping funnel, followed by 33 g of triethylamine. The solution is cooled to 0°C, then 30 g of ethyl chloroformate is added drop by drop between 0° and 5°C. When the mixture has been agitated 51 g of 1-ethyl-2-aminomethylpyrrolidine is added drop by drop between 5° and 10°C. The mixture is agitated at 10°C then at ambient temperature. The triethylamine hydrochloride which precipitates is drained, then the acetone is distilled. The residue is dissolved in 600 ml of water in the presence of caustic soda

solution. The base crystallizes after seeding and is drained, washed with water and dried. When the crystals have been purified by passing them through hydrochloride and recrystallising them in acetone, 66 g of 4-amino-N-[(1-ethyl-2-pyrrolidinyl)methyl]-5-(ethylsulfonyl)-2-methoxybenzamideis obtained (yield 61%, M.P. 126-127°C).

References

Thominet M., Acher J., Monier J.; US Patent No. 4,401,822; Aug. 30, 1983; Assigned to Societe de'Etudes Scientifiques et Industrielles de l'Ile-de France (Paris, FR)

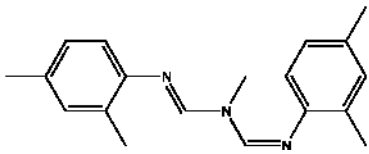
AMITRAZ

Therapeutic Function: Acaricide, Scabicide, Tickicide, Appetite stimulant

Chemical Name: Methanimidamide, N'-(2,4-dimethylphenyl)-N-(((2,4-dimethylphenyl)imino)methyl)-N-methyl-

Common Name: Amitraz; Ectodex; Topline

Structural Formula:



Chemical Abstracts Registry No.: 33089-61-1

Trade Name	Manufacturer	Country	Year Introduced
Aludex	Hoechst Roussel Vet Ltd.	-	-
Ectodex	Intevet	-	-

Raw Materials

Sodium hydroxide
N-Methylformamide
2,4-Dimethylaniline hydrochloride
4-Toluenesulfonyl chloride

Manufacturing Process

A mixture of 55.1 g 2,4-dimethylaniline hydrochloride, 83.7 g p-toluenesulphonyl chloride and 150 ml N-methylformamide was stirred with occasional cooling to maintain the temperature at 20°-35°C. When the exothermic reaction had subsided, the mixture was stirred at room temperature for 4 h, poured into a mixture of ice and water, and basified with 10 N sodium hydroxide solution, keeping the temperature of the mixture

below 10°C. The precipitated solid was filtered, washed with water until free from alkali, dried at room temperature, to give N-2,4-dimethylphenyl-N'-methylformamidine, melting point 75°-76°C (recrystallized from cyclohexane).

A solution of 19.4 g N-2,4-dimethylphenyl-N'-methylformamidine and 0.3 g p-toluenesulphonic acid in 195 ml dry xylene was refluxed under anhydrous conditions for 48 h, causing the evolution of methylamine. The xylene was distilled off under reduced pressure to give 1,5-di-(2,4-dimethylphenyl)-3-methyl-1,3,5-triaza-penta-1,4-diene, melting point 88°-89°C (crystallized twice from isopropyl).

References

Harrison I. R. et al.; US Patent No. 3,781,355; Dec. 25, 1973; Assigned: Boots Pure Drug Company Limited, Nottingham, England

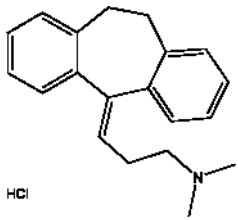
AMITRIPTYLINE HYDROCHLORIDE

Therapeutic Function: Antidepressant

Chemical Name: 3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-N,N-dimethyl-1-propaneamine hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 549-18-8; 50-48-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Elavil HCl	Merck Sharp and Dohme	US	1961
Elavil	DDSA	UK	1962
Triptizol	Merck Sharp and Dohme	Italy	1962
Laroxyl	Roche	Italy	1962
Endep	Roche	US	1975
Amitril	WL/PD	US	1978
Amitid	Squibb	US	1979
Arnavil	Mallard	US	1980

Trade Name	Manufacturer	Country	Year Introduced
Enovil	Hauck	US	1982
Adepril	Lepetit	Italy	-
Adepress	Essex-Shionogi	Japan	-
Ami-Aneiun	Lorente	Spain	-
Amilent	Warner Lambert	US	-
Amiprin	Kobayashi	Japan	-
Amiptanol	Kanto	Japan	-
Amitrip	Glebe	Australia	-
Amitriptol	Bracco	Italy	-
Annolytin	Kodama	Japan	-
Annolytin	Nippon Shoji	Japan	-
Deprestat	Script Intal	S. Africa	-
Domical	Berk	UK	-
Elatrol	ICN	Canada	-
Elatrol	Teva	Israel	-
Elatrolet	Teva	Israel	-
Lantron	Yamanouchi	Japan	-
Lentizol	Warner Lambert	US	-
Levate	ICN	Canada	-
Limbitrol	Roche	France	-
Limbitrol	Roche	US	-
Mareline	Elliott-Marion	Canada	-
Meravil	Medic	Canada	-
Miketorin	Mitsui	Japan	-
Mitaptyline	Toyo Pharm.	Japan	-
Mutanxion	Cetrane	France	-
Mutaspline	Cetrane	France	-
Normaln	Sawai	Japan	-
Novotriptyn	Novopharm	Canada	-
Redomex	Labaz	-	-
Saroten	Lundbeck	W. Germany	-
Saroten	Tropon	W. Germany	-
Saroten	Warner	UK	-
Sarotex	Lundbeck	W. Germany	-
Schuvel	Tokyo Hosei	Japan	-
Sensival	Pfizer Taito	Japan	-
Teperin	EGYT	Hungary	-
Trepiline	Lennon	S. Africa	-
Triavil	Merck Sharp and Dohme	US	-
Triptilin	Kimya Evi	Turkey	-

Trade Name	Manufacturer	Country	Year Introduced
Triptyl	Farmos	Finland	-
Tryptal	Unipharm	Israel	-
Tryptanol	Merck-Banyu	Japan	-
Tryptizol	Sharp and Dohme	W. Germany	-
Tryptizol	Sharp and Dohme	UK	-

Raw Materials

Phthalic anhydride
Hydrochloric acid
Phenylacetic acid
3-(Dimethylamino)propyl chloride
Hydrogen

Manufacturing Process

Phthalic anhydride is reacted with phenylacetic acid to form 3-benzylidenephthalide which is then hydrogenated to 2-phenethylbenzoic acid. Conversion to the acid chloride followed by intramolecular dehydrochlorination yields the ketone, 5H-dibenzo[a,d]cyclohepten-5-one. The ketone undergoes a Grignard reaction with 3-(dimethylamino)propyl chloride to give 5-(γ-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene.

Then, as described in US Patent 3,205,264, a solution of 5-(γ-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene (42 grams; 0.153 mol) in 105 ml of ethanol is hydrogenated over Raney nickel (1.5 grams) at 65°C under an initial hydrogen pressure of 450 lb. After 1 mol of hydrogen is absorbed (3.5 hours), the reaction mixture is filtered to remove the catalyst and is acidified with 80 ml of 2.5 N hydrochloric acid (0.2 mol). The acidic solution is concentrated to dryness under vacuum and is flushed three times with 100 ml of benzene to remove residual water. The solid residue then is dried under vacuum at 40°C to yield 44.9 grams (94% of theory) of the product, MP 187-189.5°C, equivalent weight 307, ultraviolet absorption A% 2380^{432}. Recrystallization from isopropyl alcohol and ether affords the product in high purity.

In practice it is usually used as hydrochloride.

References

Merck Index 496
Kleeman and Engel p. 44
PDR pp. 673, 993, 1174, 1217, 1314, 1509, 1513, 1569, 1606, 1617
OCDS Vol. 1 pp. 151, 404
DOT 9 (6) 219 (1973)
I.N. p. 76
REM p. 1093
Tristram, E.W. and Tull, R.J.; US Patent 3,205,264; September 7, 1965; Assigned to Merck and Co., Inc.

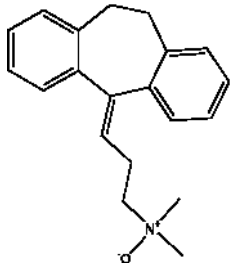
AMITRIPTYLINE OXIDE

Therapeutic Function: Antidepressant

Chemical Name: 3-(3'-Dimethylaminopropylidene)dibenzo[a,d]cyclohepta-1,4-diene N-oxide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 4317-14-0

Trade Name	Manufacturer	Country	Year Introduced
Equilibrin	Nattermann	W. Germany	1980
Ambivalon	Nattermann	W. Germany	-

Raw Materials

Dibenzo[a,d]cyclohepta-1,4-diene-5-one
3-Dimethylaminopropanol magnesium chloride
Hydrogen peroxide

Manufacturing Process

31.3 g (0.1 mol) of 3-(3'-dimethylaminopropylidene)dibenzo[a,d]cyclohepta-1,4-diene hydrochloride are dissolved in water, and the free base is liberated by means of a 28% aqueous solution of sodium hydroxide. The free base is sucked off, washed with water, and dissolved in 100 ml of methanol. To the solution are added 31 ml of 30% hydrogen peroxide. After 7 days, the reaction mixture is diluted with 200 ml of water, and the major part of the methanol is evaporated in vacuum. The precipitated N-oxide crystals are filtered off, washed with water, and dried, yielding 27 g of the dihydrate of 3-(3'-dimethylaminopropylidene)dibenzo[a,d]cyclohepta-1,4-diene N-oxide with melting point of 102° to 103°C. In dehydrated state the melting point is 228°C to 230°C.

By dissolving the N-oxide in acetone, and bubbling dry hydrogen chlorine gas through the solution until slightly acid reaction, the hydrochloride of the N-oxide is precipitated as a white crystalline substance with melting point of 172°C to 173.6°C.

The starting material can be prepared in known manner from dibenzo[a,d]cyclohepta-1,4-diene-5-one by a Grignard reaction with 3-dimethylaminopropyl magnesium chloride, hydrolysis and dehydration of the resulting carbinol.

References

Merck Index 497
DFU 5 (7) 329 (1980)
Kleeman and Engel p. 45
DOT 18 (3) 110 (1982)
I.N. p. 77
Pedersen, J.B.; British Patent 991,651; May 12, 1965; Assigned to A/S Dumex (Dumex, Ltd.)
Merck and Co., Inc.; British Patent 1,095,786; December 20, 1967
Pedersen, J.B.; US Patent 3,299,139; January 17, 1967; Assigned to A/S Dumex (Dumex, Ltd.)

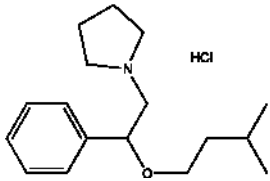
AMIXETRINE HYDROCHLORIDE

Therapeutic Function: Antiinflammatory, Anticholinergic, Antidepressant

Chemical Name: N-(2-Phenyl-2-isoamyloxy)ethylpyrrolidine hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 24622-52-4; 24622-72-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Somagest	Riom	France	1972

Raw Materials

Styrene
Hydrogen chloride
Pyrrolidine
Isoamyl alcohol
t-Butyl hypobromite

Manufacturing Process

There is heated under reflux with stirring for 10 hours: 117 g of (2-phenyl-2-

isoamyloxy)ethyl bromide, 61.5g of pyrrolidine and 250 ml of toluene.

After filtration of the pyrrolidine hydrobromide, the toluene is removed under reduced pressure. The residue is then taken up with 4 N HCl. The aqueous solution is washed with ether. It is made alkaline by a solution of 50% NaOH. It is extracted with ether. The ethereal phase is dried over anhydrous sodium sulfate, and rectified under reduced pressure after removing the solvent. There is thus obtained 90 g of a colorless oil with an amine odor.

The hydrochloride is prepared in the usual manner by dissolving the amine in anhydrous ether and adding to it the requisite amount of dry gaseous hydrochloric acid, dissolved in absolute alcohol. There is obtained a white crystalline powder melting at 150°C, very soluble in water and alcohol, very slightly soluble in ether and ethyl acetate.

The starting material above is prepared by reacting styrene with isoamyl alcohol and then reacting that product with t-butyl hypobromite.

References

Merck Index 499
Kleeman and Engel p. 46
DOT 8 (9) 334 (1972)
I.N. p. 77
Centre Europeen de Recherches Mauvernay, RIOM; British Patent 1,253,818; November 17, 1971

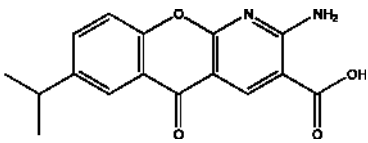
AMLEXANOX

Therapeutic Function: Antiulcer (topical)

Chemical Name: 5H-[1]Benzopyrano[2,3-b]pyridine-3-carboxylic acid, 2-amino-7-(1-methylethyl)-5-oxo-

Common Name: Amlexanox, Amoxanox

Structural Formula:



Chemical Abstracts Registry No.: 68302-57-8

Trade Name	Manufacturer	Country	Year Introduced
Aphthasol	Block Drug Company	-	-
Apthasol	Access Pharmaceuticals	-	-

Trade Name	Manufacturer	Country	Year Introduced
Apthera	Paladin Labs	-	-
OraDisc	Access Pharmaceuticals	-	-
OraRinse	Paladin Labs	-	-

Raw Materials

Morpholine
Piperidine
6-Isopropyl-4-oxo-4H-1-benzopyran-3-carbonitrile
Ethyl cyanoacetate

Manufacturing Process

A mixture of 2 ml of morpholine, 3 ml of dimethylformamide and 10 ml of water was heated to 60°C and under stirring the equal molecular quantity of 6-isopropyl-4-oxo-4H-1-benzopyran-3-carbonitrile was added for 5 minutes. The mixture was heated at that temperature for one hour and the resultant precipitate was filtered, rained with water recrystallized from acetic acid and washed with chloroform. By the above procedure was obtained 2-amino-6-isopropyl-4-oxo-4H-1-benzopyran-3-carboxaldehyde melting at 206°-208°C. A mixture of 4 ml ethyl cyanoacetate, 50 ml of ethanol, 5 ml of piperidine and the equal molecular quantity of 2-amino-6-isopropyl-4-oxo-4H-1-benzopyran-3-carboxaldehyde was refluxed for 30 minutes and, after cooling, the crystalline precipitate was filtered and washed with chloroform. By above procedure was obtained ethyl-2-amino-7-isopropyl-1-azaxanthone-3-carboxylate, melting after recrystallization from ethanol at 243°-244°C. A mixture of 10 ml of acetic acid and 10 ml of 55% sulfuric acid the equal molecular quantity and 2-ethyl-amino-7-isopropyl-1-azaxanthone-3-carboxylate was stirred at 130°C for 4 hours and, after water was added, the precipitate was collected by filtration and recrystalllized from dimethylformamide to give the 2-amino-7-(1-methylethyl)-5-oxo-5H-[1]benzopyrano[2,3-b]pyridine-3-carboxylic acid, melting point 300°C.

References

Nohara Akira et al.; US Patent No. 4,143,042; March, 6, 1979; Assigned Takeda Chemical Industries, Ltd., Osaka, Japan

AMLODIPINE BESYLATE

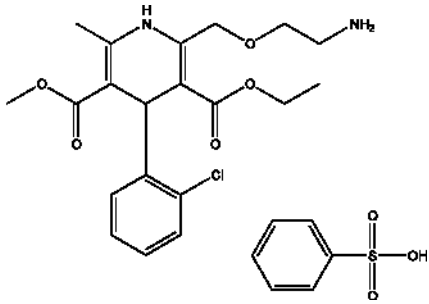
Therapeutic Function: Antianginal, Antihypertensive

Chemical Name: 2-[(2-Aminoethoxy)methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine monobenzenesulfonate

Common Name: Amlodipine besylate

Chemical Abstracts Registry No.: 111470-99-6; 881150-42-9 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Amlodin	Sumitomo Pharmaceuticals Co., Ltd.	-	-
Amlodipine besilate	Ultra-tech Spc. Pvt. Ltd.	India	-
Amlogard	Pfizer	-	-
Amlovas	Unique Pharmaceutical Laboratories	India	-
Amlovas	Macleods Pharmaceuticals Pvt. Ltd.	India	-
Normodipine	Gedeon Richter	Hungary	-
Norvasc	Lincoln	-	-
Stamlo	Dr. Reddy's Laboratories Ltd.	India	-
Tensivask	PT Pfizer	Indonesia	-

Raw Materials

Hydrazine hydrate
Phthalimide
Ethylacetoacetate
2-Chlorobenzaldehyde
Methyl-3-aminocrotonate

Manufacturing Process

2-[(2-Aminoethoxy)methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine (amlodipine) was prepared from 2-(phthalimidoaminoethoxy)acetoacetate, 2-chlorobenzaldehyde and methyl-3-aminocrotonate under refluxing in ethanol for 24 hours. The ketoester was prepared by the method of Troostwijk and Kellog (JCS Chem. Comm., 1977, p.932). Methyl-3-aminocrotonate can be prepared by known method. Phthalimido-amino-protecting group was removed using hydrazine hydrate in ethanol at the reflux temperature.

Although amlodipine is effective as the free base, in practice it is best administered form of a salt of a pharmaceutically acceptable acid.

Benzensulphonic salt of amlodipine was prepared as follows: Amlodipine base (65.6 g, 0.161 mols) was slurried in industrial methylated spirit (denatured alcohol, 326.4 ml) and cooled to 5°C. Benzensulphonic acid (26.2 g, 0.168 mols) was dissolved in industrial methylated spirit (65.6 ml) at 5°C and added to base. The resulting slurry was then granulated, filtered and washed with 2 volumes the same solvent (65.6 ml). The damp solid was slurred at 5°C for 1 hr in 327.6 ml industrial methylated spirit, filtered, washed with 2 volumes of the same solvent (65.6 ml) and dried under vacuum at 55°C for 24 hr. A yield of besylate salt of amlodipine 65 g.

References

Campbell S.F. et al.; US Patent No. 4,572,909, Feb. 25, 1986; Assigned: Pfizer Inc. (New York, NY) (Preparation 2a)
Davison E. et al.; US Patent No. 4,879,303, Nov. 7, 1989; Assigned: Pfizer Inc. (New York, NY)

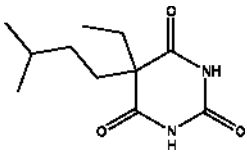
AMOBARBITAL

Therapeutic Function: Hypnotic, Antiepileptic

Chemical Name: Barbituric acid, 5-ethyl-5-isopentyl-

Common Name: 5-Ethyl-5-isopentylbarbituric acid; Amobarbitone; Amylbarbitone; Pentymal

Structural Formula:



Chemical Abstracts Registry No.: 57-43-2

Trade Name	Manufacturer	Country	Year Introduced
Hypnotal	Pharmacal	-	-
Isonal	Leiras	-	-
Sednotic	Dista	-	-
Transital	Miquel	-	-

Raw Materials

Malonic acid diethyl ester
Ethyl bromide
Sodium ethylate
Isopentyl bromide

Manufacturing Process

By interaction of malonic acid diethyl ester with sodium ethylate (molar ratio 1:1) and then with ethyl bromide (molar ratio 1:1) was prepared ethylmalonic

acid diethyl ester. From ethylmalonic acid diethyl ester and sodium ethylate (molar ratio 1:1) and then with isopentylbromide was synthesized α-ethyl-α-isopentylmalonic acid diethyl ester. By condensation of α-ethyl-α-isopentylmalonic acid diethyl ester with urea in the presence of sodium ethylate was obtained ethyl-isopentylbarbituric acid.

References

Layraud E.; GB Patent No. 191,008; Oct. 25, 1923
Shonle H.A.; US Patent No. 1,856,792; May 3, 1932; Assigned to Eli Lilly and Company, of Indianapolis, Indiana, a Corporation of Indiana

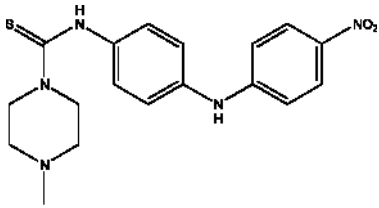
AMOCARZINE

Therapeutic Function: Anthelmintic

Chemical Name: 1-Piperazinecarbothioamide, 4-methyl-N-(4-((4-nitrophenyl) amino)phenyl)-

Common Name: Amocarzine; Phenthiourezine

Structural Formula:



Chemical Abstracts Registry No.: 36590-19-9

Trade Name	Manufacturer	Country	Year Introduced
CGP 6140	CIBA-GEIGY Corp.	-	-

Raw Materials

4-Nitro-4'-isothiocyanodiphenylamine
N-Methylpiperazine

Manufacturing Process

A solution of 4-nitro-4'-isothiocyanodiphenylamine in toluene was treated at 50°C with stirring with a solution N-methylpiperazine in toluene. After 3 hours the solution was filtered from the precipitate obtained. By recrystallization the crude product from methanol the 4-methyl-N-[4-[(4-nitrophenyl)amino]phenyl]-1-piperazinecarbothioamide was obtained; melting point 191-196°C.

References

Ruediger Spaun et al.; US Patent No. 3,781,290; Dec. 25, 1973; Assigned to Ciba-Geigy Corporation, Ardsley, N.Y.

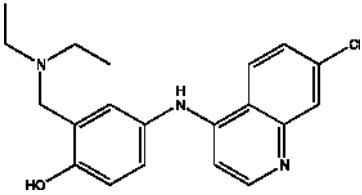
AMODIAQUIN

Therapeutic Function: Antimalarial

Chemical Name: 4-[(7-Chloro-4-quinolinyl)amino]-2-[(diethylamino)methyl] phenol

Common Name: 4-(3'-Diethylaminomethyl-4'-hydroxyanilino)-7-chloroquinoline

Structural Formula:



Chemical Abstracts Registry No.: 86-42-0 (Base); 69-44-3 (Dihydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Camoquin HCl	Parke Davis	US	1950
Flavoquine	Roussel	France	1979
Corbutyl	I.S.H.	France	-
Camoquin	Parke Davis	UK	-

Raw Materials

4,7-Dichloroquinoline
Diethylamine
p-Aminophenol hydrochloride
Paraformaldehyde

Manufacturing Process

72.8 g (0.5 mol) of p-aminophenol hydrochloride is dissolved in 500 cc of water and added to 99 g (0.5 mol) of 4,7-dichloroquinoline. After a few minutes of warming in a steam bath, 4-(4'-hydroxyanilino)-7-chloroquinoline hydrochloride, of sufficient purity for use in further experiments, precipitates as a yellow crystalline solid. Recrystallized from methanol, the MP is over 300°C.

A mixture consisting of 13.5 g of 4-(4'-hydroxyanilino)-7-chloroquinoline hydrochloride dissolved in absolute ethanol is treated with a solution of 4.38 g

of diethylamine and 1.8 g of paraformaldehyde in 20 cc of absolute ethanol. The reaction mixture is heated under reflux for 16 hours, evaporated to one-half volume and the warm solution treated with an excess of hydrogen chloride dissolved in absolute ethanol. Acetone is added to the warm solution until it becomes turbid and then the solution is cooled. The crude dihydrochloride which separates is collected and purified by recrystallization from methanol; MP 240-242°C.

By using an equivalent amount of 4-(4'-hydroxyanilino)-7-bromoquinoline in the above procedure, 4-(3'-diethylaminomethyl-4'-hydroxyanilino)-7-bromoquinoline dihydrochloride is obtained; MP (base) 206-208°C dec.

References

Merck Index 593
Kleeman and Engel p. 47
I.N. p.78
REM p. 1217
Burckhalter, J.H., Jones, E.M., Rawlins, A.L., Tendick, F.H, and Holcomb, W.F.; US Patent 2,474,821; July 5, 1949; Assigned to Parke, Davis and Co.

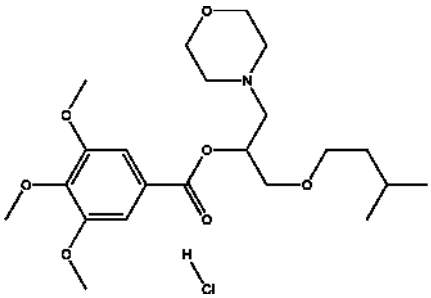
AMOPROXAN HYDROCHLORIDE

Therapeutic Function: Antiarrhythmic, Antianginal

Chemical Name: 3,4,5-Trimethoxybenzoic acid 1-[(3-methylbutoxy)methyl]-2-(4-morpholinyl)ethyl ester hydrochloride

Common Name: Amoproxan hydrochloride, Aproxim

Structural Formula:



Chemical Abstracts Registry No.: 22661-96-7

Trade Name	Manufacturer	Country	Year Introduced
Bisolaryn	Boehringer Ingelheim	-	-
Ambrobeta	Betapharm	-	-
Exabrol	Pharmacos	-	-

Raw Materials

Isoamyl alcohol
Boron trifluoride
Epichlorohydrin
Morpholine
Hydrogen chloride
(3,4,5-Trimethoxy)benzoyl chloride

Manufacturing Process

To a mixture of 176 g (2 M) of isoamyl alcohol and 4 ml of a 10% solution of BF3 in anhydrous ether, were added, with stirring, 278 g (3 M) of epichlorohydrin while maintaining the temperature at approximately 45°C. After the addition, the reaction was maintained for an additional hour at 60°C. It was then cooled and a solution of 160 g of NaOH in pellets in 200 ml H_2O was added while maintaining the temperature at approximately 15°C. Stirring was continued for an additional 2 hours, the NaCl formed was filtered and the organic phase decanted. Vacuum fractionation gave 142 g of 3-isoamyloxy-1,2-epoxypropane. Boiling point 67-68°C.

To a solution of 115.2 g (0.8 M) of 3-isoamyloxy-1,2-epoxypropane in 200 ml of absolute ethanol were added 76 g of morpholine. The temperature rose to approximately 40°C. Heating under reflux was continued for one additional hour, the solvent was distilled and the reaction mixture vacuum fractionated to obtain 166 g of 4-[3-isoamyloxy-2-hydroxy]propyltetrahydro-1,4-oxazine. Boiling point 163°C, n_D^{21} = 1.4620, yield=90%.

In a 2 liter three-neck flask, provided with a tight-fitting stirrer and a reflux condenser, were charged: 115.5 g (0.5 M) of 4-[3-isoamyloxy-2-hydroxy]propyl tetrahydro-1,4-oxazine in 750 ml of anhydrous benzene, 50.5 g of triethylamine and 115.25 g of (3,4,5-trimethoxy)benzoyl chloride. The mixture was slowly brought to reflux, which was maintained for 4 hours. After cooling, it was filtered, the solvent was stripped off under vacuum, the residue taken up in 4 N HCl (in the cold) and the aqueous solution washed with ether. The aqueous solution was then treated with sodium carbonate and the oil formed extracted with the ether. It was dried over anhydrous sodium sulfate and the solvent tripped off to obtain a highly viscous oily residue, which was taken up in 600 ml of ethyl acetate; the required quantity of absolute ethanol, with 30% HCl gas, was then added, affording the hydrochloride. After standing for several hours in the ice-box, it was filtered, and after recrystallization from anhydrous isopropyl alcohol and drying under vacuum at 60°C to constant weight, 155 g of (3,4,5-trimethoxy)benzoyl chloride were obtained. Yield=67%, melting point 145°C.

References

Mauvernay R. Y., Busch N., Simond J., Moleyre J.; US Patent No. 3,790,569; Feb. 1, 1974; Assigned to Centre Europeen de Recherches Mauvernay, Riom, France

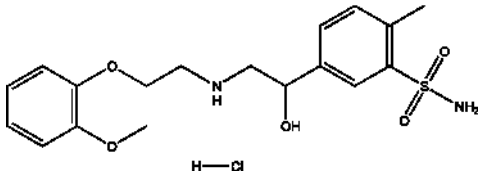
AMOSULALOL HYDROCHLORIDE

Therapeutic Function: Alpha-adrenergic blocker, Beta-adrenergic blocker, Antihypertensive

Chemical Name: (+/-)-5-(1-Hydroxy-2-((2-(o-methoxyphenoxy)ethyl)amino) ethyl)-o-toluenesulfonamide monohydrochloride

Common Name: Amosulalol hydrochloride; Lowgan

Structural Formula:



Chemical Abstracts Registry No.: 70958-86-0; 85320-68-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Amosulalol hydrochloride	Yamanouchi	-	-

Raw Materials

Methyl ethyl ketone
Sodium borohydride
Hydrogen chloride
Hydrogen
N-Benzyl-2-(2-methoxyphenoxy)ethylamine
5-Bromoacetyl-2-methylbenzenesulfonamide
Palladium on charcoal

Manufacturing Process

A mixture of N-benzyl-2-(2-methoxyphenoxy)ethylamine, methyl ethyl ketone, and 5-bromoacetyl-2-methylbenzenesulfonamide was refluxed with stirring. After cooling the reaction mixture, ethyl ketone was distilled off under reduced pressure and the residue formed was dissolved in benzene. Then, ether was added to the solution and after removing the hydrobromide of N-benzyl-2-(2-methoxyphenoxy)ethylamine precipitated, the solvent was distilled off under reduced pressure to provide a viscous oily product.

The viscous oily product was dissolved in ethanol and after adding to the solution an excess amount of sodium borohydride, the mixture was stirred at room temperature followed by distilling off ethanol under reduced pressure. The residue was dissolved in ethyl acetate and the ethyl acetate layer recovered was washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to provide a viscous oily product. The product was subjected to a silica gel column chromatography and eluted using benzene and then a mixture of benzene and ethyl acetate of 10:1 by volume ratio to provide 5-{1-hydroxy-2-[N-benzyl-2-(2-methoxyphenoxy)ethylamino]ethyl}-2-methyl-benzenesulfonamide as a viscous oily product.

In 200 ml of methanol was dissolved 20.0 g of 5-{1-hydroxy-2-[N-benzyl-2-(2-methoxyphenoxy)ethylamino]ethyl}-2-methyl-benzenesulfonamide. After adding thereto 20 ml of ethanol containing about 10% hydrogen chloride and 1.0 g of 10% palladium charcoal, the mixture was shaken in hydrogen gas stream. When the absorption of hydrogen stopped, the catalyst was filtered away and the filtrate was distilled off under reduced pressure. The residue was dissolved in 100 ml of ethanol while it was hot and the solution was allowed to stand overnight in ice chamber, whereby 12.8 g of the α-type crystals of 5-{1-hydroxy-2-[2-(2-methoxyphenoxy)ethylamino]ethyl}-2-methylbenzenesulfonamide were obtained as the colorless crystals, melting point 169°-171°C.

In practice it is usually used as monohydrochloride

References

Imai K. et al.; US Patent No. 4,217,305; August 12, 1980; Assigned: Yamanouchi Pharmaceutical Co., Ltd., Tokyo, Japan

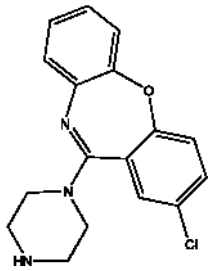
AMOXAPINE

Therapeutic Function: Antidepressant

Chemical Name: 2-Chloro-11-(1-piperazinyl)dibenz[b,f][1,4]oxazepine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 14028-44-5

Trade Name	Manufacturer	Country	Year Introduced
Asendin	Lederle	US	1980
Moxadil	Lederle	France	1980
Amoxan	Lederle	Japan	1981
Omnipress	Cyanamid	W. Germany	1983
Demolox	Lederle	-	-

Raw Materials

N-Carbethoxypiperazine
o-(p-Chlorophenoxy)aniline hydrochloride
Ethyl chlorocarbonate
Phosphorus pentoxide

Manufacturing Process

A mixture of 125 g of o-(p-chlorophenoxy)aniline hydrochloride and 100 ml of dry pyridine is treated cautiously with a solution of 90 ml of ethyl chlorocarbonate in 150 ml of ether. The mixture is kept at room temperature for 3 days, diluted with about 500 ml of water and extracted with 300 ml of ether, The ethereal extract is washed with 300 ml of water, dried over calcium chloride, filtered and concentrated. The resulting ethyl o-(p-chlorophenoxy)carbanilate is obtained in a viscous oil suitable for use in the next step without further purification.

A solution of 70 g of ethyl o-(p-chlorophenoxy)carbanilate and 120 g of N-carbethoxypiperazine in 100 ml of benzene containing a little sodium methoxide is heated on a steam bath for about 5 days. The solvent is removed by distillation and the residue is triturated with water. The resulting solid is dissolved in ether and dried over sodium sulfate. Filtration and concentration then yields ethyl 4-[[o-(p-chlorophenoxy)phenyl]carbamoyl]-1-piperazinecarboxylate, melting at 89°C to 91°C, and suitable for cyclization.

A mixture of 10 g of the above piperazine carboxylate ester, 8 g of phosphorus pentoxide and 20 ml of phosphorus oxychloride is heated under reflux for about 1 day, diluted with 100 ml each of chloroform and benzene and quenched with 200 g of ice. The mixture is made basic with 10% sodium hydroxide. The organic layer is isolated and extracted with 150 ml of dilute hydrochloric acid. The product is precipitated from the aqueous layer by addition of 10% sodium hydroxide, extracted with benzene and dried over potassium carbonate. Recrystallization from benzene-petroleum ether gives 2-chloro-11-(1-piperazinyl)dibenz[b,f][1,4]oxazepine which melts at 175°C to 176°C.

References

Merck Index 598
PDR p. 1005
DOT 8 (2) 78 (1972) and 15 (3) 73 (1979)
REM p. 1094
DFU 1 (11) 511 (1976)
OCDS Vol. 2 p. 478 (1980)
I.N. p. 79
Howell, C.F., Hardy, R.A., Jr. and Quinones, N.Q.; US Patent 3,663,696; May 16, 1972; Assigned to American Cyanamid Company
Howell, C.F., Hardy, R.A., Jr. and Quinones, N.Q.; US Patent 3,681,357; August 1, 1972; Assigned to American Cyanamid Company

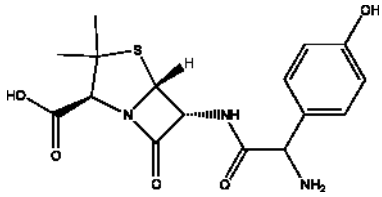
AMOXICILLIN

Therapeutic Function: Antibacterial

Chemical Name: 6-([Amino-(4-hydroxyphenyl)acetyl]amino)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid

Common Name: p-Hydroxyampicillin

Structural Formula:



Chemical Abstracts Registry No.: 26787-78-0; 61336-70-7 (Trihydrate)

Trade Name	Manufacturer	Country	Year Introduced
Arnoxil	Bencard	UK	1972
Clamoxyl	Beecham	W. Germany	1973
Clamoxyl	Beecham	France	1974
Larotid	Roche	US	1974
Amoxil	Beecham	US	1974
Polymox	Bristol	US	1975
Sawacillin	Fujisawa	Japan	1975
Pasetocin	Kyowa Hakko	Japan	1975
Velamox	Zambeletti	Italy	1975
Wymox	Wyeth	US	1978
Utimox	WL/PD	US	1979
Agerpen	Cepa	Spain	-
A-Gram	Inava	France	-
Alfamox	Alfa	Italy	-
Alfida	Esteve	Spain	-
Alfoxil	Fako	Turkey	-
Am-73	Medici	Italy	-
Amocilline	Inpharzam	Belgium	-
Amoclen	Spofa	Czechoslovakia	-
Amodex	Robert and Carriere	France	-
Amo-Flamisan	Mazuelos	Spain	-
Amoksilin	Nobel	Turkey	-
Amoksina	Mustafa Nevzat	Turkey	-

Trade Name	Manufacturer	Country	Year Introduced
Arnolin	Takeda	Japan	-
Amorion	Orion	Finland	-
Amosin	Sanli	Turkey	-
Amox	Lusofarmaco	Spain	-
Amox	Prodes	Spain	-
Amoxamil	Lafi	Brazil	-
Amoxaren	Areu	Spain	-
Arnoxi-Basileos	Basileos	Spain	-
Amoxibiotic	Aristochimica	Italy	-
Amoxicil	Dincel	Turkey	-
Amoxicillin	Toho	Japan	-
Amoxidal	Roemmers	Argentina	-
Amoxidin	Normon	Switz.	-
Amoxi-Gobens	Lagap	Spain	-
Amoxillin	Esseti	Italy	-
Amoximedical	Medical	Spain	-
Amoxipen	Gibipharma	Italy	-
Amoxipenil	Montpellier	Argentina	-
Amoxiroger	Roger	Spain	-
Amoxi-Tabs	Beecham	-	-
Amoxypen	Gruenenthal	W. Germany	-
Amplimox	Ausonia	Italy	-
Amplimox	Iton	Italy	-
Ampy-Penyl	Proto	Switz.	-
Apitart	Isei	Japan	-
Ardine	Antibioticos	Spain	-
Aspenil	Chemil	Italy	-
Augmentin	Beecham	US	-
Ax-1000	Durachemie	W. Germany	-
Axbiot	Galepharma Iberica	Spain	-
Becabil	Alfar	Spain	-
Benzoral	Biosintetica	Brazil	-
Bioxidona	Faes	Spain	-
Bristamox	Bristol	-	-
Cabermox	Caber	Italy	-
Chitacillin	Banyu	Japan	-
Cidanamox	Cidan	Spain	-
Clamox	Roussel-Diamant	Morocco	-
Clamoxyl	Wulfing	W. Germany	-

Trade Name	Manufacturer	Country	Year Introduced
Clarnoxyl	Beecham-Sevigne	France	-
Dacala	Guadalupe	Spain	-
Damoxicil	Elmu	Spain	-
Daxipen	Recofarma	Brazil	-
Delacillin	Sankyo	Japan	-
Demoksil	Deva	Turkey	-
Doksilin	Iltas	Turkey	-
Draximox	Novo	-	-
Efpenix	Toyo Jozo	Japan	-
Eupen	Uriach	Spain	-
Flemoxin	Gist Brocades	-	-
Fullcilina	Sintyal	Argentina	-
Grinsil	Argentia	Argentina	-
Hiconcil	Allard	France	-
Himinomax	Kaken	Japan	-
Hosboral	Hosbon	Spain	-
Ibiamox	IBI	Italy	-
Imacillin	Astra	-	-
Infectomycin	Heyden	W. Germany	-
Isimoxin	ISI	Italy	-
Kapoxi	Kappa	Spain	-
Largopen	Bilim	Turkey	-
Majorpen	Cyanamid	US	-
Megacillin	Mulda	Turkey	-
Metifarma	Novofarma	Spain	-
Morgenxil	Morgens	Spain	-
Moxacin	C.S.L.	Australia	-
Moxal	Roger Bellon	Italy	-
Moxalin	Mead Johnson	US	-
Moxilean	Organon	-	-
Moxipin	Gamir	Spain	-
Moxypen	Teva	Israel	-
Novamoxin	Novopharm	Canada	-
Nuvosyl	Mepha	Switz.	-
Optium	Disprovent	Argentina	-
Ospanox	Biochemie	Austria	-
Pamocil	Lancet	Italy	-
Paradroxil	Bristol	-	-
Pasetocin	Kyowa	Japan	-

Trade Name	Manufacturer	Country	Year Introduced
Penamox	Beecham	-	-
Penimox	Ibsa	Switz.	-
Piramox	Pharmax	Italy	-
Precopen	Fides	Spain	-
Primasin	Eczacibasi	Turkey	-
Raudopen	Alter	Spain	-
Raylina	Robert	Spain	-
Reloxyl	Biologia Marina	Spain	-
Remoxil	Kimya Evi	Turkey	-
Rivoxicillin	Rivopharm	Switz.	-
Robamox	Robins	US	-
Sancixomal	Santos	Spain	-
Sawamezin	Sawai	Japan	-
Sigamopen	Siegfried	Switz.	-
Simplamox	ISF	Italy	-
Sinacilin	Galenika	Yugoslavia	-
Sint edix	Castillon	Spain	-
Sintoplus	Aesculapius	Italy	-
Sumox	Reid-Provident	US	-
Superpeni	Efeyn	Spain	-
Tolodina	Estedi	Spain	-
Triamoxil	Squibb	US	-
Trifamox	Bago	Argentina	-
Trimoksilin	Abdi Ibrahim	Turkey	-
Trimox	Squibb	US	-
Unicillin	Tobishi	Japan	-
Uro-Clamoxyl	Beecham	-	-
Utimox	Parke Davis	-	-
Wassermox	Wassermann	Spain	-
Widecillin	Meiji	Japan	-
Zamocillin	Zambon	Italy	-
Zimox	Farmitalia	Italy	-

Raw Materials

6-Aminopenicillanic acid
Sodium bicarbonate
Ethyl chlorocarbonate
Hydrogen
O,N-Dibenzyloxycarbonyl-p-oxy-di-α-aminophenylacetic acid

Manufacturing Process

Ethyl chlorocarbonate (2.2 ml) was added to an ice cold solution of O,N-

dibenzyloxycarbonyl-p-oxy-dl-α-aminophenylacetic acid (10 grams) and triethylamine (3.85 ml) in dry acetone (193 ml). The mixture was stirred at 0°C for 5 minutes during which triethylamine hydrochloride precipitated. The suspension was cooled to -30°C and stirred vigorously while adding as rapidly as possible an ice cold solution of 6-aminopenicillanic acid (5.85 grams) in 3% aqueous sodium bicarbonate (193 ml), the temperature of the mixture never being allowed to rise above 0°C. The resulting clear solution was stirred for 30 minutes at 0°C, and then for a further 30 minutes, without external cooling, and finally extracted with diethyl ether (3 x 200 ml) only the aqueous phase being retained.

This aqueous solution was brought to pH 2 by the addition of hydrochloric acid and the 6-(O,N-dibenzyloxycarbonyl-p-oxy-dl-α-aminophenylacetamido)penicillanic acid so liberated was extracted into diethyl ether (50 ml and 2 portions of 30 ml). The ether phase was washed with water (3 x 5 ml) and the water washings were discarded.

Finally, the penicillin was converted to the sodium salt by shaking the ether solution with sufficient 3% sodium bicarbonate to give a neutral aqueous phase, separating the latter and evaporating it at low pressure and temperature below 20°C. The product was finally dried over phosphorus pentoxide in vacuo to give sodium 6-(O,N-dibenzyloxycarbonyl-p-oxy-dl-α-aminophenylacetamido)-penicillanate (9.2 grams).

A suspension of palladium on calcium carbonate (36 grams of 5%) in water (150 ml) was shaken in an atmosphere of hydrogen at room temperature and atmospheric pressure for 1 hour. A neutral solution of sodium 6-(O,N-dibenzyloxycarbonyl-p-oxy-dl-α-aminophenylacetamido)penicillanate (9 grams) in water (100 ml) was then added and shaking in hydrogen was resumed for one hour. The suspension was then filtered and the collected catalyst was washed well with water without being allowed to suck dry between washings. The combined filtrate and washings were then brought to pH 6.5 with dilute hydrochloric acid and evaporated to dryness at reduced pressure and temperatures below 20°C. The product was finally dried over phosphorus pentoxide in vacuo to give a solid (5.4 grams) containing 6-(p-hydroxy-dl-α-aminophenylacetamido)penicillanic acid.

References

Merck Index 600
Kleeman and Engel p. 48
PDR pp.658, 673, 705, 993, 1315, 1606, 1769, 1997
OCDS Vol. 1 p. 414
DOT 19 (3) 169 (1983)
I.N. p. 79
REM p. 1193
Nayler, J.H.C. and Smith, H.; US Patent 3,192,198; June 29, 1965

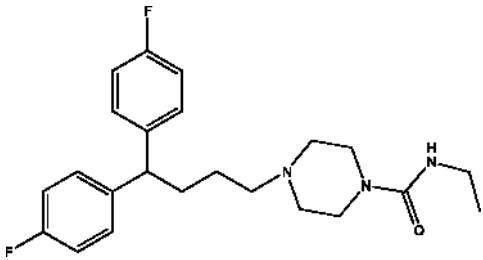
AMPEROZIDE

Therapeutic Function: Anti-aggressive, Antiarrhythmic

Chemical Name: 4-[4,4-Bis(4-fluorophenyl)butyl]-N-ethyl-1-piperazinecarboxamide

Common Name: Amperozide; Hogpax

Structural Formula:



Chemical Abstracts Registry No.: 75558-90-6

Trade Name	Manufacturer	Country	Year Introduced
Amperozide	Ferrosan	-	-
FG 5606	Kabi Pharmacia	-	-

Raw Materials

Sodium bicarbonate
Hydrogen chloride
Potassium carbonate
Phenyl N-ethylcarbamate
N'-Ethyl-1-piperazinecarboxamide
4-Chloro-1,1-(di-p-fluorophenyl)butane
1-[4,4-(Di-p-fluorophenyl)butyl]piperazine

Manufacturing Process

(1). A stirred mixture of 4.7 g (0.03 mole) of N'-ethyl-1-piperazinecarboxamide, 10.1 g (0.036 mole) of 4-chloro-1,1-(di-p-fluorophenyl)butane, 5.0 g of sodium bicarbonate and 10 ml of ethanol was heated at reflux for 60 hours. 50 ml of water was added. The mixture was extracted twice with ether. The combined extracts were dried over sodium sulfate and concentrated. The residue was dissolved in ethanol-ether and the hydrochloride was precipitated with hydrogen chloride in ethanol. The solid was collected by filtration and recrystallised from 2-butanone-isopropanol 4:1 to give 6.4 g of N'-ethyl-4-[4,4-(di-p-fluorophenyl)butyl]-1-piperazinecarboxamide hydrochloride. Melting point 177-178°C.

(2). A stirred mixture of 9.9 g (0.03 mole) of 1-[4,4-(di-p-fluorophenyl)butyl]piperazine, 5,0 g (0,03 mole) of phenyl N-ethylcarbamate, 6,6 g of potassium carbonate and 100 ml of toluene was heated at reflux for 45 minutes. The mixture was filtered and the solvent was removed. The residual oil was dissolved in ethanol-ether and the hydrochloride was precipitated with hydrogen chloride in ethanol. The solid was collected by filtration and recrystallized from 2-butanone-isopropanol 4:1 to give 6.8 g of N'-ethyl-4-[4,4-(di-p-fluorophenyl)butyl]-1-piperazinecarboxamide hydrochloride. Melting point 177-178°C.

References

Bjork Anders K. K., Olsson Knut G., Abramo Aina L., Christensson Erik G.; US Patent No. 4,308,387; December 29, 1981; Assigned to AB Ferrosan (Malmo, SE)

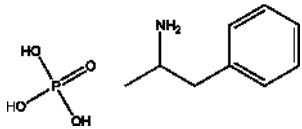
AMPHETAMINE PHOSPHATE

Therapeutic Function: Central stimulant

Chemical Name: 1-Phenyl-2-aminopropane monophosphate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 139-10-6

Trade Name	Manufacturer	Country	Year Introduced
Raphetamlne	Strasenburgh	US	1950
Amphate	Storck	US	-
Leptamine	Bowman	US	-
Monophos	Durst	US	-
Profetamine	Clark and Clark	US	-

Raw Materials

Phenyl nitropropylene
Phosphoric acid

Manufacturing Process

1 mol of phenyl-nitropropylene, $C_6H_5CH=C(CH_3)NO_2$, is dissolved with a solvent prepared by mixing one liter of ethanol with one-half liter of acetic acid and one-half liter of 12 N sulfuric acid. The resultant solution is placed in the cathode compartment of a divided electrolytic cell containing a metallic cathode of mercury, copper, or other metal of similar nature. Current is passed, using a current density of ~0.2 amp/cm^2 of cathode surface. The temperature is kept at about 40°C during the electrolysis which is continued until at least eight Faradays of electricity have been passed.

When the reduction is completed, the 1-phenyl-2-aminopropane may be separated from the solution. A convenient way of doing this is by removing

the ethanol and ethyl acetate present by evaporation and then making the residual solution strongly alkaline by addition of caustic alkali. The basic layer thus formed is separated from the aqueous solution and contains the desired 1-phenyl-2-aminopropane.

135 g (1 mol) of amphetamine (1-phenyl-2-aminopropane) were stirred into 300 cc of acetone in a stainless-steel vessel. To the resultant solution there were slowly added under constant agitation 115.3 g of 85% phosphoric acid (containing 1 mol of H_3PO_4), care being taken to avoid any sudden rise in temperature or local overheating due to the considerable amount of heat that is evolved. During the addition of the phosphoric acid a fine, white, flocculent precipitate appears which becomes more and more dense and abundant, as the quantity of added acid increases.

When the entire quantity of the phosphoric acid has thus been added, agitation of the mixture is continued for about a half-hour or more to insure complete conversion. The precipitate is then allowed to settle, the supernatant liquid is drawn off, and the residue is filtered. The precipitate thus separated may, if desired, be washed with acetone and is then dried by evaporation to constant weight. It forms a fine, white, impalpable powder consisting of pure monobasic amphetamine phosphate.

References

Merck Index 607
I.N. p. 80
Alles, G.A.; US Patent 1,879,003; September 27, 1932 (amphetamine base mfg.)
Goggin, T.C.; US Patent 2,507,468; May 9, 1950; Assigned to Clark and Clark Co. (amphetamine conversion to phosphate)

AMPHOMYCIN CALCIUM

Therapeutic Function: Antibiotic

Chemical Name: Amphomycin calcium

Common Name: Glumamicin

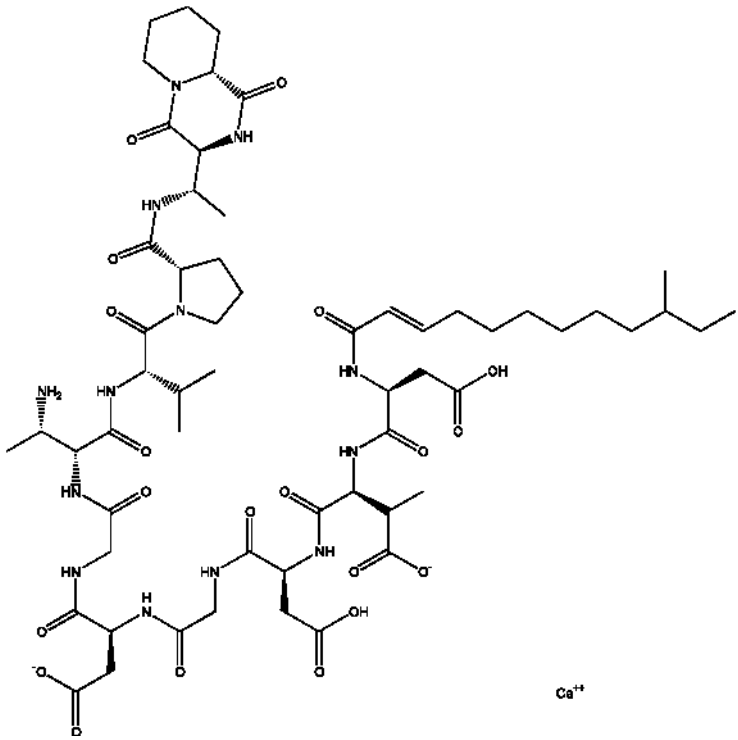
Chemical Abstracts Registry No.: 1402-82-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Amphocortrin CR	Warner Lambert	US	1963

Raw Materials

Amphomycin
Calcium hydroxide

Structural Formula:



Manufacturing Process

The process for producing amphomycin comprises cultivating a strain of Streptomyces canus in an aqueous, nutrient-containing carbohydrate solution under submerged aerobic conditions until substantial antibacterial activity is imparted to the solution and then recovering the so-produced amphomycin from the fermentation broth.

The process of decolorizing solutions of amphomycin then involves treatment with activated charcoal, followed by the steps of (1) extracting the antibiotic into a water-immiscible organic solvent under strongly acid conditions or precipitating the amphomycin from aqueous solution by adjusting the pH to a point within the range of pH 3.0 to 4.0, (2) removing impurities from strongly acid, aqueous solution of amphomycin by extraction of the impurities with methyl isobutyl ketone and amyl acetate, (3) extracting the amphomycin from a strongly acid solution in butanol by the use of water having a pH higher than 4, (4) extracting the amphomycin from solution in water-immiscible organic solvent into water whose pH is greater than 6.0, (5) precipitating amphomycin from solution by formation of insoluble derivatives of the basic function, and (6) precipitating amphomycin from solution by formation of insoluble derivates of the acidic function.

The amphomycin is then converted to the calcium salt with calcium hydroxide.

References

Merck Index 609
Heinemann, B., Cooper, I.R. and Kaplan, M.A.; US Patent 3,126,317; March 24, 1964; Assigned to Bristol-Myers Co.

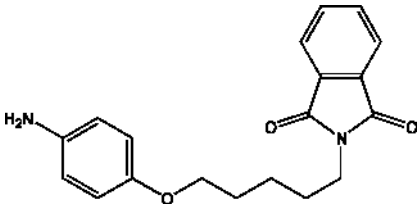
AMPHOTALIDE

Therapeutic Function: Antischistosomal

Chemical Name: 1H-Isoindole-1,3(2H)-dione, 2-(5-(4-aminophenoxy) pentyl)-

Common Name: Amphotalide; Schistomide

Structural Formula:



Chemical Abstracts Registry No.: 1673-06-9

Trade Name	Manufacturer	Country	Year Introduced
Amphotalide	ZYF Pharm Chemical	-	-
Amphotalide	May and Baker Ltd.	-	-

Raw Materials

5-Phthalimidopentyl bromide
Hydrogen
Potassium p-nitrophenoxide
Platinum oxide

Manufacturing Process

A mixture of 5-phthalimidopentyl bromide (Drake and Garman, J.Amer. Chem. Sec, 1949, 71, 2426) (296.0 g) and potassium p-nitrophenoxide (177.0 g) in ethanol (1.5 L) was stirred mechanically, boiled under reflux for 20 h, concentrated to half its volume, cooled and filtered. The product was washed with water, dried and crystallised from acetone, giving 1-p-nitrophenoxy-5-phthalimidopentane, melting point 123°-124°C.

The foregoing 1-p-nitrophenoxy-5-phthalimidopentane (100.0 g) in ethanol (1 L) was reduced by hydrogen over 2% of platinum oxide at 74°C/73 lb. per sq. in. The filtered solution on cooling gave L-p-aminophenoxy-5-

phthalimidopentane, melting point 111°-112° C (recrystallisation from ethanol).

References

Barber H.J. et al.; GB Patent No. 769,706; April 20, 1955; Assigned: May and Baker Limited, British Company, of Dagenham, Essex

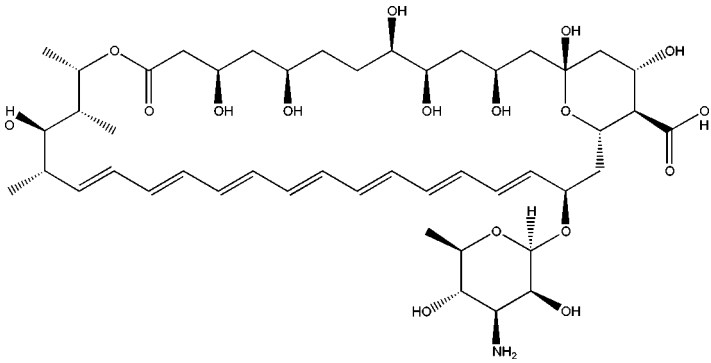
AMPHOTERICIN B

Therapeutic Function: Antifungal

Chemical Name: Amphotericin B

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 1397-89-3

Trade Name	Manufacturer	Country	Year Introduced
Fungizone	Squibb	US	1958
Ampho-Moronal	Heyden	W. Germany	-
Fungizone	Squibb	France	1969
Amphocycline	Squibb	France	-
Amphozone	Squibb	-	-
Fungilin	Squibb	UK	-
Fungilin	Squibb	Italy	-
Fungizone	Squibb-Sankyo	Japan	-
Mysteclin	Heyden	W. Germany	-

Raw Materials

Carbohydrates
Streptomyces nodosus

Manufacturing Process

The process for producing amphotericin comprises cultivating a strain of Streptomyces nodosus in an aqueous nutrient medium comprising an assimilable, fermentable carbohydrate and an assimilable organic nitrogen source, under submerged aerobic conditions, until substantial antifungal activity is imparted to the medium and recovering amphotericin from the medium.

References

Merck Index 611
Kleeman and Engel p. 50
PDR pp. 1743, 1752
DOT 7 (5) 192 (1971)
I.N. p. 81
REM p. 1226
Dutcher, J.D., Gold, W., Pagano, J.F. and Vandeputte, J.; US Patent 2,908.611; October 13, 1959; Assigned to Olin Mathieson Chemical Corporation

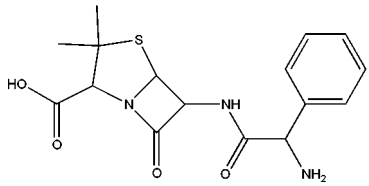
AMPICILLIN

Therapeutic Function: Antibacterial

Chemical Name: 6-[D-Amino-(2-phenylacetamido)]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid

Common Name: Di-α-aminobenzylpenicillin

Structural Formula:



Chemical Abstracts Registry No.: 69-53-4

Trade Name	Manufacturer	Country	Year Introduced
Binotal	Bayer	W. Germany	1962
Penicline	Delagrange	France	1963
Penbritin	Ayerst	US	1963
Penbritin	Beecham	UK	1963
Omnipen	Wyeth	US	1966
Ampisint	Proter	Italy	1969
Acucillin	Fuji	Japan	-

Trade Name	Manufacturer	Country	Year Introduced
Adobacillin	Tobishi	Japan	-
Albipen	Gist Brocades	-	-
Alfasilin	Fako	Turkey	-
Almopen	Gist Brocades	-	-
Alpen	Lederle	US	-
Amblosen	Hoechst	W. Germany	-
Amcill	Parke Davis	US	-
Amfipen	Gist Brocades	UK	-
Amfipen	Schering	W. Germany	-
Amipenix	Toyo Jozo	Japan	-
Ampen	Medosan	Italy	-
Ampen	ICN	Canada	-
Ampensaar	Chephasaar	W. Germany	-
Ampibeta	Violani-Farmavigor	Italy	-
Ampibiotic	Ottolenghi	Italy	-
Ampicil	Ausonia	Italy	-
Ampicillina Pharmax	Pharmax	Italy	-
Ampicillina Pierrel	Pierrel	Italy	-
Ampicina	Sigma Tau	Italy	-
Ampicyn	Protea	Australia	-
Ampifen	Intersint	Italy	-
Ampikel	Dreikehl	Spain	-
Ampilan	Ibern	Italy	-
Ampiland	Landerlan	Spain	-
Ampilisa	Lisapharma	Italy	-
Ampilux	Tubi Lux Pharma	Italy	-
Ampimed	Aristochimica	Italy	-
Ampinebiot	Bertran Hathor	Spain	-
Ampinova	Cheminova Espanola	Spain	-
Ampinoxi	Therapia	Spain	-
Ampiopen	Ibern	Italy	-
Ampi-Plena Simple	Pradel	Spain	-
Ampisil	Dif-Dogu	Turkey	-
Ampisina	Mustafa Nevzat	Turkey	-
Ampi-Tablinen	Sanorania	W. Germany	-
Ampitex	Neopharmed	Italy	-
Ampivax	Ripari-Gero	Italy	-
Ampixyl	Pharma-Plus	Switz.	-
Amplenil	Orma	Italy	-

Trade Name	Manufacturer	Country	Year Introduced
Amplibios	Panther-Osfa	Italy	-
Amplicid	Cifa	Italy	-
Amplipen	Labif	Italy	-
Amplipenyl	ISF	Italy	-
Ampliscocil	I.C.I.	Italy	-
Amplisom	Isom	Italy	-
Amplital	Farmitalia	Italy	-
Amplizer	O.F.F.	Italy	-
Anhypen	Gist Brocades	-	-
Anidropen	Wyeth	Italy	-
Anticyl	San Carlo	Italy	-
A-Pen	Orion	Finland	-
Argocillina	Beta	Italy	-
Austrapen	CSI	Australia	-
Benusel	ICN	-	-
Bio-Ampi	Donatello	Italy	-
Biocellina	Magis	Italy	-
Bionacillin	Takata	Japan	-
Bonapicillin	Taiyo	Japan	-
Britapen Oral	Federico Bonet	Spain	-
Britcin	DDSA	UK	-
Bropicilina	Byk Gulden	-	-
Cilleral	Bristol Banyu	Japan	-
Citicil	C.T.	Italy	-
Combipenix	Toyo Jozo	Japan	-
Copharcilin	Cophar	Switz.	-
Deripen	Schering	W. Germany	-
Doktacillin	Astra	-	-
Domicillin	Dainippon	Japan	-
Drisilin	Drifen	Turkey	-
Espectrosira	Clariana	Spain	-
Eurocillin	Borromeo	Italy	-
Farmampil	Gazzini	Italy	-
Fidesbiotic	Fides	Spain	-
Fortapen	Continental Pharma	Belgium	-
Geycillina	Geymonat	Italy	-
Gramcillina	Caber	Italy	-
Grampenil	Argentia	Argentina	-
Guicitrina	Perga	Spain	-
Hostes Pedriatico	Lando	Argentina	-

Trade Name	Manufacturer	Country	Year Introduced
Ikapen	Ikapharm	Israel	-
Isocillin	Kanto	Japan	-
Iwacillin	Iwaki	Japan	-
Lampocillina Orale	Sidus	Italy	-
Lifeampil	Lifepharma	Spain	-
Marisilan	Wakamoto	Japan	-
Makrosilin	Atabay	Turkey	-
Maxicilina	Antibioticos	Spain	-
Napacil	Montefarmaco	Italy	-
NC-Cillin	Nippon Chemiphar	Japan	-
Negopen	Deva	Turkey	-
Nuvapen	Cepa	Spain	-
Orocilin	Isa	Brazil	-
Overcillina	Lepetit	Italy	-
Overcillina	Archifar	Italy	-
Pen Ampil	Nuovo. Const. Sanit. Naz.	Italy	-
Penbrock	Beecham	-	-
Penibrin	Teva	Israel	-
Penimic	SS Pharmaceutical	Japan	-
Peninovel	Larma	Spain	-
Penisint B.G.	Boniscontro	Italy	-
Penoral	Nobel	Turkey	-
Penorsin	Wassermann	Spain	-
Pentrex	Banyu	Japan	-
Pentrexyl	Galenika	Yugoslavia	-
Pharcillin	Toyo Pharm.	Japan	-
Platocillina	Crosara	Italy	-
Plumericin	Torlan	Spain	-
Policilin	Bristol	-	-
Polycillin	Bristol	US	-
Principen	Squibb	US	-
Quimetam	Ouimicos Unidos	Spain	-
Radiocillina	Radiumpharma	Italy	-
Recenacillin	Maruko	Japan	-
Resan	Alacan	Spain	-
Rivocillin	Rivopharm	Switz.	-
Saicil	Libra	Italy	-
Sentapent	Kimya Evi	Turkey	-
Sernabiotic	Libra	Italy	-
Sesquicillina	Ita	Italy	-
Sintopenyl	Aesculapius	Italy	-
SK-Ampicillin	SK and F	US	-
Togram	Morgens	Spain	-

Trade Name	Manufacturer	Country	Year Introduced
Tokiocillin	Isei	Japan	-
Totacillin	Beecham	Japan	-
Totaclox	Beecham	Japan	-
Totalciclina	Benvegna	Italy	-
Totapen	Bristol	France	-
Trafarbiot	Novopharm	Spain	-
Ultrabion	Lifasa	Spain	-
Vastacyn	Ankerfarm	Italy	-
Vexampil	Ifi	Italy	-
Vicclilin	Meiji	Japan	-

Raw Materials

α-Aminophenylacetic acid
6-Aminopenicillanic acid
Hydrogen
Ethyl chlorocarbonate
Benzyl chlorocarbonate

Manufacturing Process

α-Carbobenzyloxyaminophenylacetic acid (0.1 mol), which is obtained by the reaction of equivalent quantities of α-aminophenylacetic acid and benzyl chlorocarbonate in aqueous sodium hydroxide, dissolved in dry acetone is stirred and cooled to approximately -5°C. To this there is added dropwise with continued cooling and stirring a solution of ethyl chlorocarbonate (0.1 mol). After approximately 10 minutes, the acylating mixture is cooled to about -5°C and then is slowly added to a stirred ice-cold mixture of 6-aminopenicillanic acid (0.1 mol), 3% sodium bicarbonate solution (0.1 mol) and acetone. This reaction mixture is allowed to attain room temperature, stirred for an additional thirty minutes at this temperature and then is extracted with ether.

The extracted aqueous solution is covered with butanol and the pH adjusted to 2 by the addition of HCl. The acidified aqueous phase is extracted with butanol, the pH of the aqueous phase being adjusted to pH 2 each time. The combined butanol solutions which contain the free acid, α-carbobenzyloxyaminobenzylpenicillin, are washed with water, and are then shaken with water to which sufficient 3% sodium bicarbonate has been added to bring the aqueous phase to pH 7. The process of washing and shaking is repeated with fresh water and bicarbonate solution. The combined aqueous solutions are washed with ether and then are evaporated under reduced pressure and low temperature. The product, the sodium salt of α-carbobenzyloxyaminobenzylpenicillin, is obtained as a yellow solid in a yield of 65%.

A suspension of palladium on barium carbonate (3.7 grams of 30%) in water (20 ml) is shaken in an atmosphere of hydrogen at room temperature. The catalyst is then filtered and washed well with water, care being taken that it does not become dry. A solution of the sodium salt of α-carbobenzyloxyaminobenzylpenicillin (4 grams) in water (20 ml) is added to the pretreated catalyst and the suspension is shaken in an atmosphere of hydrogen at room temperature and pressure for one hour. The catalyst is then

filtered off, washed well with water, and the combined filtrate and washings adjusted to pH 7 with hydrochloric acid. The resulting solution is evaporated in vacuum at a temperature below 20°C to give α-aminobenzylpenicillin (2.4 grams, 74% yield), which is assayed at approximately 48% pure by the manometric method.

References

Merck Index 612
Kleeman and Engel p. 50
PDR pp.673, 703, 1314, 1722, 1964
OCDS Vol. 1 p. 413; Vol. 2 p. 437
I.N. p. 81
REM p. 1194
Doyle, F.P., Nayler, J.H.C., and Smith, H.; US Patent 2,985,648; May 23, 1961
Kaufmann, W. and Bauer, K.; US Patent 3,079,307; Feb. 26, 1963; Assigned to Farben-fabriken Bayer AG, Germany
Johnson, D.A. and Wolfe, S.; US Patent 3,140,282; July 7, 1964; Assigned to Bristol-Myers Company
Grant, N.H. and Alburn, H.E.; US Patent 3,144,445; August 11, 1964; Assigned to American Home Products Corporation

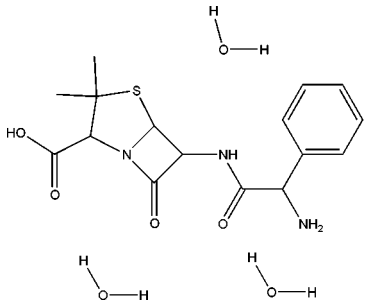
AMPICILLIN TRIHYDRATE

Therapeutic Function: Antibacterial

Chemical Name: 6-[D-Amino-(2-phenylacetamido)]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 7177-48-2

Trade Name	Manufacturer	Country	Year Introduced
Polycillin	Bristol	US	1963
Principen	Squibb	US	1967

Trade Name	Manufacturer	Country	Year Introduced
Amcill	Parke Davis	US	1968
Alpen	Lederle	US	1969
Totacillin	Beecham	US	1970
Pensyn	Upjohn	US	1972
Ro-Ampen	Rowell	US	1972
Pen A	Pfizer	US	1972
Trimox	Squibb	US	1978
AB-PC	Tojo Jozo	Japan	-
Acillin	ICN	-	-
Amblosin	Hoechst	-	-
Amcap	Circle	US	-
Amperil	Geneva	US	-
Ampexin	Therapex	Canada	-
Ampicsl	Uva	France	-
Ampichelle	Rachelle	US	-
Ampicil	Jeba	Spain	-
Ampiciman	Liberman	Spain	-
Ampi-Co	Coastal	US	-
Ampifar	Benedetti	Italy	-
Ampikel	Dreikehl	Spain	-
Ampilag	Lagap	Switz.	-
Ampileta	Lagap	Switz.	-
Ampi-Oral	Biologia Marina	Spain	-
Ampiorus	Horus	Spain	-
Ampiscel	Rachelle	US	-
Ampixyl	Pharma-Plus	Switz.	-
Ampi-Zoja	Zoja	Italy	-
Amplin	Winston	US	-
Arcocillin	ICN	-	-
Benusel	ICN	-	-
Binotal	Bayer	-	-
Cetampin	CTA Pharma	Switz.	-
Cetampin	Scarium	Switz.	-
Cimexillin	Cimex	Switz.	-
Cymbl	Dolorgiet	W. Germany	-
Citicil	C.T.	Italy	-
D-Amp	Dunhall	US	-
D-Cillin	Dunhall	US	-
Delcillin	Marlop	US	-
Divercillin	Ascher	US	-
Dumopen	Dumex	Denmark	-
Dur Ampicillin	Durachemie	W. Germany	-

Trade Name	Manufacturer	Country	Year Introduced
Espimin-Cilin	Spyfarma	Spain	-
Fuerpen	Hermes	Spain	-
Gobemicina Simple	Normon	Spain	-
Helvecillin	Helvepharm	Switz.	-
Lifeampil	Lifepharma	Spain	-
Morepen	Morejon	Spain	-
Novoexpectro	Aldon	Spain	-
Penbristol	Bristol-Myers	Austria	-
Penimaster	Liade	Spain	-
Peninovel	Larma	Spain	-
Pentraxyl	Bristol	-	-
Pentrexyl Oral	Antibioticos	Spain	-
Pentricine	Ibsa	Switz.	-
Poenbiotico	Poen	Argentina	-
Prestacilina	Pental	Spain	-
Q I Damp	Mallinckrodt Inc.	US	-
Rosampline	Rosa-Phytopharma	France	-
Servicillin	Servipharm	Switz.	-
Standacillin	Biochemie	Austria	-
Sumipanto Oral	Asla	Spain	-
Texcillin	First Texas	US	-
Trafarbior	Novopharm	Spain	-
Trafacilina	Bago	Argentina	-
Vampen	Vangard	US	-
Vidopen	Berk	UK	-

Raw Materials

Ampicillin beta-naphthalene sulfonate
Secondary amines

Manufacturing Process

The known methods for the preparation of D-(-)-α-aminobenzylpenicillin by the acylation of 6-aminopenicillanic acid result in the preparation of aqueous mixtures which contain, in addition to the desired penicillin, unreacted 6-aminopenicillanic acid, hydrolyzed acylating agent, and products of side reactions such as the products of the acylating agent reacted with itself and/or with the desired penicillin, as well as other impurities.

The D-(-)-α-aminobenzylpenicitlin may then be recovered from the aqueous reaction mixture by concentration to small volume and recovering the product by filtration. However, due to the fact that anhydrous D-(-)-α-aminobenzylpenicillinis soluble in water to the extent of about 20-25 mg/ml at 20°-25°C, it is very difficult to recover the product in high yields.

Furthermore, the recovered D-(-)-α-aminobenzylpenicillin may be obtained in the form of a monohydrate. The monohydrates (as well as the dihydrates) of D-(-)-α-aminobenzylpenicillin possess poor biological stability.

The trihydrate which is obtained in high yields, is relatively insoluble in water, possesses high biological stability and can be obtained by contacting, at a temperature not above 60°C, an acid addition salt of D-(-)-α-aminobenzylpenicillin with an amine in a water immiscible solvent containing at least 3 mols of water per mol of such penicillin.

The following is an example of the conduct of such a process. To a vigorously agitated mixture of 100 ml of methyl isobutyl ketone there are added at 25° to 30°C 15 ml of water and 10 ml of a mixture of secondary amines.

To this mixture there is then added slowly over a period of 30 minutes 10 grams of D-(-)-α-aminobenzylpenicillin α-naphthalenesulfonate. The mixture is agitated for 3 hours at 25-30°C. The product, D-(-)-α-aminobenzylpenicillin trihydrate precipitates and is collected by filtration. The filter cake of the product is washed several times with methyl isobutyl ketone and is dried at 40°C. The product is obtained in about a 90% yield and has a potency of 865 mcg/mg. It is determined by Karl Fischer analysis to have a moisture content of 13.4% by weight.

References

Merck Index 612
Kleeman and Engel p. 81
PDR pp. 993, 1606, 1758
I.N. p. 50
Johnson, D.A. and Hardcastle, G.A., Jr.; US Patent 3,157,640; November 17, 1964; Assigned to Bristol-Myers Company

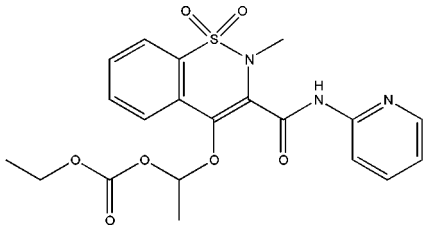
AMPIROXICAM

Therapeutic Function: Antiinflammatory

Chemical Name: Carbonic acid ethyl 1-[[2-methyl-3-[(2-pyridinyl) aminocarbonyl]-2H-1,2-benzothiazin-4-yl]oxy]ethyl ester, S,S-dioxide

Common Name: Ampiroxicam

Structural Formula:



Chemical Abstracts Registry No.: 99464-64-9

Trade Name	Manufacturer	Country	Year Introduced
Ampiroxicam	NANJING PHARMA	-	-

Raw Materials

Piroxicam	α-Chloroethyl ethyl carbonate
Potassium carbonate	Sodium iodide

Manufacturing Process

To a round bottomed flask equipped with a reflux condenser and stirring bar were added 2-methyl-N-(2-pyridyl)-4-hydroxy-2H-1,2-benzodiazine-3-carboxamide 1,1-dioxide (piroxicam, 10.0 g, 30.2 mmol), potassium carbonate (8.35 g, 60.4 mmol), α-chloroethyl ethyl carbonate (12.35 mL, 13.81 g, 90.6 mmol) and acetone (350 mL). The heterogenous reaction mixture was heated to reflux under a nitrogen atmosphere. After 19 hours, anhydrous sodium iodide (22.6 g, 150.7 mmol) was added and reflux continued for an additional 5 hours. The acetone was removed in vacuum leaving a brown residue which was treated with water (250 mL) and methylene chloride (250 mL). The organic layer was separated and the aqueous layer extracted with additional methylene chloride (250 mL). The combined organic extracts were washed with water (250 mL), brine (250 mL), dried (Na_2SO_4) and concentrated in vacuum to a brown oil. Column chromatography on silica gel (1:9 ethyl acetate:methylene chloride) afforded a pale yellow foam (10.67 g, 79.0%). The 4-[1-(ethoxycarbonyloxy)ethoxy]-2-methyl-N-(2-pyridyl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide was recrystallized from toluene to give 9.50 g of pure white crystals; melting point 159-161°C.

References

European Patent No.147,177
Marfat A.; US Patent No. 4,551,452; Nov. 5, 1985; Assigned to Pfizer Inc. (New York, NY)

AMPRENAVIR

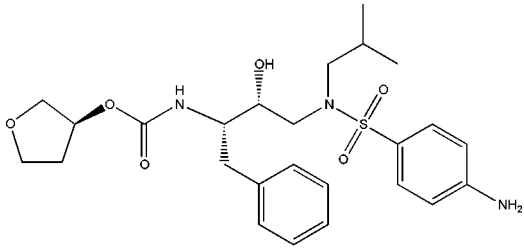
Therapeutic Function: Antiviral

Chemical Name: Carbamic acid, ((1S,2R)-3-(((4-aminophenyl)sulfonyl)(2-methylpropyl)amino)-2-hydroxy-1-(phenylmethyl)propyl)-, (3S)-tetrahydro-3-furanyl ester

Common Name: Amprenavir

Chemical Abstracts Registry No.: 161814-49-9

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Agenerase	GlaxoSmithKline	UK	-
Amprenavir	Vertex Pharmaceuticals Inc	-	-
Amprenavir	GlaxoSmithKline	UK	-
KVX-478	Glaxo Wellcome	-	-
Prozei	Kissei Pharmaceutical Co., Ltd.	-	-
VX-478	Glaxo Wellcome	-	-
141W94	Glaxo Wellcome	-	-

Raw Materials

Isobutylamine
(1-Oxiranyl-2-phenylethyl)-carbamic acid t-butyl ester
Benzyl chloroformate
Diisopropylethylamine
(S)-(+)-3-Hydroxytetrahydrofuran
Phosgene
p-Nitrobenzenesulfonyl chloride

Manufacturing Process

(1-Oxiranyl-2-phenylethyl)-carbamic acid t-butyl ester may be synthesized from available starting materials (see B. E. Evans et al., J. Org. Chem., 50, p.4615 (1985)). The amprenavir may be preparated with the next steps.

1. (1-Benzyl-3-isobutylaminopropyl)-carbamic acid t-butylester. A solution of 4.1 g of epoxide (1-oxiranyl-2-phenylethyl)-carbamic acid t-butyl ester in 30 ml of ethanol was treated with 22.4 ml of isobutylamine and heated under reflux for 1 h. The mixture was concentrated to yield the title compound as a white solid which was used without subsequent purification.

2. To a solution of the above compound (2.5 g, 7.43 mmol) in CH_2Cl_2 (50 ml) was added triethylamine (2.1 ml, 14.9 mmol) followed by addition of benzyl chloroformate (1.2 ml, 8.1 mmol). The mixture was allowed to stir at ambient temperature for 6 h. The solution was diluted with 1 L of CH_2Cl_2 and washed with water. The organics were dried over anhydrous $MgSO_4$, concentrated

under reduced pressure, then purified via silica gel chromatography. Gradient solvent system: CH_2Cl_2 followed by 3:97 methanol/CH_2Cl_2. (3-t-Butoxycabonylamino-4-phenylbutyl)-isobutylcarbamic acid benzyl ester (2.97 g) was obtained as a colorless oil. TLC: R_f= 0.14, 3:97 methanol/CH_2Cl_2.

3. BOC - protecting group was removed as followed: to a solution of 1.5 g (3.187 mmol) of the above compound of in ethyl acetate (25 ml) at - 20°C was bubbled anhydrous HCl gas for 10 min. The ice bath was removed and after an additional 15 min the reaction mixture was sparged with nitrogen, then concentrated in vacuo to provide 1.29 g of deprotected product as a white solid which was used directly for the next reaction TLC: R_f= 0.14, 10% methanol/CH_2Cl_2.

4. Isobutyl[4-phenyl-(S)-3-tetrahydrofuran-3-yl-oxycarbonylamino)-butyl]-carbamic acid benzyl ester. To a solution of 1.077 g of the above resultant crude compound (2.647 mmol) in acetonitrile (10 ml) was added sequentially at ambient temperature under an atmosphere of nitrogen, 1.61 ml (9.263 mmol) of diisopropylethylamine and 910 mg (3.97 mmol) of the N-succinimidyl-(S)-3-tetrahydrocfuryl carbonate. The last one was prepared from phosgene and (S)-(+)-3-hydroxytetrahydrofuran by usual procedure. After stirring for 3 h, an additional 223 mg (0.973 mmol) of the N-succinimidyl-(S)-3-tetrahydrocfuryl carbonate was added. The mixture was stirred for 16 h and then concentrated in vacuo. The residue was taken up in ethyl acetate and washed with water, 0.5 N HCl, saturated sodium bicarbonate, saturated brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by low pressure silica gel column chromatography using a gradient 10% to 25% ethyl acetate in CH_2Cl_2 eluent to yield 1.025 g of the title product as a white solid. TLC: R_f= 0.10, 10% ethyl acetate/CH_2Cl_2.

5. A solution of 872 mg (1.799 mmol) isobutyl[4-phenyl-(S)-3-tetrahydrofuran-3-yl-oxycarbonylamino)-butyl]-carbamic acid benzyl ester in (10 ml) of ethyl alcohol was added, at ambient temperature under a nitrogen atmosphere, to a slurry of 87 mg (10% by weight) of 10% palladium on carbon in (5 ml) ethyl alcohol and hydrogenated for 16 h under a slight positive pressure of hydrogen. The mixture was filtered and concentrated in vacuo to yield 553.2 mg of the carbamic acid as a colorless glass which was used directly for ensuing reaction. TLC: R_f = 0.46, 10% methanol/CH_2Cl_2.

6. A solution of 102 mg of the resultant compound of a step 5 in 4:1 CH_2Cl_2/saturated aqueous $NaHCO_3$ was treated sequentially, at ambient temperature under an atmosphere of nitrogen, with 65 mg of p-nitrobenzenesulfonyl chloride and 51 mg of sodium bicarbonate. The mixture was stirred for 14 h, diluted with CH_2Cl_2, washed with saturated NaCl, then dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by low pressure silica gel chromatography using 20% diethyl ether/CH_2Cl_2 as eluent to provide 124 mg of the 1-benzyl-3-[isobutyl-(4-nitrobenzenesylfonyl)-amino]-propylcarbamic acid tetrahydrofuran-3(S)-yl] ester as a white solid. TLC: R_f = 0.36, 20% diethyl ether/CH_2Cl_2, HPLC: R_t = 15.15 min. (^{1}H)-NMR ($CDCl_3$) consist with structure.

7. A solution of 124 mg of the resultant compound of the step 6 in ethyl acetate was treated, at ambient temperature, with 13 mg of 10% palladium

on carbon. The mixture was stirred for 14 h under an atmosphere of hydrogen, filtered through a pad of celite filter agent, and concentrated in vacuo. The residue was subjected to preparative HPLC to yield 82 mg of the ((1S,2R)-3-(((4-aminophenyl)sulfonyl)(2-methylpropyl)amino)-2-hydroxy-1-(phenylmethyl)propyl)-, (3S)-tetrahydro-3-furanyl carbamic ester a white solid. TLC: R_f= 0.10, 20% ether/CH_2Cl_2, HPLC: R_t= 13.16 min. (^{1}H)-NMR ($CDCl_3$) consistent with structure.

References

Tung et al.; US Patent No. 5,691,372; Nov. 25, 1997; Assigned Vertex Pharmaceuticals Incorporated
Tung et al.; WO 94/05639, March 1994

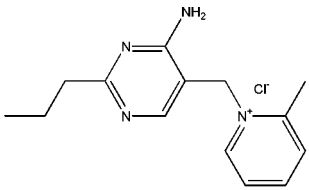
AMPROLIUM CHLORIDE

Therapeutic Function: Coccidiostatic

Chemical Name: Pyridinium, 1-((4-amino-2-propyl-5-pyrimidinyl)methyl)-2-methyl-, chloride

Common Name: Amprocidum; Amprolium chloride; Mepyrium

Structural Formula:



Chemical Abstracts Registry No.: 121-25-5

Trade Name	Manufacturer	Country	Year Introduced
Neoprol	SIMB	-	-

Raw Materials

4-Toluenesulfonyl chloride
2-n-Propyl-4-amino-5-hydroxy-methyl pyrimidine
2-Methylpyridine
Hydrochloric acid

Manufacturing Process

1.9 grams of p-toluene sulfonyl chloride was added gradually with shaking to a cooled (0-5°C) solution of 1.67 grams of 2-n-propyl-4-amino-5-hydroxy-methyl pyrimidine in 10 ml of 2-methylpyridine. The reaction mixture, after

standing three hours in an ice bath, and 15 hours at room temperature, was evaporated to dryness in vacuo. The residue was dissolved in 20 ml of water, acidified with hydrochloric acid and poured over a column of Amberlite IRA-400 ion exchange resin on the chloride cycle. The eluate was evaporated to dryness to give a residue of 1-(2-n-propyl-4-amino-5-pyrimidylmethyl)-2-methyl pyridinium chloride hydrochloride. On recrystallization from a methanol-ethanol mixture, the quaternary had melting point 246°C (dec.).

References

Rogers E.F., Sarett L.H.; US Patent No. 3,020,277; Feb. 6, 1962; Assigned to Merck and Co, Inc., Rahway, N.J.., a corporation of New Jersey

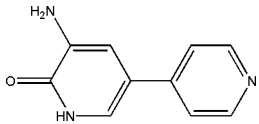
AMRINONE

Therapeutic Function: Cardiotonic

Chemical Name: 3-Amino-5-(4-pyridinyl)-2(1H)-pyridinone

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 60719-84-8

Trade Name	Manufacturer	Country	Year Introduced
Inocor	Sterling Winthrop	Philippines	1982
Inocor	Sterling Winthrop	Mexico	1983

Raw Materials

3-Nitro-5-(4-pyridinyl)-2(1H)-pyridinone
Hydrogen

Manufacturing Process

A mixture containing 10g of 3-nitro-5-(4-pyridinyl)-2(1H)-pyridinone, 200 ml of dimethylformamide and 1.5 g of 10% palladium-on-charcoal was hydrogenated under pressure (50 psi) at room temperature until the uptake of hydrogen ceased (about 30 minutes). The reaction mixture was filtered through infusorial earth and the filtrate was heated in vacuum to remove the solvent. The residual material was crystallized from dimethylformamide, washed successively with ethanol and ether, and dried in a vacuum oven at 80°C for 8 hours to yield 6 g of 3-amino-5-(4-pyridinyl)-2(1H)-pyridinone, melting point 294° to 297°C with decomposition.

References

Merck Index 616
DFU 4 (4) 245 (1979)
PDR p. 1909
OCDS Vol. 3 p. 147
DOT 18 (10) 547 (1982) and 19 (10) 581 (1983)
I.N. p.85
Lesher, G.Y. and Opalka, C.J.; US Patent 4,004,012; January 18, 1977; Assigned to Sterling Drug Inc.
Lesher, G.Y. and Opalka, C.J.; US Patent 4,107,315; August 15, 1978; Assigned to Sterling Drug Inc.

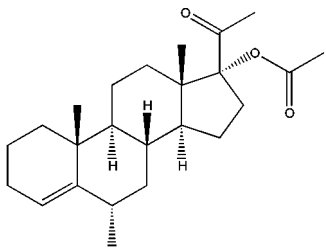
ANAGESTONE ACETATE

Therapeutic Function: Progestin

Chemical Name: Pregn-4-en-20-one, 17-hydroxy-6α-methyl-, acetate

Common Name: Anagestone acetate; Anapregnone

Structural Formula:



Chemical Abstracts Registry No.: 3137-73-3

Trade Name	Manufacturer	Country	Year Introduced
ORF 1658	ZYF Pharm Chemical	-	-
Anagestone acetate	Ortho Pharm	-	-

Raw Materials

Ethanedithiol
Nickel
Acetic acid
Acetic anhydride
6α-Methyl-4-pregnen-17α-ol-3,20-dione
Pyridine chlorhydrate
4-Toluenesulfonic acid

Manufacturing Process

To solution of 6α-methyl-4-pregnen-17α-ol-3,20-dione (1.0 g) in ethane-

dithiol (1 ml) and methylene chloride (2 ml) pyridine chlorhydrate (1 g) was added and mixed 3 min at room temperature. Then to reaction mixture methanol (30 ml) was added and cooled in ice bath during of 2 min. Precipitate was filtered and washed with cool methanol. 6α-Methyl-4-pregnen-17α-ol-20-one-3-thioacetal was obtained (0.9 g), melting point 186°-188°C (recrystalisation from methanol-dichlormethane).

To the solution of 6α-methyl-4-pregnen-17α-ol-20-one-3-thioacetal (2 g) in 95% ethanol (200 ml) Ni (Renney) (50 g) was added and mixed at heating. Then reaction mixture was cooled to room temperature. The mixture was filtered, and filtrate was evaporated, obtaining residue was crystallisated from methanol with dichloromethane and in the result 6α-methyl-4-pregnen-17α-ol-20-one (0.95 g) was produced, melting point 190°-193°C.

To the solution of 6α-methyl-4-pregnen-17α-ol-20-one (1.5 g) in acetic acid (75 ml) and acetic anhydride (15 ml) p-toluenesulfonic acid was added and the reaction mixture allayed to stand at room temperature any time. Then crystals were recrystallised from methanol with dichlormethane. Acetate 6α-methyl-4-pregnen-17α-ol-20-one (1.3 g) was obtained, melting point 173°-175°C.

References

BE Patent No. 624,370; Oct. 31, 1962; Assigned: Ortho Pharmaceutical Corporation

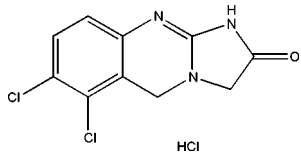
ANAGRELIDE HYDROCHLORIDE

Therapeutic Function: Platelet aggregation inhibitor

Chemical Name: 6,7-Dichloro-1,5-dihydroimidazo[2,1-b]quinazolin-2(3H)-one hydrochloride

Common Name: Anagrelide hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 58579-51-4; 68475-42-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Agrylin	Shire Pharmaceuticals	-	-
Agrelin	Pharma Internacional	-	-
Anagrelide Hydrochloride	Cipla Limited	India	-

Raw Materials

6-Chloro-2-nitrobenzylchloride
Cyanogen bromide
Ethylglycine hydrochloride
Ferric chloride anhydrous
Chlorine
Bromine

Manufacturing Process

6,7-Dicloro-1,2,3,5-tetrahydroimidazo[2,1-b]quinazolin-2-one was produced from 6-chloro-7-bromo-1,2,3,5-tetrahydroimidazo[2,1-b]quinozolin-2-one by substitution the bromine an equimolar quantity chlorine.

6-Chloro-7-bromo-1,2,3,5-tetrahydroimidazo[2,1-b]quinazolin-2-one was produced next way: to a solution of 1.30 g (8 mmole) of anhydrous ferric chloride in 30 ml of nitromethane was added 1.30 g (5 mmole) of solid 6-chloro-1,2,3,5-tetrahydroimidazo[2,1-b]quinazolin-2-one and 0.80 g (5 mmole) of bromine. The system was stoppered, warmed to 50°C in an oil bath overnight, cooled to room temperature and the solvent removed in vacuo. The resulting solid was suspended in water (50 ml), the mixture was made basic (pH=10) with sodium bicarbonate and stirred at home temperature for 20 min. The solid was filtered under suction, washed with water, then isopropyl alcohol and dried yielding 1.19 g of 6-chloro-7-bromo-1,2,3,5-tetrahydroimidazo[2,1-b]quinazolin-2-one (78% yield). Purification was effected by formation of the hydrochloride salt (mp 275°C) from acetonitrile.

6-Chloro-1,2,3,5,-tetrahydroimidazo[2,1-b]quinazolin-2-one was produced from 6-chloro-2-nitrobenzylchloride, ethylglycine hydrochloride and cyanogen bromide in 3 steps.

References

Beveriung Jr. et al.; US Patent No. 3,932,407; Jan. 13, 1976; Assigned: Bristol-Myers Company (New York, NY)

ANASTRAZOLE

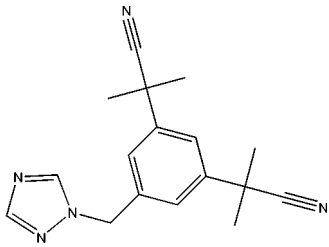
Therapeutic Function: Antitumor

Chemical Name: 1,3-Benzenediacetonitrile, $\alpha,\alpha,\alpha',\alpha'$-tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl)-

Common Name: Anastrozole

Chemical Abstracts Registry No.: 120511-73-1

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Altraz	Alkem Laboratories Ltd.	India	-
Anastrozole	AstraZeneca	UK	-
Arimidex	AstraZeneca	UK	-

Raw Materials

N-Bromosuccinimide
1,2,4-Triazole sodium salt
Tetrabutylammonium bromide
Iodomethane
Benzoyl peroxide
3,5-Bis(bromomethyl)toluene
Potassium cyanide
Sodium hydride

Manufacturing Process

A mixture of 2,2-(5-methyl-1,3-phenylene)di(2-methylpropionitrile) (2.26 g), N-bromosuccinimide (1.78 g), benzoylperoxide (0.05 g) and carbon tetrachloride (50 ml) was refluxed for 2 hours, cooled and filtered, and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in dimethylformamide (20 ml), sodium triazole (1.8 g) was added, and the mixture was stirred at room temperature for 18 h. Water (100 ml) was added, and the mixture was extracted twice with ethyl acetate, dried and evaporated to dryness and the residue was purified by flash column chromatography, eluting with ethyl acetate to give 2,2-[5-(1H-1,2,4-triazol-1-ylmethyl)-1,3-phenylene]di(2-methylpropionitrile), mp 81-82°C after crystallization from ethyl acetate/cyclohexane.

The 5-methyl-1,3-phenylene compound used as starting material in above process may be prepared as follows. The mixture of 3,5-bis(bromomethyl)toluene (30 g), tetrabutyl-ammonium bromide (1 g), KCN (17.6 g), dichloromethane (100 ml) and water (30 ml) was stirred vigorously and refluxed for 3 h. The mixture was cooled, diluted with water (100 ml) and extracted three times with ethyl acetate, dried and evaporated to dryness, the residue was purified by flash chromatography, eluting with petroleum ether/ethyl acetate (3:1) to give 2,2-(5-methyl-1,3-phenylene)diacetonitrile, mp 73-74°C after crystallization from carbon tetrachloride. A mixture of this diacetonitrile (11.5 g), iodomethane (42 g) and dimethylformamide (150 ml) was cooled in an ice and stirred while sodium hydride (50% dispersion in mineral oil, 15 g) was added slowly, over 1 hour, then the mixture was allowed to warm to room temperature, stirred for 2 h, 500 ml of water was added, and the mixture was extracted twice with ethyl acetate, the extracts were dried and evaporated to dryness and the residue was crystallized from carbon tetrachloride to give the required 5-methyl-1,3-phenylene starting

material, mp 126-127°C.

References

Edwards P.N. et al.; US Patent No. RE36,617 Mar. 14, 2000; Assigned: Zeneca Limited (London, GB)
Thomson and Siiteri, J. Biol. Chem., 249, 5364 (1974)

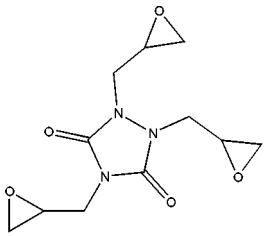
ANAXIRONE

Therapeutic Function: Antineoplastic

Chemical Name: 1,2,4-Triazolidine-3,5-dione, 1,2,4-tris(oxiranylmethyl)-

Common Name: Anaxirone; Triglycidylurazol

Structural Formula:



Chemical Abstracts Registry No.: 77658-97-0

Trade Name	Manufacturer	Country	Year Introduced
Anaxirone	Onbio Inc.	-	-

Raw Materials

Triazolidine-3,5-dione
Epichlorohydrin
Triethylamine

Manufacturing Process

In a 4-liter three-necked flask equipped with a stirrer, thermometer and reflux condenser, 101 g (1 mole) of triazolidine-3,5-dione, 2775 g (30 moles) of epichlorohydrin and 2 ml of triethylamine are heated to 80°C by means of an oil bath. The mixture reacts exothermically so that the oil bath may be removed. After the exothermic reaction has abated, the reaction mixture is stirred at 80°C. The total reaction time is 10 hours. 250 g of 50% sodium hydroxide solution are added dropwise to the solution obtained over a period of 4 hours at from 30 to 40°C in such a way that the water added and the water formed during the reaction is continuously removed by azeotropic

distillation at from 30 to 60 Torr using a water separator. To complete the reaction, the reaction mixture is stirred for another hour and the sodium chloride formed is separated by filtration. The sodium chloride is washed twice with 200 g of epichlorohydrin and the combined epichlorohydrin solutions are washed with 200 ml of water. After the organic phase has been dried over sodium sulfate, the solvent is removed by concentration in a rotary evaporator and the residue is dried, ultimately at 80°C/0.2 mbar, to constant weight. 240 g of a light brown viscous oil are obtained. It was found to have an epoxide value of 0.93 and has a chlorine content of 2.75%. The viscous oil crystallizes after standing for from a few hours to days. The practically pure 1,2,4-triglycidyl triazolidine-3,5-dione melting at from 98° to 103°C crystallizes by dissolution in methanol and cooling to 5°C. IR- and NMR-spectra in conjunction with elemental analysis and epoxide determination confirm the assumed structure. Melting point 94-96°C.

References

Rottmaier Ludwig, Merten Rudolf; US Patent No. 4,283,546; Aug. 11, 1981; Assigned to Bayer Aktiengesellschaft (DE)

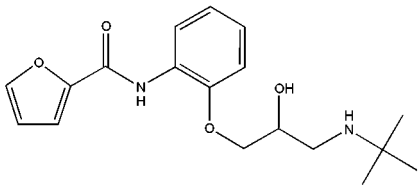
ANCAROLOL

Therapeutic Function: Beta-adrenergic blocker

Chemical Name: N-[2-[3-[(1,1-Dimethylethyl)amino]-2-hydroxypropoxy] phenyl]-2-furancarboxamide (+/-)

Common Name: Ancarolol

Structural Formula:



Chemical Abstracts Registry No.: 75748-50-4

Trade Name	Manufacturer	Country	Year Introduced
Ancarolol	ZYF Pharm Chemical	-	-
Ancarolol	Onbio Inc.	-	-

Raw Materials

2'-(2,3-Epoxypropoxy)-furan-2-carboxylic acid anilide
t-Butylamine

Manufacturing Process

A mixture of 23 g of 2'-(2,3-epoxypropoxy)-furan-2-carboxylic acid anilide, 7.3 g of t-butylamine and 50 ml of isopropanol is boiled under reflux for 10 hours. On cooling, 2'-(2-hydroxy-3-t-butylaminopropoxy)-furan-2-carboxylic acid anilide (ancarolol) crystallizes out from the solution. The chromatographically pure base is obtained in the form of a white solid of melting point 112°-113°C by recrystallization from ethyl acetate. The yield is 12 g. The colorless, crystalline base is dissolved in alcohol, alcoholic HCl is added and the hydrochloride is induced to crystallize by adding ether dropwise. After isolation, the salt is recrystallized again from ethanol. This gives 10 g of the hydrochloride, melting point 189°-191°C.

References

Ulendorf J. et al.; US Patent No. 4,269,855; May 26, 1981; Assigned to A. Nattermann and Cie, GmbH, Cologne, Fd.Rep. of Germany

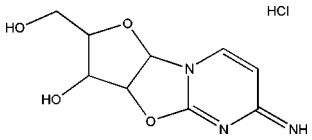
ANCITABINE HYDROCHLORIDE

Therapeutic Function: Antineoplastic

Chemical Name: 2,3,3a,9a-Tetrahydro-3-hydroxy-6-imino-6H-furo[2',3';4,5]oxazolo[3,2-a]pyrimidine-2-methanol hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 10212-25-6; 31698-14-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Cyclo-C	Kohjin	Japan	1975

Raw Materials

Uridine
Imidazole
Hydrogen sulfide
Acetic anhydride
Ammonia
Hydrogen chloride
Trityl chloride
Thiophosgene
Acetic acid
Phosphorus pentasulfide
Bromine

Manufacturing Process

A series of reaction steps may be employed in which: (1) Uridine is reacted with trityl chloride to give 5'-o-trityluridine; (2) Imidazole is reacted with thiophosgene and that product reacted with the 5'-o-trityluridine to give 2,2'-anhydro-1-(5'-o-trityl-β-D-arabinofuranosyl)uracil; (3) The preceding uracil product is converted to the thiouracil using hydrogen sulfide; (4) The trityl group is removed by treatment with 80% acetic acid; (5) A triacetylated product is obtained using acetic anhydride; (6) A dithiouracil is prepared from the uracil intermediate using phosphate pentasulfide.

Preparation of 1-(β-D-arabinofuranosyl)-2-thiocytosine: A solution of 2.0 g of 1-(2',3',5'-O-triacetyl-β-D-arabinofuranosyl)-2,4-dithiouracilin 100 ml of methanol is saturated with anhydrous ammonia at 0°C. The mixture, in a glass liner, is heated in a pressure bomb at 100°C for three hours. The reaction mixture is concentrated to a gum in vacuum, and most of the byproduct acetamide is removed by sublimation at 60°C/0.1 mm. The residue is chromatographed on 100 g of silica gel. Elution of the column with methylene chloride-methanol mixtures with methanol concentrations of 2-25% gives fractions containing acetamide and a series of brown gums. The desired product is eluted with 30% methanol-methylene chloride to give a total yield of 0.386 g (30%), MP 175-180°C (dec.). Recrystallization from methanol-isopropanol furnishes an analytical sample, MP 180-182°C (dec.).

To a solution of 80 mg of 1-(β-D-arabinofuranosyl)-2-thiocytosine in 12 ml of water is added dropwise 3 ml of a 1 M bromine solution in carbon tetrachloride. At this point the color of the bromine persists for about 2-3 minutes after each addition. The unreacted bromine is blown off with a stream of nitrogen, and the reaction mixture is concentrated to a syrup in vacuum using a bath temperature less than 50°C. The residue is evaporated three times with 10 ml portions of ethanol, whereupon it crystallizes. The product is triturated with cold ethanol and with ether to obtain 17 mg of 2,2'-anhydro-1-(β-D-arabinofuranosyl)cytosine hydrobromide, MP 240°C (dec.).

Treatment of the hydrobromide with a slight excess of ethanolic ammonia yields the base which may then be converted to the hydrochloride.

References

Merck Index 654
Kleeman and Engel p. 53
DOT 12 (8) 304 (1976)
I.N. p.87
Shen, T.Y. and Ruyle, W.V.; US Patent 3,463,850; August 26, 1969; Assigned to Merck and Co., Inc.

ANCROD

Therapeutic Function: Anticoagulant

Chemical Name: Agkistrodon serine proteinase

Common Name: Ancrod; Venacil

Chemical Abstracts Registry No.: 9046-56-4

Trade Name	Manufacturer	Country	Year Introduced
Viprinex	Knoll Pharmaceuticals	-	-
Arvin	Knoll AG/BASF Pharma	-	-

Raw Materials

Venom of the Malayan pit-viper Agkistrodon rhodostoma
Triethylaminoethyl cellulose powder (Serva)
tris(Hydroxymethyl)aminomethane

Manufacturing Process

Triethylaminoethyl cellulose powder (Serva) of capacity 0.71 m.equiv./gm is suspended in 2 M sodium chloride buffered with 0.1 M tris/phosphate pH 6.0 and the slurry is packed into a glass column 3.6 cm in diameter until the height of the packed material reaches 20 cm. The column is washed with a further 2 L of the solvent used for preparing the slurry and is then equilibrated with 0.01 M tris/phosphate buffer pH 8.5. Tris is an abbreviation for tris(hydroxymethyl)aminomethane. 330-360 mg of crude A. rhodostoma venom is dissolved in 20 ml of 0.01 M tris/phosphate buffer pH 8.5, centrifuged to remove insoluble material, and the clear supernatant is applied to the column. The fractionation is carried out at room temperature at a flow rate of 90-100 ml (35 ml/hour). The protein concentration in the eluate is estimated from the extinction of the solution at 280 m/t in 1 cm cells. The chromatogram is developed with the following buffers. In all cases the molarity of the buffers are with respect 40 to tris.

0.01 M tris/phosphate pH 8.5 (to wash venom onto the column) (fractions 1, 2, 3). 0.01 M tris/phosphate pH 7.0 (fraction 4), 0.02 M tris/phosphate pH 6.0, 0.04 M tris/phosphate pH 6.0 (fraction 5), 0.10 M tris/phosphate pH 6.0 (fraction 6), 0.10 M tris/phosphate + 0.10 M NaCl pH 6.0 (fraction 7).

The changes in eluting buffer are made after the column has equilibrated with the buffer. The protein fractions obtained in this way are assayed for coagulant activity.

Less than 1% of the applied coagulant activity is recovered in fraction Nos. 1, 2, 3, 4. Fraction 1 however possesses proteolytic activtity which in concentrated solutions would dissolve fibrin clots. The thrombin-like activity is eluted from these columns in significant amounts at a buffer strength of 0.04 M or greater.

The eluate is freeze dried to give a light powdery product. Yield: 18-20 mg per 350 mg dry venom. Calculation of molecular weight of the protein based on the amino acid composition gives a value of 30.000 which is in a very good agreement with that obtained by physical methods.

References

Reid H.A. et al.; US Patent No. 3,657,416; April 18, 1972; Assigned to Natinal Research Development Corporation, London, England

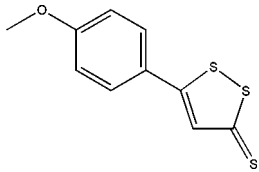
ANETHOLTRITHION

Therapeutic Function: Salivation stimulant, Choleretic, Neuroprotective

Chemical Name: 3H-1,2-Dithiole-3-thione, 5-(4-methoxyphenyl)-

Common Name: Anethole dithiolthione; Trithioparamethoxyphenylpropene; Anethole trithione

Structural Formula:



Chemical Abstracts Registry No.: 532-11-6

Trade Name	Manufacturer	Country	Year Introduced
Sialor	Paladin Labs	-	-
Anetholtrithion	Shanghai Jinsai Medicine Chemical Industry Co. Ltd.	-	-
Anetholtrithion	Tianjin Mid-Chem Co., Ltd.	-	-
Anetholtrithion	Shanghai Lansheng Corporation	-	-
Secrebil	Wassermann	-	-
Secrebil	Vicente Scavone y CIA. C.I.S.A.	-	-
Bilitherap	Kaigen	-	-
Felviten	Nippon Shinyaku	-	-
Halpen	Toho Kagaku	-	-
Mucinol	Sanofi-Synthelabo OTC, D-Berlin	-	-
Sialor	Solvay-Kingswood	-	-
Sonicur	Kalifarma	-	-
Sufralen	Solvay	-	-
Sulfarlem	Solvay	-	-

Trade Name	Manufacturer	Country	Year Introduced
Sulfarlem	Solvay-Kingswood	-	-
Sulfarlem	UCM	-	-
Sulfarlem	Tobishi	-	-
Sulfarlem	Ouiheng	-	-
Sulfarlem	Frik	-	-
Sulfarlem	Ethimed	-	-

Raw Materials

Anethol (1-Methoxy-4-propenyl-benzene)
Sulfur

Manufacturing Process

1 mol anethol (1-methoxy-4-propenyl-benzene) and 3 mol sulfur were heated in an open vessel to temperature 190°-200°C. H_2S was removed at this temperature. On cooling the reaction mixture was getting solid. The solid product was recrystallizated from acetone or ethanol to give the orange-red needles of 5-(4-methoxyphenyl)-3H-1,2-dithiole-3-thione; MP 108.5°C.

References

Boettcher B.; D.B. Patent No. 869,799; May 8, 1940

ANGIOTENSIN AMIDE

Therapeutic Function: Vasoconstrictor

Chemical Name: L-Asparaginyl-L-arginyl-L-valyl-L-tyrosyl-L-valyl-L-histidyl-L-protyl-L-phenylalanine

Common Name: -

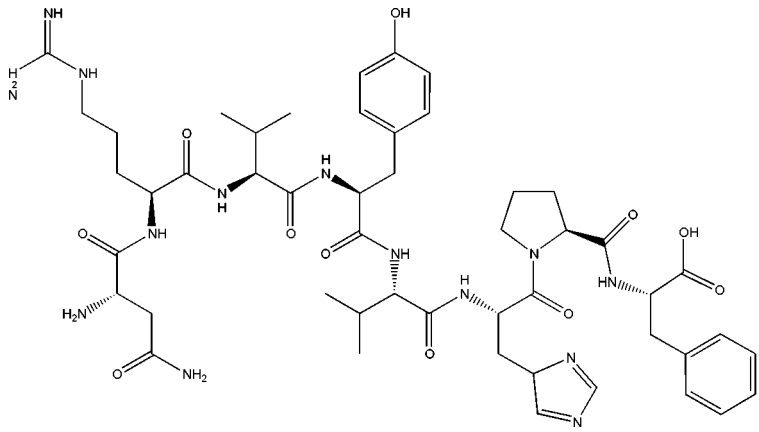
Chemical Abstracts Registry No.: 53-73-6

Trade Name	Manufacturer	Country	Year Introduced
Hypertensin	Ciba	W. Germany	1961
Hypertensin	Ciba	US	1962

Raw Materials

L-Asparaginyl-L-arginyl-L-valyl-L-tyrosyl-L-valyl-L-histidyl-L-prolyl-L-phenylalanine methyl ester trihydrochloride
Sodium hydroxide

Structural Formula:



Manufacturing Process

48 mg (0.042 mmol) of L-asparaginyl-L-arginyl-L-valyl-L-tyrosyl-L-valyl-L-histidyl-L-prolyl-L-phenylalanine methyl ester trihydrochloride are suspended in 0.5 ml of methanol, and treated gradually in the course of one hour with 0.3 ml of N-caustic soda solution (about 7 equivalents) so that the pH value of the solution is maintained between 10.5 and 11.5. After a further 30 minutes the solution is freed from methanol under vacuum at room temperature, adjusted with 1 N acetic acid to pH 7.4 and lyophilized. The residual mixture of free peptide and inorganic salts (79 mg) is fractionated by countercurrent distribution in the system butanol/0.1 N ammonium hydroxide. The pure octapeptide is obtained as a colorless powder which is soluble in water and methanol, more sparingly soluble in ethanol, and insoluble in acetone.

References

Merck Index 674
Kleeman and Engel p. 55
I.N. p. 89
Schwyzer, R., Iselin, B., Kappeler, H., Ritter, W. and Riuiker, B.; US Patent 2,978,444; April 4, 1961; Assigned to Ciba Pharmaceutical Products, Inc.

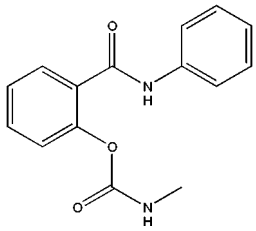
ANILAMATE

Therapeutic Function: Antiinflammatory

Chemical Name: 2-[[(Methylamino)carbonyl]oxy]-N-phenylbenzamide

Common Name: Anilamate

Structural Formula:



Chemical Abstracts Registry No.: 5591-49-1

Trade Name	Manufacturer	Country	Year Introduced
Anilamate	Onbio Inc.	-	-

Raw Materials

Salicylanilide
Triethylamine
Methyl isocyanate

Manufacturing Process

32 g of salicylanilide was dissolved in 1000 ml of diethyl ether, 2 ml of triethylamine and 25 ml of a 50% solution of methyl isocyanate in toluene were added to the solution and the reaction mixture was allowed to stand overnight at about 25°C. The resulting crystals of salicylanilide methylcarbamate were removed by filtration, washed with 100 ml of diethyl ether, and dried in vacuo to provide 37.5 g (92% yield) of salicylanilide methylcarbamate having melting point of 160-161°C.

References

Strube R.E.; US Patent No. 3,091,633; May 28, 1963; Assigned to The Upjon Company, Kalamazoo, Mich., a corporation of Delawere

ANILERIDINE DIHYDROCHLORIDE

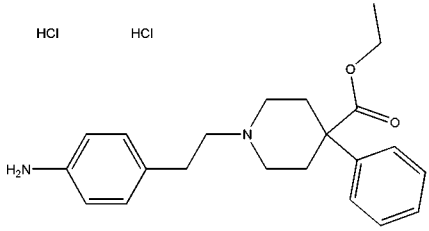
Therapeutic Function: Narcotic analgesic

Chemical Name: 1-[2-(4-Aminophenyl)ethyl]-4-phenyl-4-piperidinecarboxylic acid ethyl ester dihydrochloride

Common Name: -

Chemical Abstracts Registry No.: 126-12-5; 144-14-9 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Leritine HCl	Merck Sharp and Dohme	US	1958
Apodol Tabs	Squibb	US	1965
Leritine	Merck-Frosst	Canada	-

Raw Materials

Sodium carbonate
Hydrogen chloride
β-(p-Aminophenyl)ethyl chloride
4-Phenyl-4-carbethoxypiperidine carbonate

Manufacturing Process

A mixture of 7.8 grams (0.05 mol) of β-(p-aminophenyl)ethyl chloride hydrochloride, 12.5 grams (0.025 mol) of 4-phenyl-4-carboethoxypiperidine carbonate, 10.5 grams (0.125 mol) sodium bicarbonate, and 100 cc of anhydrous ethanol are mixed, stirred and heated under reflux for a period of approximately 40 hours and then concentrated in vacuum to dryness. The residual material is triturated with 50 cc of water, decanted, washed by decantation with an additional 50 cc of water, and then dried in vacuum to give N-[β-(p-aminophenyl)ethyl]-4-phenyl-4-carboethoxypiperidine.

The N-[β-(p-aminophenyl)ethyl]-4-phenyl-4-carboethoxypiperidine is dissolved in 50 cc of hot anhydrous ethanol, an excess (about 20 cc) of 20% alcoholic hydrochloric acid solution is added; upon scratching the side of the container crystals form. One hundred cubic centimeters of ether are then added to the mixture, the ethereal mixture is cooled, and the crystalline material which precipitates is recovered by filtration, washed with ether, and dried to give 12.7 grams of N-[β-(p-aminophenyl)ethyl]-4-phenyl-4-carboethoxypiperidine dihydrochloride which can be further purified by recrystallization from ethanol or methanal to give substantially pure material; MP 275-277°C.

References

Merck Index 680
Kleeman and Engel p. 56
OCDS Vol. 1 p. 300 (1977)
I.N. p. 90
Weijlard, J. and Pfister, K., III; US Patent 2,966,490; December 27, 1960; Assigned to Merck and Co., Inc.

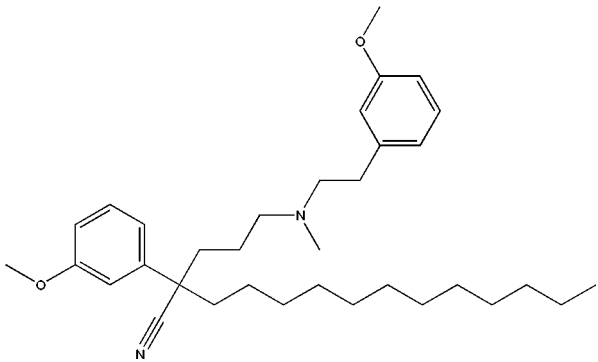
ANIPAMIL

Therapeutic Function: Coronary vasodilator, Antihypertensive

Chemical Name: 2-[3-[(m-Methoxyphenethyl)methylamino]propyl]-2-(m-methoxyphenyl)tetradecanenitrile

Common Name: Anipamil; LU 42668

Structural Formula:



Chemical Abstracts Registry No.: 83200-10-6

Trade Name	Manufacturer	Country	Year Introduced
Anipamil	Onbio Inc.	-	-
Anipamil	ZYF Pharm Chemical	-	-

Raw Materials

3-Methoxyphenylacetonitrile
1-Bromododecane
1-Bromo-3-chloropropane
1-Cyano-1-(3-methoxyphenyl)tridecane
N-Methyl-β-(3-methoxyphenyl)ethylamine
Sodium amide

Manufacturing Process

1,7-Bis-(3-ethoxyphenyl)-3-methylaza-7-cyano-nonadecane:

0.06 mole of 1-cyano-1-(3-methoxyphenyl)tridecane (prepared by phase transfer-catalyzed alkylation of 3-methoxyphenylacetonitrile with 1-bromododecane) and 0.06 mole of 1-chloro-4-methylaza-6-(3-methoxyphenyl)hexane [prepared from N-methyl-β-(3-methoxyphenyl)ethylamine and 1-bromo-3-chloropropane by a method similar to that described in Arzneim.-Forsch. 28 (II) (1978), 2048] were dissolved in 100 ml of dry toluene in a three-necked flask provided with a stirrer, dropping funnel, reflux condenser and thermometer. 9.3 g (0.07 mole) of a 30% strength suspension of sodium amide in toluene were then added dropwise at from 100° to 110°C, with stirring, and stirring was continued under reflux for a further 90 minutes.

The resulting reaction solution was poured into 200 ml of ice water, and the toluene phase was separated off and washed twice with water. The required amount of hydrochloric acid was added to the toluene solution, the toluene was distilled off under reduced pressure and the residue, which remained was recrystallized from acetone to give 1,7-bis-(2-methoxyphenyl)-3-methylaza-7-cyanononadecane hydrochloride or α-dodecyl-3-methoxy-α-[3-[[2-(3-methoxyphenyl)ethyl]methylamino]propyl]benzene-acetonitrile (anipamil); MP: 60°-69.5°C.

References

Ehrmann O. et al.; US Patent No. 4,438,131; March 20, 1984; Assigned to BASF Aktiengesellshaft, Fed. Rep. of Germany

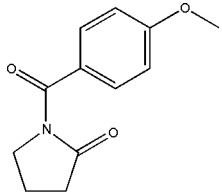
ANIRACETAM

Therapeutic Function: Nootropic

Chemical Name: 2-Pyrrolidinone, 1-(4-methoxybenzoyl)-

Common Name: Aniracetam; Memodrin

Structural Formula:



Chemical Abstracts Registry No.: 72432-10-1

Trade Name	Manufacturer	Country	Year Introduced
Pergamid	Rontag	-	-
AM Ro13-5057	ABATRA Technology Co., Ltd.	-	-
Memodrin	Lavipharm Group	-	-

Raw Materials

2-Pyrrolidinone	p-Methoxybenzoyl chloride
Triethylamine	p-Methoxybenzoic acid pentachlorophenyl ester
Sodium hydride	1-Trimethylsilyl-2-pyrrolidinone

Manufacturing Process

There are a few versions of synthesis of title compound.

Preparation of 1-(p-methoxybenzoyl)-2-pyrrolidinone:

1. 40.0 g of p-methoxybenzoyl chloride, 25.0 g of 2-pyrrolidinone and 110 ml of absolute diethyl ether are treated at between 0°C and 10°C while stirring with 52.5 ml of triethylamine. The mixture is stirred at room temperature for a further 30 minutes and at reflux for 3 hours, then cooled down and treated at 2°C with cold water. The insoluble constituents are filtered off under suction and washed with water and diethyl ether. The thus obtained solid substance is recrystallized from alcohol after drying over phosphorus pentoxide. There is obtained 1-(p-methoxybenzoyl)-2-pyrrolidinone which melts at 121°-122°C.

2. 20.2 g of the sodium salt of 2-pyrrolidinone (prepared using sodium hydride) suspended in 270 ml of dimethylformamide are added in four portions at -10°C to a solution of 37.0 g of p-methoxybenzoyl chloride in 50 ml of dimethylformamide. Subsequently, the mixture is stirred at room temperature for 1 hour and then at 40°C for 4 hours. The solvent is evaporated and the residue is treated with diethyl ether and with cold sodium bicarbonate solution. The insoluble crystalline constituents are filtered off, washed with water and diethyl ether and dried in vacuum over phosphorus pentoxide. There is obtained 1-(p-methoxybenzoyl)-2-pyrrolidinone having a melting point of 120°-121°C.

3. 20 g of p-methoxybenzoyl chloride and 20 g of 2-pyrrolidinone are boiled at reflux in 20 ml of diethyl ether for 16 hours and then diethyl ether, ice and 2 N aqueous ammonia are added to the mixture. The insoluble constituents are filtered off and washed ion-free with diethyl ether and water. The filter cake is dried and there is obtained 1-(p-methoxybenzoyl)-2-pyrrolidinone having a melting point of 119.5°-120.5°C.

4. 20 g of p-methoxybenzoyl chloride and 20 g of 2-pyrrolidinone are boiled at reflux in 20 ml of diethyl ether for 16 hours and then diethyl ether, ice and 2 N aqueous ammonia are added to the mixture. The insoluble constituents are filtered off and washed ion-free with diethyl ether and water. The filter cake is dried and there is obtained 1-(p-methoxybenzoyl)-2-pyrrolidinone having a melting point of 119.5°-120.5°C. The procedure described in item is followed, but the starting materials are heated in 20 ml of toluene instead of diethyl ether. The resulting 1-(p-methoxybenzoyl)-2-pyrrolidinone melts at 117°-118°C.

5. 10 g of 2-pyrrolidinone and 10 g of p-methoxybenzoyl chloride are heated at 80°-90°C (internal temperature) in the absence of a solvent for 1 hour. The mixture is then left to cool down and is worked-up as described in item 3. After recrystallization from alcohol, there is obtained 1-(p-methoxybenzoyl)-2-pyrrolidinone having a melting point of 120°-121°C.

6. 24.4 g of p-methoxybenzoyl chloride and 22.5 g of 1-trimethylsilyl-2-pyrrolidinone are mixed and the mixture is stirred at room temperature for 10 minutes. Then, the resulting trimethylchlorosilane is distilled off under reduced pressure in an oil bath at 80°C. The residue is triturated with 100 ml of diethyl ether. The mixture is filtered and the filter cake is recrystallized from ethanol. There is obtained 1-(p-methoxybenzoyl)-2-pyrrolidinone having a melting point of 120°-121°C.

7. 7.0 g of the sodium salt of 2-pyrrolidinone (prepared using sodium hydride)

suspended in 120 ml of dimethylformamide are added at -10°C to a solution of 20.0 g of p-methoxybenzoic acid pentachlorophenyl ester in 100 ml of dimethylformamide. Subsequently, the mixture is stirred at room temperature for 1 hour and at 55°C for 8 hours. The solvent is evaporated, the residue is treated with cold aqueous acetic acid solution and the mixture is extracted with ethyl acetate. The organic phase is washed with cold sodium bicarbonate solution and water, dried over sodium sulfate, filtered and evaporated. The residue is taken up in ethanol and stirred in an ice bath. The separated crystals are filtered off and there is obtained 1-(p-methoxybenzoyl)-2-pyrrolidinone having a melting point of 119°-120°C.

References

Kyburz E. et al.; US Patent No. 4,369,139; Jan. 18, 1983; Assigned to Hoffmann-La Roche Inc., Nutaey, N.J.

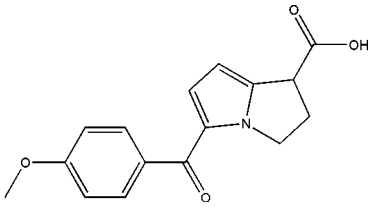
ANIROLAC

Therapeutic Function: Antiinflammatory, Analgesic

Chemical Name: 1H-Pyrrolizine-1-carboxylic acid, 2,3-dihydro-5-(4-methoxybenzoyl)-, (+-)-

Common Name: Anirolac

Structural Formula:



Chemical Abstracts Registry No.: 66635-85-6

Trade Name	Manufacturer	Country	Year Introduced
Anirolac	Syntex Inc.	-	-
Anirolac	Onbio Inc.	-	-

Raw Materials

N,N-Dimethyl-p-methoxybenzamide
Phosphorous oxychloride
Isopropyl 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate

Manufacturing Process

A solution of 1.1 equivalent of N,N-dimethyl-p-methoxybenzamide and 1

equivalent of phosphorous oxychloride in 2 ml of 1,2-dichloroethane is refluxed for 30 minutes. To this solution is added a solution of 1 equivalent of isopropyl 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate in 2 ml of 1,2-dichloroethane. The reaction mixture is refluxed under an argon atmosphere for 8 hours, treated with equivalent of sodium acetate and refluxed for a further 5 hours. The resultant mixture is then evaporated to dryness and the residue is chromatographed on 12 g of silica gel, eluting with hexane: ethyl acetate (3:1), monitoring the course of the reaction by TLC. Isopropyl 5-p-methoxybenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate was obtained as an oil. UV, IR, NMR spectrum confirmed the structure of obtained compound.

A solution of 1 equivalent of isopropyl 5-p-methoxybenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate in 10 ml of methanol is treated with a solution of 1 equivalent of potassium carbonate in 5 ml of water. The reaction mixture is refluxed under nitrogen atmosphere for 30 minutes, cooled, and evaporated to dryness. The residue is taken up in 10 ml of 10% aqueous hydrochloric acid and 50 ml of water and the resultant mixture extracted with ethyl acetate (2x50 ml). The combined extracts are dried over magnesium sulfate and evaporated to dryness under reduced pressure. Crystallization of the residue from ethyl acetate-hexane affords 5-p-methoxybenzoyl-1,2-dihydro-3H-pyrrolo[1, 2-a]pyrrole-1-carboxylic acid (anirolac); MP: 187°-187.5°C.

References

Syntex (USA) Inc.; G.B. Patent No. 1,554,075; Oct. 17, 1979

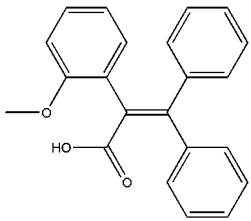
ANISACRIL

Therapeutic Function: Anorexic, Antihyperlipidemic

Chemical Name: Acrylic acid, 2-(o-methoxyphenyl)-3,3-diphenyl-

Common Name: Anisacril

Structural Formula:



Chemical Abstracts Registry No.: 5129-14-6

Trade Name	Manufacturer	Country	Year Introduced
SCF 16046	Smith Kline	-	-

Raw Materials

o-Bromoanisole	Magnesium
Hydrochloric acid	Diphenyl pyruvic acid
Sodium hydroxide	

Manufacturing Process

A solution of Grignard reactive (prepared from 247 g of o-bromoanisole and 31.6 g of magnesium in 1500 ml of ether) is added dropwise to a solution of 91 g of diphenyl pyruvic acid in ether. The mixture is refluxed for 2 hours. After cooling to the reaction mixture is added 5% hydrochloric acid and the product is extracted with 5% solution of sodium hydroxide. α-(o-Anisyl)-β,β-diphenyl lactic acid is precipitated by addition of concentrated hydrochloric acid; yield 62 g, melting point 194-195°C.

4 g of α-(o-anisyl)-β,β-diphenyl lactic acid is heated at 210-215°C for 10-15 min. The α-(o-anisyl)-β,β-diphenyl acrylic acid is recrystallized from benzene, yield 2.85 g (74%), melting point 195-196°C.

References

FR Patent No. 1,442,295; Oct. 8, 1964; Assigned to Smith Kline and French Laboratories residant aux Etats-Unis d'Amerique

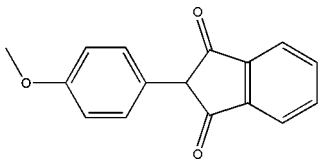
ANISINDIONE

Therapeutic Function: Anticoagulant

Chemical Name: 2-(4-Methoxyphenyl)-1H-indene-1,3(2H)-dione

Common Name: Anisindandione

Structural Formula:



Chemical Abstracts Registry No.: 117-37-3

Trade Name	Manufacturer	Country	Year Introduced
Miradon	Schering	US	1960
Unidone	Unilabo	France	1964
Unidone	Centrane	France	-

Raw Materials

p-Methoxybenzaldehyde
Sodium ethoxide
Phthalide

Manufacturing Process

To a hot solution of 20.6 g of sodium in 400 ml of absolute ethanol, there is added a solution of 110 g of phthalide and 110 g of p-methoxybenzaldehyde. A vigorous reaction ensues and one-half of the alcohol is distilled off over a two hour period. Ice and water are added to the red solution and the diluted solution is acidified with hydrochloric acid. The resulting gum solidifies and the aqueous phase is removed by decantation. The crude solid is recrystallized twice from two liters of ethanol yielding 2-(p-methoxyphenyl)-1,3-indandione as pale yellow crystals, MP 155-156°C.

References

Merck Index 690
Kleeman and Engel P.57
OCDS Vol. 1 p. 147 (1977)
I.N. p.90
REM p.828
Sperber, N.; US Patent 2,899,358; August 11, 1959; Assigned to Schering Corporation

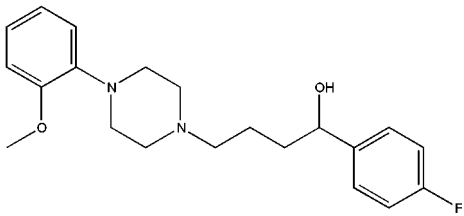
ANISOPIROL

Therapeutic Function: Neuroleptic

Chemical Name: (+/-)-α-(4-Fluorophenyl)-4-(2-methoxyphenyl)-1-piperazinebutanol

Common Name: Anisopirol

Structural Formula:



Chemical Abstracts Registry No.: 442-03-5

Trade Name	Manufacturer	Country	Year Introduced
Anisopirol	ZYF Pharm Chemical	-	-

Raw Materials

γ-Chloro-4-fluorobutyrophenone
1-(2-Methoxyphenyl)piperazine
Sodium borohydride

Manufacturing Process

A mixture of 6.6 parts of γ-chloro-4-fluorobutyrophenone and 12.5 parts of 1-(2-methoxyphenyl)piperazine, heated for 10 hours at a temperature of 110°C. The reaction mixture is treated with 800 parts of ether and filtered. The ether layer is washed with water, dried over anhydrous potassium carbonate and filtered, whereupon hydrogen chloride gas is introduced into the solution. The precipitate is collected on a filter and dissolved in a mixture of 240 parts of 2-propanol and 80 parts of acetone to yield 1-[γ-(4-fluorobenzoyl)propyl]-4-(2-methoxyphenyl)piperazine hydrochloride. This monohydrochloride is collected on a filter and dissolved in 240 parts of 2-propanol. Anhydrous, gaseous hydrogen chloride is passed through the solution. On cooling, the 1-[γ-(4-fluorobenzoyl)propyl]-4-(2-methoxyphenyl)piperazine hydrochloride precipitates.

A second crop of product is obtained by passing hydrogen chloride gas through the solution of mother liquors. The pale-brown, amorphous powder is collected on a filter and found to melt at about 205°-205.5°C. This salt is dissolved in water and treated with sodium hydroxide. The precipitated base is recovered by filtration and recrystallized from diisopropylether. The white crystals melt about 67.5°-68.5°C.

By dissolving 4 parts of 1-[γ-(4-fluorobenzoyl)propyl]-4-(2-methoxyphenyl) piperazine dihydrochloride in 800 parts of water, rendering alkaline, extracting with 400 parts of ether, drying over calcium chloride, filtering, and evaporating the resulting solution, the free base of 1-[γ-(4-fluorobenzoyl) propyl]-4-(2-methoxyphenyl)piperazine is obtained. This product is dissolved in 120 parts of absolute ethanol and 0.03 part of sodium borohydride is added portionwise at 35°C. After decomposition with 150 parts of 1 N hydrochloric acid, the mixture is diluted with 500 parts of water, made alkaline with 4 N sodium hydroxide, and further diluted to a volume of 1,000 parts. Upon cooling for 4 hours at 0°C the precipitate formed is filtered, dried, and recrystallized from diisopropyl ether to yield 1-(4-fluorophenyl)-4-[4-(2-methoxyphenyl)piperazine]-1-butanol (anisopirol). The white granular powder of this compound has a melting point of about 105°-106°C.

References

Jansen P. A.J.; US Patent No. 2,997,474; August 22, 1961

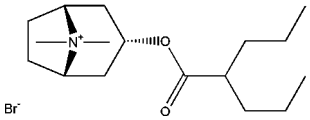
ANISOTROPINE METHYLBROMIDE

Therapeutic Function: Anticholinergic

Chemical Name: endo-8,8-Dimethyl-3-[(1-oxo-2-propylpentyl)oxy]-8-azoniabicyclo[3.2.1]octane bromide

Common Name: Octatropine methyl bromide

Structural Formula:



Chemical Abstracts Registry No.: 80-50-2

Trade Name	Manufacturer	Country	Year Introduced
Valpin	Endo (Du Pont)	US	1963
Valpinax	Crinos	Italy	1966
Valpin	Lacer	Spain	-
Valpin	Sankyo	Japan	-

Raw Materials

Tropine
Di-n-propyl acetyl chloride
Methyl bromide

Manufacturing Process

Preparation of Di-n-propyl acetyl tropine hydrochloride: Tropine (11.12 grams) was dissolved in 100 ml of anhydrous pyridine and to this solution was added 15.64 grams of di-n-propyl acetyl chloride. The mixture was refluxed for 6 hours. This solution was then cooled and the pyridine removed in vacuum. The residue was dissolved in chloroform. The chloroform solution was washed with 10% hydrochloric acid to remove the residual trace of pyridine. The hydrochloride of the product ester is soluble in chloroform and is not extracted from chloroform by hydrochloric acid. This is an unexpected property.

The chloroform solution of the hydrochloride was dried over anhydrous calcium sulfate, and evaporated to dryness, leaving a semisolid residue of product ester hydrochloride. This was recrystallized from chloroform-hexane mixture, MP 186°C.

Preparation of the Anisotropine Methyl Bromide: To the acetone solution of the free base was added an acetone solution, containing an excess of methyl bromide. Within a few minutes the methobromide started to crystallize. The mixture was allowed to stand for several hours. The crystallized solid was filtered, and additional product was obtained by evaporation of the filtrate. The yield was nearly quantitative. After recrystallization from acetone, the product melted at 329°C.

References

Merck Index 693
Kleernan and Engel p. 655
PDR p. 865
I.N. p. 699
REM p.913
Weiner, N. and Gordon, S.M.; US Patent 2,962,499; November 29, 1960; Assigned to Endo Laboratories, Inc.

ANISTREPLASE

Therapeutic Function: Thrombolytic

Chemical Name: Anisoylated plasminogen streptokinase activator complex

Common Name: Eminase; Fibrit; Iminase; Multilase; Anisoylated plasminogen streptokinase activator complex

Structural Formula: Binary complex of streptokinase and human plasminogen

Chemical Abstracts Registry No.: 81669-57-0

Trade Name	Manufacturer	Country	Year Introduced
Anistreplase	Beecham	-	-

Raw Materials

Streptokinase (250,000 units, Kabi, Stockholm, Sweden)
0.1 M p-amidinophenyl p'-anisate in dimethylsulphoxide
Human lys-plasminogen [Kabi, Stockholm]
L-Lysine-sepharose 4B
0.1 M ε-aminocaproic acid

Manufacturing Process

Preparation of freeze dried p-anisoyl streptokinase/plasminogen complex without internal peptide bond cleavages:

Streptokinase (250,000 units, Kabi, Stockholm, Sweden) was dissolved in 0.1 M trishydroxymethylmethane hydrochloride pH 7.4 (2.5 ml) and a solution of 0.1 M p-amidinophenyl p'-anisate in dimethylsulphoxide (0.25 ml) added. A slight cloudiness resulted. To this mixture was added 0.5 ml of a solution of human lys-plasminogen (8.99 mg/ml in the above buffer) [Kabi, Stockholm] and the solution was thoroughly and rapidly mixed. After standing on ice for 15 minutes, the solution was stored on ice until use. After approximaely 2 hours 0.4 ml (40,000 units) of the material was diluted with 3.0 ml of a slurry of L-lysine-sepharose 4B (a 33% wet wt/volume suspension in the above buffer) and stood at 0°C for 1 hour. The gel was filtered on a glass sinter

funnel at 4°C under suction and washed with the buffer (100 ml). The gel was eluted under gentle suction with the same buffer containing 0.1 M ε-aminocaproic acid (3 lots of 5 ml). The combined filtrates were dialysed for 2 hours at 4°C against ammonium bicarbonate buffer (50 mM pH 7.0) containing 2.5% w/v mannitol. The product was then freeze dried to 0.799 g of a white solid. Approximately 195 mg of this material was analysed by slab gel polyacrylamide gel electrophoresis using 10% w/v gels in the presence of sodium dodecyl sulphate. Two main polypeptide bands were observed corresponding to lys-plasminogen (m.w. 84,000) and streptokinase (m.w. 47,000). There was also a trace of contaminating human serum albumin derived from the commercial streptokinase preparation.

References

Smith R.A.G. et al.; US Patent No. 4,808,405; Feb. 28, 1989; Assigned Beecham Group P.L.C., England

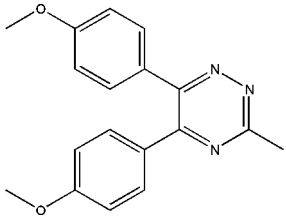
ANITRAZAFEN

Therapeutic Function: Antiinflammatory

Chemical Name: 1,2,4-Triazine, 5,6-bis(4-methoxyphenyl)-3-methyl-

Common Name: Anitrazafen

Structural Formula:



Chemical Abstracts Registry No.: 63119-27-7

Trade Name	Manufacturer	Country	Year Introduced
Lilly 122512	Eli Lilly	-	-

Raw Materials

3-Hydroxy-5,6-bis(4-methoxyphenyl)-1,2,4-triazine
Anisil (4,4'-dimethoxybenzil)
Semicarbazide hydrochloride
Phosphorous oxychloride
Methyltriphenylphosphonium bromide
Butyl lithium

Manufacturing Process

Preparation of 5,6-bis(4-methoxyphenyl)-3-methyl-1,2,4-triazine:

(A) 3-Hydroxy-5,6-bis(4-methoxyphenyl)-1,2,4-triazine 2 moles, 540 g of anisil (4,4'-dimethoxybenzil), 222 g (2 moles) of semicarbazide hydrochloride, 180 g (2.2 moles) of sodium acetate, and 2.5 liters of acetic acid were heated at reflux overnight. The cooled reaction mixture was poured into 5 liters of water. The crude solid product was collected by filtration, washed with water, and recrystallized from acetic acid, giving 434 g of 3-hydroxy-5,6-bis(4-methoxyphenyl)-1,2,4-triazine; MP: about 272°-274°C.

(B) 3-Chloro-5,6-bis(4-methoxyphenyl)-1,2,4-triazine:

10 grams of 3-hydroxy-5,6-bis(4-methoxyphenyl)-1,2,4-triazine and 50 ml of phosphorous oxychloride were heated at reflux for 1.5 hours. The cooled mixture was poured onto crushed ice and the resultant mixture was extracted with diethyl ether. The extract was washed successively with 2% sodium hydroxide and water until the washings were neutral. The ether extract was dried over anhydrous sodium sulfate and evaporated. The residue was taken up in ether, filtered, and the filtrate was evaporated to yield 9.0 g of 3-chloro-5,6-bis(4-methoxyphenyl)-1,2,4-triazine; MP: about 130°-132°C.

(C) 5,6-Bis(4-methoxyphenyl)-3-methyl-1,2,4-triazine:

To a slurry of 11.7 g (0.33 mole) of methyltriphenylphosphonium bromide in 150 ml of dry tetrahydrofuran at -35°C was added, over a 15-minute period, 20 ml (0.033 mole) of n-butyl lithium. The reaction mixture was stirred for one hour. To the reaction mixture at -35° to -40°C was added over a 10-minute period a solution of 5.7 g (0.0165 mole) of 3-chloro-5,6-bis(4-methoxyphenyl)-1,2,4-triazine in 50 ml of tetrahydrofuran. The reaction mixture was allowed to warm to ambient temperature and was stirred overnight. A solution of 1.05 g (0.0165 mole) of sodium carbonate in 50 ml of water was added dropwise to the reaction mixture which then was heated at reflux for three hours. The reaction mixture was cooled, poured over ice, and extracted with diethyl ether. The diethyl ether extract was washed with water, dried over anhydrous sodium sulfate, and concentrated. The concentrate was chromatographed over silica gel, with three fractions being collected. After evaporation of solvent, the third fraction solidified; MP: about 109°-113°C. The solid was identified as 5,6-bis(4-methoxyphenyl)-3-methyl-1,2,4-triazine by nuclear magnetic resonance analysis, mass spectrographic analysis, and elemental microanalysis.

References

Lacefield W.B.; US Patent No. 4,190,725; Feb. 26, 1980; Assigned to Eli Lilly and Company, Indianapolis, Ind.

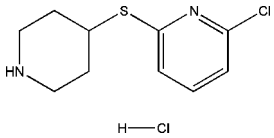
ANPIRTOLINE HYDROCHLORIDE

Therapeutic Function: Analgesic, Antidepressant

Chemical Name: 2-Chloro-6-(4-piperidinylthio)pyridine monohydrochloride

Common Name: Anpirtoline hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 99201-87-3; 98330-05-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Anpirtoline Hydrochloride	YQBio (Shanghai) Co. Ltd.	-	-
Anpirtoline Hydrochloride	Biomol Research Lab.	-	-

Raw Materials

Sodium hydride
Silica gel
4-Mercaptopiperidine hydrochloride
2,6-Dichloropyridine

Manufacturing Process

2-Chloro-6-(4-piperidinylthio)pyridine:

The reaction is carried out under an argon atmosphere. 0.27 g of 80% sodium hydride (0.009 mol) are suspended in 10 ml of dimethylacetamide; the mixture is cooled with ice and then 0.615 g (0.004 mol) of solid 4-mercaptopiperidine hydrochloride are added and stirred for 10 minutes. A solution of 0.588 g (0.004 mol) of 2,6-dichloropyridine in 5 ml of dimethylacetamide are then added dropwise to this mixture and the reaction mixture is stirred for 2.5 hours at room temperature.

Working up of the reaction mixture: 25 ml of water are added dropwise with cooling, 20 ml of methylene chloride are then added, the organic phase is separated off, the aqueous phase is then extracted twice with 15 ml of methylene chloride each time, the combined organic phase is washed twice, in each case with 10 ml of water, dried with sodium sulfate, the solution is concentrated on a rotary evaporator, the residue is mixed with 10 ml of absolute ethanol and then reconcentrated.

The product which is obtained on removal of the eluant is diluted with 10 ml of ether, an equivalent quantity of HCl in isopropanol is added dropwise and the mixture is placed for several hours in a deep freezer after addition of seed crystals. The hydrochloride of the 2-chloro-6-(4-piperidinylthio)pyridine which crystallizes out is filtered off with suction, washed with ether and dried under oil pump vacuum at 50°C. Melting point of the hydrochloride 132°-133°C.

References

Engel J. et el.; US Patent No. 4,643, 995; Feb. 17, 1987; Assigned to Deguss Akkktiengesellschaft, Frankfurt am Main, Fed. Rep. of Germany

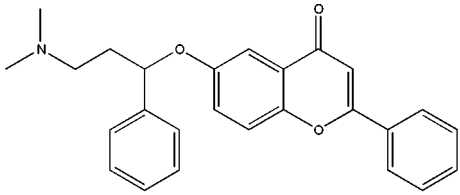
ANSOXETINE

Therapeutic Function: Antidepressant

Chemical Name: 6-[3-(Dimethylamino)-1-phenylpropoxy]-2-phenyl-4H-1-benzopyran-4-one

Common Name: Ansoxetine

Structural Formula:



Chemical Abstracts Registry No.: 79130-64-6

Trade Name	Manufacturer	Country	Year Introduced
Ansoxetine	ZYF Pharm Chemical	-	-

Raw Materials

1-Chloro-1-phenyl-3-dimethylaminopropane

Manufacturing Process

A solution of 1 gram-equivalent of 6-hydroxyflavanone in equivalent of 0.5 N ethanolic NaOH is evaporated, the residue is dissolved in 200 ml of DMF and the solution is heated to 150°C; a solution of g-eguivalent of 1-chloro-1-phenyl-3-dimethylaminopropane in 50 ml of DMF is added, while stirring. The mixture is stirred for 1.5 hours at 150°C and 6-(1-phenyl-3-dimethylaminopropoxy)flavonone is precipitated by adding water.

References

Hausberg H.-H. et al.; US Patent No. 4,780,478; October 25, 1988; Assigned to Merck Patent Gesellschaft mit Berschrankter Heftung, Darmstadt, Fed.Rep. of Germany

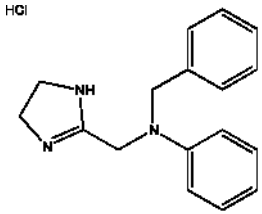
ANTAZOLINE HYDROCHLORIDE

Therapeutic Function: Antihistaminic

Chemical Name: 4,5-Dihydro-N-phenyl-N-(phenylmethyl)-1H-imidazole-2-methanamine hydrochloride

Common Name: Imidamine

Structural Formula:



Chemical Abstracts Registry No.: 2508-72-7; 91-75-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Antistine HCl	Ciba	US	1948
Antistine	Ciba Geigy	France	-
Antistine	Ciba	W. Germany	-
Antasten	Ciba	-	-
Arithmin	Lannett	US	-
Azalone	Smith, Miller and Patch	US	-
Histotab	Boots	UK	-
Phenazoline	Polfa	Poland	-

Raw Materials

2-Chloromethylimidazoline hydrochloride
N-Benzylaniline
Hydrogen chloride

Manufacturing Process

15.4 parts of 2-chloromethylimidazoline hydrochloride, 45.8 parts of N-benzylaniline and 150 parts of alcohol are heated in an oil bath at 100° to 110°C. After distilling off the alcohol, the reaction mass is maintained at this temperature for a further 3 hours and then triturated with water and 10 parts of sodium bicarbonate. The unconsumed benzylaniline is extracted with ether and the aqueous solution neutralized with dilute hydrochloric acid. By evaporating this solution and extracting the residue with alcohol there is obtained 2-(N-phenyl-N-benzylaminomethyl)imidazoline hydrochloride in the

form of colorless crystals of melting point 227° to 229°C.

References

Merck Index 701
Kleeman and Engel p. 57
OCDS Vol. 1 p. 242 (1977)
I .N. p. 91
Miescher, K. and Klarer, W.; US Patent 2,449,241; September 14, 1948; Assigned to Ciba Pharmaceutical Products, Inc.

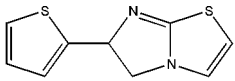
ANTIENITE

Therapeutic Function: Anthelmintic

Chemical Name: Imidazo[2,1-b]thiazole, 5,6-dihydro-6-(2-thienyl)-, (+/-)-

Common Name: Antienite; Thiazothielite

Structural Formula:



Chemical Abstracts Registry No.: 5029-05-0

Trade Name	Manufacturer	Country	Year Introduced
Antienite	Onbio Inc.	-	-
Antienite	ZYF Pharm Chemical	-	-

Raw Materials

2-Iminothiazoline
Acetic anhydride
Thionyl chloride
Oxalic acid dihydrate
Bromomethyl-2-thienylketone
Sodium borohydride
Phosphoroxy chloride

Manufacturing Process

A mixture of 4 parts of 2-iminothiazoline, 8.3 parts of bromomethyl-2-thienylketone and 40 parts of absolute ethanol is stirred and refluxed for 2 hours in a water-bath. After cooling, the precipitated hydrobromide is filtered off. From this salt the free base is liberated on treating with ammonium hydroxide solution and it is extracted with chloroform. The organic extract is separated, treated with activated charcoal, filtered and the filtrate is first dried over magnesium sulfate and then evaporated. The solid residue is recrystallized from 24 parts 2-propanol, to yield 2-imino-3-[(2-thienylearbonyl)-methyl]-thiazoline; MP: 117.5°-118.5°C.

A mixture of 4 parts of 2-imino-3-[(2-thienylcarbonyl)methyl]thiazoline, 50 parts of acetic anhydride and 1.15 parts of sodium acetate is stirred and refluxed for 15 minutes. The formed sodium bromide is filtered off. From the filtrate, the excess of acetic anhydride is distilled and the residual solid is recrystallized from 2-propanol. The solid is filtered off and dried in vacuum, yielding 2-(acetylimino)-3-[(2-thienylcarbonyl)methyl]thiazoline; MP: 146°-147.5°C.

To a stirred mixture of 13 parts of 2-(acetylimino)-3-(2-thienylcarbonyl)methyl]thiazoline hydrobromide and 64 parts of ethanol are added portion wise 3 parts of sodium borohydride (exothermic reaction). After the addition is complete, the whole is stirred and refluxed for one hour. The solvent is evaporated. The solid residue is dissolved in hydrochloric acid 4 N. After keeping at room temperature, it crystallizes again. The solid is filtered off and dissolved in water. The aqueous solution is rendered alkaline with ammonium hydroxide and extracted with chloroform. The chloroform extract is dried over magnesium sulfate and evaporated. The solid residue is recrystallized twice: first from 4-methyl-2-pentanone and once more from 400 parts of water. After drying in vacuum, DLl-2-(acetylimino)-3-[2-hydroxy-2-(2-thienyl)ethyl]thiazoline is obtained; MP: 132.5°-133°C.

A solution of 2 parts of DL-2-(acetylimino)-3-[2-hydroxy-2-(2-thienyl)ethyl]thiazoline in 16 parts of thionylchloride and 45 parts chloroform is stirred and refluxed for one hour. After cooling the whole is extracted with water. The acid aqueous solution is separated, washed with toluene, alkalized with ammonium hydroxide solution and extracted with chloroform. The extract is dried over magnesium sulfate and evaporated. The oily residue is dissolved in 40 parts boiling 2-propanol. To this warm solution is added a warm solution of an equivalent quantity of oxalic acid dihydrate in 2-propanoL After cooling to room temperature, the precipitated oxalate is filtered off and dried in vacuum, yielding DL-5,6-dihydro-6-(2-thienyl)imidazo[2,1-b]thiazole oxalate; MP: 192°-193°C.

A mixture of 6 parts DL-2-(acetylimno)-3-[2-hydroxy-2-(2-thienyl)ethyl]thiazoline and 80 parts phosphoroxy-chloride is heated in a water-bath for 2 hours at a temperature of 100°C. On cooling, the reaction mixture is poured into water. The whole is alkalized with ammonium hydroxide solution and extracted with toluene. The extract is dried over magnesium sulfate and evaporated in vacuum. The oily residue is dissolved in 40 parts boiling 2-propanol. To this warm solution is added a warm solution of an equivalent quantity of oxalic acid dihydrate in 2-propanol. After cooling to room temperature, the precipitated salt is filtered off and dried in vacuum, yielding DL-5,6-dihydro-6-(2-thienyl)imidazo[2,1-b]thiazole oxalate; MP: 193°-194°C.

An aqueous solution of this salt is alkalized with ammonium hydroxide and extracted with toluene. The extract is dried over magnesium sulfate and evaporated. The oily residue is crystallized from 12 parts xylene. The solid is filtered off and dried in vacuum, yielding DLl-5,6-dihydro-6-(2-thienyl)imidazo[2,1-b]thiazole; MP: 58°-62°C.

To a solution of 1.2 parts of DL-5,6-dihydro-6-(2-thienyl)imidazo[2,1-b]thiazole in 24 parts acetone is added a slight excess of a solution of hydrogen chloride in 2-propanol. The oily precipitate solidifies on seeding with

the solid hydrochloride salt and scratching. The salt is filtered off and dried, to yield DL-5,6-dihydro-6-(2-thienyl)imidazo[2,1-b]thiazole hydrochloride; M.P. 159°-160.5°C.

References

Raenmaekers A. et al.; US Patent No. 3,274,209; Sept. 20, 1966; Assigned to Janssen Pharmaceutica N.V., a corporation of Belgium

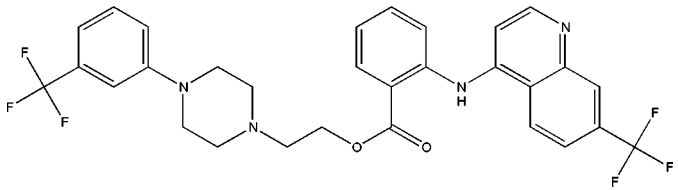
ANTRAFENINE

Therapeutic Function: Analgesic

Chemical Name: 2-(4'-m-Trifluoromethylphenylpiperazino)ethyl 2-(7'-trifluoromethyl-4'-quinolylamino)benzoate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 55300-29-3

Trade Name	Manufacturer	Country	Year Introduced
Stakane	Dausse	France	1977

Raw Materials

Allyl 2-(7'-trifluoromethyl-4'-quinolinylamino)benzoate
2-(4'-m-Trifluoromethylphenylpiperazino)ethanol
Sodium

Manufacturing Process

A mixture of 18.65 g (0.05 mol) of allyl 2-(7'-trifluoromethy-4'-quinolylamino)benzoate, 16.2 g (0.059 mol) of 2-(4'-m-trifluoromethylphenylpiperazino)ethanol, 150 ml of anhydrous toluene and 0.03 g of sodium is heated under reflux for 2 ½ hours, while the allyl alcohol formed during the reaction is slowly removed by distillation. A slight amount of insoluble matter is filtered off and the toluene is evaporated from the filtrate. The residue is dissolved in a mixture of methylene chloride and acetone (8:2) and this solution is passed through a silica column. Elution is carried out with the same mixture of solvents and the eluate is collected in 50

ml fractions. These fractions are examined by thin layer chromatography. Those which contain the desired almost pure ester are combined and the solvent is driven off from them. The residual product is triturated in a mixture of ether and petroleum ether, filtered off and dried. 16.8 g (yield 57%) of 2-(4'-m-trifluoromethylphenylpiperazino)ethyl 2-(7'-trifluoromethyl-4'-quinolylamino)benzoate, melting point 88° to 90°C, are thus isolated.

References

Merck Index 746
DFU 2 (12) 786 (1977)
Kleeman and Engel p. 57
DOT 14 (2) 55 (1978)
I.N. p. 94
Giudicelli, D.P.R.L., Najer, H., Manory, P.M.J. and Dumas, A.P.F.; US Patent 3,935,229; January 27, 1976; Assigned to Synthelabo

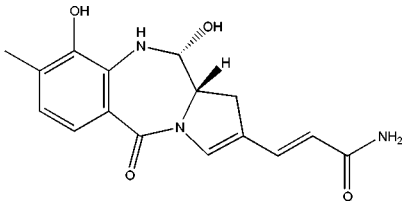
ANTRAMYCIN

Therapeutic Function: Antineoplastic

Chemical Name: 2-Propenamide, 3-(5,10,11,11a-tetrahydro-9,11-dihydroxy-8-methyl-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-yl)-, (11R-[2(E),11α11aβ])-

Common Name: Anthramycin; Antramycin; Refuin

Structural Formula:



Chemical Abstracts Registry No.: 4803-27-4

Trade Name	Manufacturer	Country	Year Introduced
Anthramycin	ZYF Pharm Chemical	-	-
Antramycin	Onbio Inc.	-	-

Raw Materials

Streptomyces sp. NRRL 1143
Bacto yeast extract
Enzyme hydrolyzed casein
Bacto tryptone
Bacto soytone
Enzyme hydrolyzed soy protein

Manufacturing Process

Several loopfuls of spores of Streptomyces sp. NRRL 1143 are transferred from a mature (2-3 day old) 45° stock agar slant to 100 ml of germination medium composed as follows in g/liter:

Bacto tryptone	5 g
Bacto yeast extract	2 g
Bacto soytone	2 g
Soluble starch	10 g
Mannitol	5 g
Magnesium sulfate·$7H_2O$	200 mg
Ferrous ammonium sulfate·$6H_2O$	10 mg
Zinc chloride	2.1 mg
Manganous chloride·$4H_2O$	1.8 mg
Copper sulfate·$5H_2O$	0.3 mg
Cobalt nitrate·$6H_2O$	0.5 mg
Boric acid	0.6 mg

The medium is contained in a 1000 ml Pyrex Blake mottle. After inoculation the medium is incubated at 45°C with constant vigorous agitation, on a rotary shaker for 16 hours. During this period a vigorous growth of the organism ensues. The contents of two such incubated Blake bottles are pooled into a 500 ml Pyrex inoculum transfer bottle fitted with a tubulature at the bottom and containing 150 ml of sterile water.

The entire contents of the inoculum transfer bottle are transferred to a 100-gallon stainless steel fermentor, which is prepared for it as follows:

To 25 gallons of clean tap water contained in a stainless steel fermentor fitted for controlled agitation, aeration, and temperature control are added the following inegredients:

Potato starch	1500 g
Bacto yeast extract	2 g
Enzyme hydrolyzed casein	750 g
Enzyme hydrolyzed soy protein	300 g
Aqueous extract of yeast	300 g
Mannitol	750 g
Magnesium sulfate·$7H_2O$	30 g
Ferrous ammonium sulfate·$6H_2O$	1.5 g
Zinc chloride	315 mg
Manganous chloride·$4H_2O$	270 mg
Copper sulfate·$5H_2O$	45 mg
Cobalt nitrate·$6H_2O$	75 mg
Boric acid	90 mg
Dow Coming Silicone A emulsion	2.5 g

When all the ingredients are dissolved the volume is brought to 40 gallons (150 liters) with tap water and the pH adjusted to 7.2 with about 60 ml of 5 N potassium hydroxide. The fermentor is then closed and the contents sterilized by being brought to a temperature of 120°C and maintained at that

temperature from 30-40 minutes. The batch is then cooled to 48°C and inoculated as described above. After inoculation the batch is aerated with 3 cubic feet per minute of sterile air and agitated at a shaft speed of 400 r.p.m., the while maintaining a temperature of 48°C. Foam is controlled by the addition, as needed, of a sterile 2.5% suspension of Dow Silieone Emulsion AF. About 3000 ml of defoamer suspension is used during the batch. Hourly samples are taken aseptically from the 12th hour on and assayed for in vitro potency. This batch reaches its maximum potency in 18-20 hours.

The above process is repeated ten times, the broths obtained are combined, the pH is adjusted to 6, the combined broths are filtered, and the resulting filtrate is extracted countercurrently at the rate of 128 gallons per hour with about the same rate of butanol, in a 12" diameter by 11 ft. high Karr extraction column. A water backwash of 0.2 times the butanol rate is employed at the top of the extraction column to minimize the carry-over of water soluble components. The butanol extract is concentrated to approximately a 5% solution which comprises the feed to the center of a 3" diameter by 20 ft. high Karr fractional liquid extraction column. This column is operated at a water to butanol ratio of about 10 to 1, and the butanol extract contains the product. The butanol extract is concentrated by evaporation to a solution or paste containing about 5 to about 20% ent solids; then about 25 to about 50 volumes of n-hexane are added, and the resulting slurry filtered. The precipitated product is then vacuum-dried to give a solid compound.

7 g of the product prepared by the above process is dissolved in 350 ml of chloroform-isopropanol (1:1) which was previously equilibrated with water. This solution is introduced into the center of a one-inch diameter by twenty-foot high Karr extraction column at the rate of 0.5 ml/min. Simultaneously 60 ml/min of equilibrated aqueous phase is introduced at the bottom of the column and 14.6 ml/min of equilibrated solvent phase is introduced at the top of the column. Most of the product is extracted into the aqueous phase leaving the top of the column. The aqueous phase is re-extracted countercurrently in a one-inch diameter by ten-foot high extraction column employing a 1:1 isopropanol-chloroform solvent at a solvent to water ratio of 1:1. The product passes into the isopropanol-chloroform solvent, which leaves at the bottom of the extraction column. This solution is concentrated to 58 ml, filtered, and then treated with 2.9 liters of technical hexane to precipitate the product. The product is filtered and dried. The dried product, which is 90% pure is crystallized from acetone to yield a highly active purified material.

20 g of the product above was distributed between 120 ml each of upper and lower phases of a solvent system consisting of isopropanol;chloroform: water (1:1:2). The phases were then introduced into the first three tubes of a 200-tube Craig countercurrent distribution apparatus and run at room temperature for 197 transfers. The upper and lower phases of tubes 45 to 75 were combined, the organic phase evaporated at a temperature below 35°C in vacuum and the residue added to the corresponding aqueous phase, and the aqueous phase lyophylized. The lyophylized residue was crystallized from acetone to yield a purified antibiotic antramycin.

Yellow prisms decomposed at 188°-194°C; $[\alpha]_D^{25}$ = +930° (DMF).

References

Berger J. et al.; US Patent No. 3,361,742; January 2, 1966; Assigned to Hoffmann-La Roche Inc.,Nutley, N.J.,a corporation of New Jersey

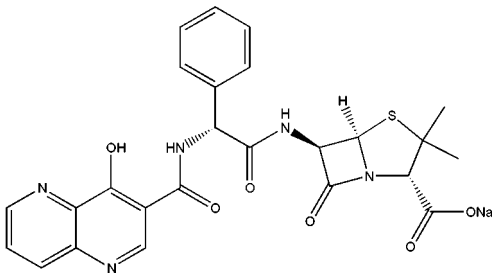
APALCILLIN SODIUM

Therapeutic Function: Antibacterial

Chemical Name: 6-[[[[(4-Hydroxy-1,5-naphthyridin-3-yl)carbonyl] amino]phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0]heptane-2-carboxylic acid sodium salt

Common Name: D-α-(4-Hydroxy-1,5-naphthyridine-3-carbonamido) benzylpenicillin sodium

Structural Formula:



Chemical Abstracts Registry No.: 58795-03-2; 63469-19-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Lumota	Thomae	W. Germany	1982

Raw Materials

Phenacyl-6-aminopenicillate hydrochloride
D-Phenylglycyl chloride hydrochloride
4-Hydroxy-1,5-naphthyridine-3-carboxylic acid N-succinimide ester
Sodium bicarbonate
Sodium thiophenoxide
Triethylamine

Manufacturing Process

(a) Preparation of 6-D-α-aminobenzylpenicillin phenacyl ester: To a suspension of phenacyl 6-aminopenicillanate hydrochloride (1.85 g) and D-phenylglycyl chloride hydrochloride (1.29 g) in dichloromethane (20 ml), sodium bicarbonate (1.05 g) was added, and the resultant mixture was stirred

while cooling with ice for 6 hours. The reaction mixture was filtered to eliminate the by-produced sodium chloride. The filtrate was admixed with isopropanol and concentrated under reduced pressure by the aid of a rotary evaporator. After the evaporation of dichloromethane, the precipitate was collected by filtration to give the objective compound in the form of the hydrochloride (2.19 g) MP 142° to 148°C (decomposition).

(b) Preparation of D-α-(4-hydroxy-1,5-naphthyridine-3-carbonamido)benzylpenicillin: To a solution of 6-D-α-aminobenzylpenicillin phenacyl ester (hydrochloride) (2.01 g) and triethylamine (0.808 g) in dimethylformamide (20 ml), 4-hydroxy-1,5-naphthyridine-3-carboxylic acid N-succinimide ester [MP 310° to 311°C (decomposition)] (1.15 g) was added while cooling with ice, and the resultant mixture was stirred for 1 hour. Stirring was further continued at room temperature for 2 hours. After cooling with ice, 1% sodium bicarbonate solution (100 ml) was added thereto. The precipitated crystals were collected by filtration, washed with water and dried over phosphorus pentoxide to give D-(α-4-hydroxy-1,5-naphthyridine-3-carboxamido)benzylpenicillin phenacyl ester (2.17 g).

The above product was dissolved in dimethylformamide (65 ml), sodium thiophenoxide (0.89 g) was added thereto, and the resultant mixture was stirred at room temperature for 1 hour. To the resultant mixture, acetone (650 ml) was added, and the separated crystals were collected by filtration and washed with acetone and ether in order to give the objective compound in the form of the sodium salt (1.3 g).

In the above procedure, the use of 4-hydroxy-1,5-naphthyridine-3-carbonyl chloride in place of 4-hydroxy-1,5-naphthyridine-3-carboxylic acid N-succinimide ester can also afford the same objective compound as above. The use of sodium thio-n-propoxide in place of sodium thiophenoxide can also give the objective compound in the form of the sodium salt.

References

Merck Index 748
DFU 4 (3) 225 (1979)
DOT 19 (2) 110 (1983)
I.N. p. 94
Yamada, H., Tobiki, H., Nakatsuka, I., Tanno, N., Shimago, K. and Nakagome, T.; US Patent 4,005,075; January 25, 1977; Assigned to Sumitomo Chemical Co., Ltd.

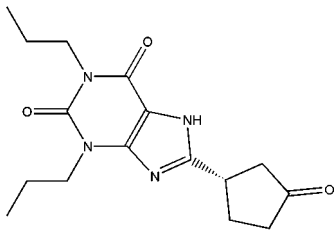
APAXIFYLLINE

Therapeutic Function: Adenosine A_1-antagonist, Nootropic

Chemical Name: (S)-3,7-Dihydro-8-(3-oxocyclopentyl)-1,3-dipropyl-1H-purine-2,6-dione

Common Name: Apaxifylline

Structural Formula:



Chemical Abstracts Registry No.: 151581-23-6

Trade Name	Manufacturer	Country	Year Introduced
Apaxifylline	Boehringer Ingelheim/Upjohn	-	-

Raw Materials

3-Oxocyclopentancarboxylic acid methyl ester
Carbonyldiimidazole
1,6-Diamino-1,3-di-n-propyluracil

Manufacturing Process

1,3-Dipropyl-8-(3-oxocyclopentyl)xanthyne:

1). 100 g 3-oxocyclopentancarboxylic acid methyl ester (0.7 moles) was heated with 1000 ml of 2 M hydrochloric acid to reflux for 10 hours. On cooling the solution was evaporated in vacuum. Residual water was removed by azeotropic dehydratation. The residue was distilled in high vacuum to give 3-oxocyclopentancarboxylic acid as colorless oil, b.p.: 116°-121°C/0.002 mm; yield 74.0 g (82 %).

2). 11.6 g carbonyl diimidasole was added to 8.8 g 3-oxocyclopentancarboxylic acid (0.072 moles) in 240 ml methylene chloride at 20°-25°C and stirred for 2 hours at room temperature. Then 16.0 g 1,6-diamino-1,3-di-n-propyluracil (0.072) at 20°-25°C was added and was stirred 3 hours at room temperature. The mixture was evaporated in vacuum to dryness. The residue oil was diluted with 3200 ml water, 35 g of calcium hydroxide was added and all taken was heated at 80°C for 0.5 hour by stirring. The mixture was cooled to 5°C, acidified with pH 1-2 with hydrochloric acid and extracted with CH_2Cl_2 (3x100 ml). The organic phase was washed with 1x100 ml water and dried over magnesium sulfate. The solution was purified with of 350 g silica gel S 160. CH_2Cl_2 : CH_3OH (99:1) was used as eluent. Refined residue was evaporated and treated with 100 ml ether. 11.5 g 1,3-dipropyl-8-(3-oxocyclopentyl)xanthyne (apaxifylline) obtained (50.2 %). MP: 164-168°C.

References

Kufter-Muuhl U. et al.; Europe Patent No. 0,374,808; Dec. 18, 1989; Boehringer Ingelheim International G.M.B.H.

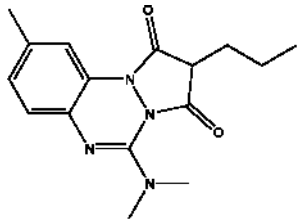
APAZONE

Therapeutic Function: Antiarthritic

Chemical Name: 5-(Dimethylamino)-9-methyl-2-propyl-1H-pyrazolo[1,2-a][1,2,4]benzotriazine-1,3(2H)-dione

Common Name: Azapropazone

Structural Formula:



Chemical Abstracts Registry No.: 113539-598

Trade Name	Manufacturer	Country	Year Introduced
Prolixan	Siegfried	W. Germany	1970
Prolixan	Siegfried	Switz.	1970
Cinnamin	Nippon Chemiphar	Japan	1971
Rheumox	Robins	UK	1976
Prolixan	Logeais	France	1976
Prolixan	Malesci	Italy	1977
Prolixan	Embil	Turkey	-
Prodisan	Embil	Turkey	-
Prodisan	Roche	-	-
Prolix	Roche	-	-
Prolixano	Leo	-	-
Rheumox	Robins	US	-
Xani	Farmakos	Yugoslavia	-

Raw Materials

3-Dimethylamino-(1,2-dihydro-1,2,4-benzotriazine)
Diethyl propyl malonate
Sodium
Triethylamine
3-Dimethylamino-1,2,4-benzotriazine oxide
Propyl malonyl chloride
Hydrogen

Manufacturing Process

The following describes two alternatives for the synthesis of the closely related butyl analog.

Alternative (a): In a three-neck flask with descending condenser to 3.8 grams of 3-dimethylamino-(1,2-dihydro-1,2,4-benzotriazine) are added 0.52 gram metallic sodium, dissolved in a small volume of absolute alcohol, 4.5 g of diethylbutylmalonate (diethylpropylmalonate for Apazone) and 15 ml of xylene, in a nitrogen atmosphere. The mixture is heated for 2 hours to 70°C, then for 3 hours to 110-130°C and for one more hour to 150°C, slowly distilling off the alcohol and most of the xylene. To the resulting light brown colored mass are added 200 ml of water. The resulting solution is extracted twice with ether or benzene and afterwards acidified with HCl. Yield 3.6 g of 1,2-butylmalonyl-3-dimethylamino-(1,2-dihydro-1,2,4-benzotriazine). After crystallization from alcohol the melting point is 189-190°C.

Alternative (b): 3-Dimethylamino-1,2,4-benzotriazine oxide is shaken in the presence of Raney nickel in 15 volume parts of an alcohol-acetic acid (9:1) mixture in a hydrogen atmosphere. The mixture absorbs 2 mols hydrogen per 1 mol starting material. Hydrogenation can also be effected using a palladium catalyst with a suitable solvent. After reduction it is filtered on a Buchner-funnel through a Hyflow-layer and the solvent is evaporated in vacuum under nitrogen. The residue is dissolved in 20 parts of water-free dioxane and treated at 60°C with the calculated amount of butylmalonyl chloride (propyl malonyl chloride for Apazone) (1 mol/mol) and triethylamine (2 mol/mol). The separated triethylamine hydrochloride is filtered, the dioxane-solution is evaporated under vacuum to dryness, and the residue is dissolved in 7 volume parts of boiling acetic acid. After cooling, the product separates in lightly yellowish crystals. They are dissolved in the calculated amount of 0.25 N NaOH, treated with a small amount of carbon and precipitated with HCl. Melting point of the purified product is 187°C. Yield: approximately 60% of the theoretical amount.

References

Merck Index 750
Kleeman and Engel p. 66
OCDS Vol. 2 p. 475 (1980)
I.N. p. 110
Molnar, I., Wagner-Jauregg, T., Jahn, U. and Mixich, G.; US Patent 3,349,088; October 24, 1967; Assigned to Siegfried AG, Switzerland
Molnar, I., Wagner-Jauregg, T., Jahn, U. and Mixich, G.; US Patent 3,482,024; December 2, 1969; Assigned to Siegfried AG.

APICYCLINE

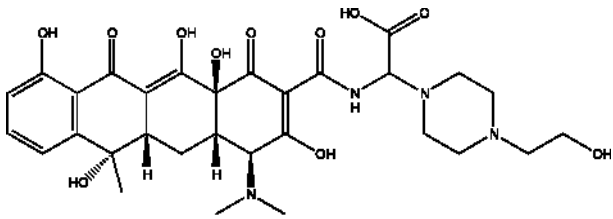
Therapeutic Function: Antibiotic

Chemical Name: α-(4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamido)-4-(2-hydroxyethyl)-1-piperazineacetic acid

Common Name: Apicycline; Traserit

Chemical Abstracts Registry No.: 15599-51-6

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Travert	Baxter	-	-
Travert	Pharmacia Upjohn	-	-

Raw Materials

Glyoxylic acid monohydrate
N-(2-Hydroxyethyl)piperazine|
Tetracycline base trihydrate

Manufacturing Process

Glyoxylic acid monohydrate (1.96 g, 20 mrnoles) is dissolved in 200 ml of methanol, and a solution of 2.60 g (20 mmoles) of N-(2-hydroxyethyl) piperazine in 50 ml of methanol is slowly added thereto with stirring.

Stirring is maintained for 15 minutes and the medium is cooled to 5°C. There is then added 10.2 g (20 mmoles) of tetracycline base trihydrate and the reaction medium is maintained for 20 hours at 5°C under stirring. After that reaction time, the solution is concentrated up to 50 ml and 0.25 liter of acetone is added for precipitating a yellowish product which is filtered and dried to yield N-[(carboxy)(4-β-hydroxyethylpiperazino)methyl] tetracycline (apicycline).

When tested for antibiotic potency against Bacillus cereus var. mycoides ATCC 9634 (diffusion method), the product is shown to present an antibiotic potency equivalent to 97% of the tetracycline present therein.

Anhydrous tetracycline base (0.90 g, 2 mmoles) is dissolved in 30 ml of n-butanol at about 40°C. There is then added thereto under stirring a solution of 0.26 g (2 mmoles) of N-(2-hydroxyethyl)piperazine in 10 ml of butanol and 0.191 g (2 mmoles) of glyoxylic acid monohydrate. A precipitate appears after a few minutes and the suspension is maintained for six hours under stirring and at room temperature.

After that reaction time, precipitation is completed by addition of 120 ml of ether. The yellowish precipitate is filtered and dried to yield N-[(carboxy)(4-β-hydroxyethylpiperazino)methyl]tetracycline (apicycline). Yellow, amorphous powder with slight amine odor, MP: 144.5°C (dec). Freely solves in water. $[\alpha]_D$ =-123° (c = 0.5 in methanol); $[\alpha]_D$ =-133° (c = 0.5 in water).

The pH value of a 2% aqueous solution of this product is 6.2. When tested for antibiotic potency against Bacillus cercus var. mycoides ATCC 9634 (diffusion method), the product is shown to present an antibiotic potency equivalent to 95% of the tetracycline present therein.

References

Rondelet J.; US Patent No. 3,456,007; July 15, 1969; Assigned to Recherche et Industrie Therapeutiques R.I.T., Genval, Belgium, a corporation of Belgium

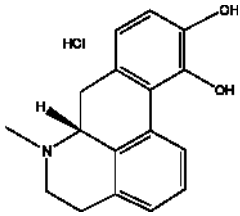
APOMORPHINE HYDROCHLORIDE

Therapeutic Function: Emetic, Expectorant, Hypnotic, Antiparkinsonian, Dopamine agonist

Chemical Name: 4H-Dibenzo(de,g)quinoline-10,11-diol, 5,6,6a,7-tetrahydro-6-methyl-, (R)-, hydrochloride

Common Name: Apafinum; Apomorfin; Apomorphine

Structural Formula:



Chemical Abstracts Registry No.: 314-19-2; 58-00-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Apomorphine hydrochloride	Nastech Pharmaceuticals Company, Inc.	-	-
Apofin	Chiesi Farmaceutici	-	-
Apofin	Amro Trust Company (Suisse) SA	-	-
Apokyn	Mylan Bertek Pharmaceuticals	-	-
Apokyn	Bertek Pharmaceuticals	-	-
Apokinon	Aguettant	-	-
Apomine	Faulding	-	-
Britaject	Britannia	-	-
Ixense	Takeda	-	-
Uprima	Abbott Laboratories	-	-

Raw Materials

Morphine
Phosphoric acid
Hydrogen hydrochloride

Manufacturing Process

2 Methods of producing of apomorphine

1. The apomorphine was obtained by dehydratation of morphine at heating to 120°C in the presence phosphoric acid and rendering of HCl gas over reaction mixture.

2. The morphine was converted to β-chloromorphine and then to dichlorodihydrodesoxymorphine at heating to 140°-150°C in the presence hydrochloric acid. Then apomorphine is obtained by dehydratation of dichlorodihydrodesoxymorphine.

References

Chaletsky A.M.; Pharmaceutical chemistry, Medicina, L., 1966, 761p.
Belikov V.G.; Pharmaceutical chemistry, Pyatigorsk, 2003, 713p.
Fiser L., Fiser M.; The chemistry of natural compounds of phenantren line. 1953, 656 p.

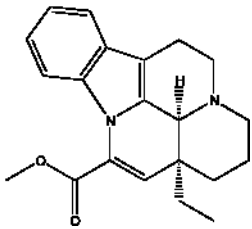
APOVINCAMINE

Therapeutic Function: Vasodilator

Chemical Name: Eburnamenine-14-carboxylic acid methyl ester, (3α,16α)-

Common Name: Apovincamine

Structural Formula:



Chemical Abstracts Registry No.: 4880-92-6

Trade Name	Manufacturer	Country	Year Introduced
Apovincamine	GC Promochem	-	-

Raw Materials

Vincamine
Tartaric acid, dibenzoate, (-)-

Manufacturing Process

Apovincamine is semisynthethetic derivative of (+)-vincamine. Vincamine is alkaloid of Vinca minor. Alcoloid of Tabernaemontana rigida (Apocynaceae) also is used as raw material for preparing of apovincamine. (+)- Vincamine was transformed into oxime ester by reaction with $NaNO_2$ in acetic acid at 0°C -(+/-)-methyl-3-((12bR)-1-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-1-yl)-2-(hydroxyimino)propanoate, which was resolved on the isomers with dibenzoyl D-tartratic acid. (-)-Methyl 3-((12bR)-1-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-1-yl)-2-(hydroxyimino)propanoate was re-crystallized from methanol to afford (-)-methyloxime ester, MP: 195°C.

2 g of above oxime methyl ester was heated in mixture of methanol (37.5 ml) and conc. H_2SO_4 (13.5 ml) on water bath for 1 hour. The solution was poured into ice-water (80 ml), basified with conc. NH_4OH to pH 9, and extracted with CH2Cl2 (3x20 ml). The combined extracts were dried ($MgSO_4$), filtered, evaporated in vacuum and the residue was re-crystallized from MeOH (5 ml) to yield 1.32 g (72.5%) of (+)-apovincamine, MP: 160°-162°C.

References

Szabo L. et al., Tetrahedron; V. 39, No 22, pp 3737-3737; 1983

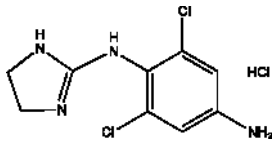
APRACLONIDINE HYDROCHLORIDE

Therapeutic Function: Antiglaucoma

Chemical Name: 1,4-Benzenediamine, 2,6-dichloro-N^1-(4,5-dihydro-1H-imidazol-2-yl)-, hydrochloride

Common Name: p-Aminoclonidine hydrochloride; Apraclonidine hydrochloride; Aplonidine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 73218-79-8; 66711-21-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Alfadrops	Cipla Limited	India	-
Iopidine	Alcon	-	-

Raw Materials

2,6-Dichloro-4-nitroaniline
t-Butyl methyl ether
Methanol
Ethylenediamine
Hexane
Nickel Raney
Thiophosgene
2-Propanol
Toluene

Manufacturing Process

The preparation of p-aminoclonidine (apraclonidine) consists of 6 steps.

In the first step 2,6-dichloro-4-nitroaniline was converted to 2,6-dicloro-4-nitrophenylisothiocyanate by addition of thiophosgene in toluene according to the method described in Great Britain Patent No.: 1,131,780 (Beck et al.).

The second step involved the conversation of 2,6-dichloro-4-nitrophenyl-isothiocyanate to 1-(2-aminoethyl)-3-(2,6-dichloro-4-nitrophenyl)-thiourea ethylenediamine solvate. The solution of 2,6-dicloro-4-nitrophenyl-isothiocyanate (432 g, 1.73 mol) in 2 L of toluene was added dropwise to the cooled (0°C) solution ethylenediamine (244 ml, 3.66 mol, 2.1 eq.) in toluene (4 L) under a nitrogen atmosphere. 2-Propanol (1 L) was added and after 5 minutes, the solid was collected by filtration, washed with 20% 2-propanol/toluene, and dried to a constant weight of 602 g (94%). This product is hygroscopic, mp 120°C (dec.).

The third step was the conversation of 1-(2-aminoethyl)-3-(2,6-dichloro-4-nitrophenyl)-thiourea ethylenediamine solvate to 2-[(2,6-dicloro-4-nitrophenyl)imino]imidazoline ethylenediamine solvate. (500 g, 1.35 mol) of above prepared thiourea solvate was suspended with toluene (4 L) and was heated at reflux for 15 hours. The mixture was cooled to 23°C and 1 M aqueous hydrochloric acid (4 L) was added. After stirring for 10 min the biphasic mixture was filtered to remove a sticky insoluble material. The aqueous phase was neutralized to pH=7.0 using 50% NaOH. After stirring for 1 hour the yellow solid was collected by filtration, washed with water (4 L) and t-butyl methyl ether (2 L) and dried in air to constant weight of 195 g (52%), m.p. 289-292°C.

The fourth step was the conversation of 2-[2,6-dichloro-4-nitrophenyl) imino]imidazoline (150 g, 0.55 mol) in methanol (1,5 L) to 2-[(2,6-dichloro-4-aminophenyl)imino]imidazoline by hydrogen with 30 g Raney nickel catalyst at 23°C for 22 hours. After removing the catalyst hydrogen chloride gas was bubbled into solution until pH of the reaction mixture was 1.0. The solvent was rotary removed in vacuum and the residual solid was slurried with 2-propanol (1 L). The solvent was again removed by rotary evaporation, the cream solid was triturated with 2-propanol (600 ml). After aging for 1 hour, the solid was collected by filtration, washed with 2-propanol and t-butyl methyl ether, and dried for 15 hours at 6°C and t-butyl methyl ether, and dried for 15 hours at 60°C and 20 mm Hg. Yield of dihydrochloride 167 g

(96%), mp 260°C (dec.).

The dihydrochloride was converted to the monochloride (step 5) by adding 5 M aqueous sodium hydroxide dropwise to pH=6.5 at 5°C for 2 hours. Yield of hydrochloride 87%.

The last step was recrystallization of product from water. The recrystallized material had m.p. 300°C. Calculated for: $C_9H_{10}Cl_2N_4HCl$: C, 38.39; H, 3.94; N, 19.90; Cl, 37.78. Found: C, 38.36; H, 3.91; N, 19.83; Cl, 37.77.

References

Councel, J. Med Chem., v 30, p.1214 (1987)
Pierce D.R., Dean W.D., Deason M.E.; Patent WO9521818; 17.08.1995; Assigned to Alcon Laboratories Inc.

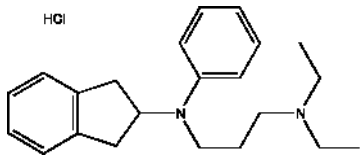
APRINDINE HYDROCHLORIDE

Therapeutic Function: Antiarrhythmic

Chemical Name: N-[3-(Diethylamino)propyl]-N-phenyl-2-indanamine hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 33237-74-0; 37640-71-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Amidonal	Madaus	W. Germany	1976
Fiboran	Sedaph	France	1977
Fibocil	Lilly	US	-
Fiboran	Christiaens	Belgium	-
Ritmusin	Gebro	Austria	-

Raw Materials

N-Phenyl-2-aminoindane
Sodium hydroxide
Hydrogen chloride
γ-Chloropropyl diethylamine
Sodium amide

Manufacturing Process

104.6 g (0.5 mol) N-phenyl-2-aminoindane and 2.5 liters benzene are introduced into a reaction vessel of 5 liters, under an atmosphere of nitrogen. 37 g (0.95 mol) sodium amide are added and the mixture is stirred during 3 hours at room temperature.

119.7 g (0.8 mol) of γ-chloropropyl diethylamine are then quickly added. After agitation during 1 hour at room temperature, the reaction mixture is refluxed and stirred under nitrogen during 21 hours. The mixture is then allowed to cool and poured onto ice. The obtained aqueous phase is extracted by means of 500 cm3 of benzene. The benzene extract is washed two times with 200 cm^3 of water and the benzene is then evaporated.

The residue is treated with 500 cm^3 of hydrochloric acid (2 N). The obtained solution is evaporated to dryness and the oily residue is recrystallized from ethanol. 176.9 g (yield 89.4%) of dihydrochloride of N-phenyl-N-diethylaminopropyl-2-aminoindane are obtained, MP 208° to 210°C.

The dihydrochloride is converted into monohydrochloride by dissolving 26.36 g (0.066 mol) of dihydrochloride into 158 cm^3 of water, adding drop by drop a suitable amount (0.066 mol) of caustic soda (1 N), evaporating the aqueous solution to dryness, drying by means of benzene, filtering the formed sodium chloride (3.8 g) and crystallizing the cooled obtained benzene solution. 22.6 g (95%) of monohydrochloride are obtained, MP 120° to 121°C.

References

Merck Index 776
Kleeman and Engel p. 58
OCDS Vol. 2 p. 208
DOT 10 (4) 120 (1974)
REM p. 860
Vanhoof, P. and Clarebout, P.; British Patent 1,321,424; June 27, 1973; Assigned to Manufacture de Produits Pharmaceutiques A. Christiaens, SA

APROBARBITAL

Therapeutic Function: Sedative, Hypnotic

Chemical Name: 5-Allyl-5-isopropylbarbituric acid

Common Name: Allopropylbarbital; Allylcarbamidum; Allypropymal; Aprobarbital; Aprobarbitone

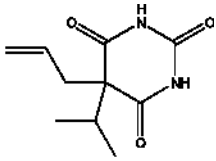
Chemical Abstracts Registry No.: 77-02-1

Raw Materials

Isopropylbarbituric acid

Sodium hydroxide
Allyl bromide

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Alurate	Roche	-	-
Aprobarbital	Arocor Holdings Inc.	-	-
Isonal	Leo	-	-

Manufacturing Process

170 parts of isopropylbarbituric acid are mixed with 500 parts of water and dissolved by adding 135 parts of a 30 percent of the solution of sodium hydroxide. To this solution are added 130 parts of 130 parts of allylbromide. An emulsion obtained is stirred at an inner temperature of about 25°C. The reaction is at first accompanied by a slight development of heat. After 12 hours the reaction is brought to a close. When cooled down the isopropylallylbarbituric acid is drawn off. The yield is more than 80 percent of the theoretically calculated quantity. By crystallization from diluted alcohol the pure isopropylallylbarbituric acid is obtained in colorless crystals of the melting point 137-138°C.

References

Merck Index, Monograph number: 794, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Kurz F. and Kappeler V.W.; US Patent No. 1,444,802; Feb. 13, 1923; Assigned to Ernst Preiswerk

APROFENE

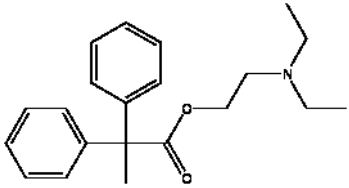
Therapeutic Function: Spasmolytic

Chemical Name: Benzeneacetic acid, α-methyl-α-phenyl-, 2-(diethylamino) ethyl ester

Common Name: Aprofene; Aprophene

Chemical Abstracts Registry No.: 3563-01-7

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Aprofene	ZYF Pharm Chemical	-	-
Aprofene	ICN Pharmaceuticals	-	-

Raw Materials

Diphenylpropionic acid
Thionyl chloride
Diethylaminoethanol
Diphen (CIS prep.)

Manufacturing Process

32 parts of α,α-diphenylpropionic acid chloride (made from diphenylpropionic acid and thionyl chloride, B.P./12 mm 170°C) are mixed with 50 parts of diethylaminoethanol. The mixture is heated for two hours to 150°-160°C. It is then suspended in dilute hydrochloric acid. The solution is treated with ether. After separation of the aqueous solution, the base is precipitated with sodium hydroxide solution and suspended in ether.

After removal of the ether by distillation, the residue is distilled in a vacuum. α,α-Diphenylpropionic acid β-diethylaminoethyl ester is obtained as a thick oil by distilling under 2 mm pressure at 180°-185°C. It is readily soluble in diluted acids.

References

Wander A.; G.B. Patent No. 641,573; Dec. 19, 1947; Switzerland

APROTININ

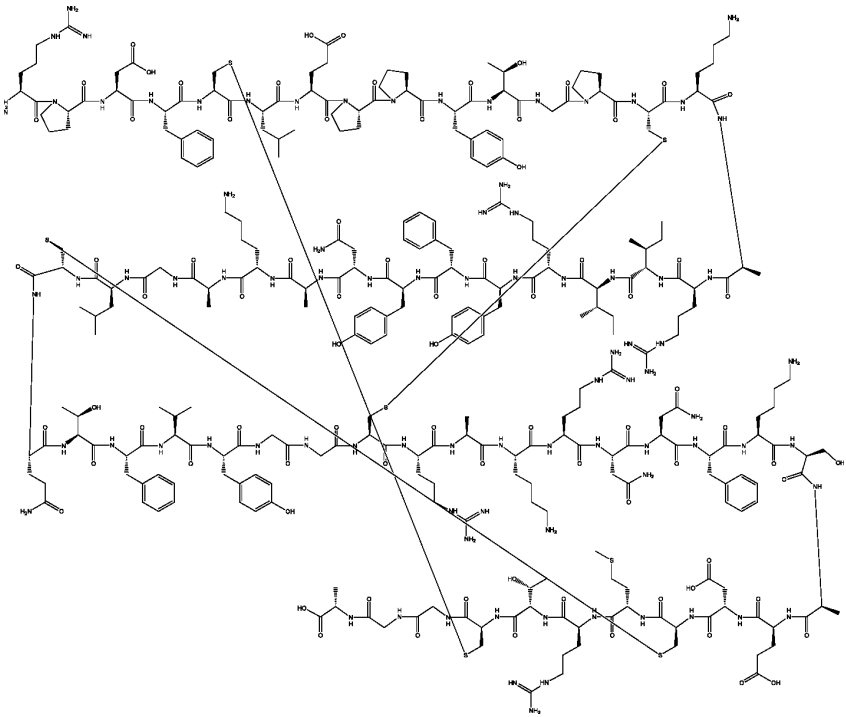
Therapeutic Function: Proteinase inhibitor

Chemical Name: Trypsin inhibitor, pancreatic basic

Common Name: Aprotinin; Frey inhibitor; Kallikrein-trypsin inhibitor

Chemical Abstracts Registry No.: 9087-70-1

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Trasylol	Bayer	-	-
Antagosan	Hoechst Marion R. d.o.o	-	-
Antilysin Spofa	Spofa	-	-
Apronin	Chandra Bhagat Pharma Pvt. Ltd.	-	-
Aprotimbin	Biochemie GmbH	-	-
Contrykal	AWD GmbH and Co.KG	-	-
Gordox	Gedeon Richter	-	-
Iniprol	Sanofi-Winthrop	-	-
Inibil	Sclavo	-	-
Kallikrein-trypsin inhibitor	Bayer	-	-
Kontrikal	Pliva d. d.	-	-
Trasylol	Bayer	-	-

Raw Materials

Parotid of cattle	Acetone
Acetic acid	Ammonia

Manufacturing Process

1 kg of parotid of cattle, which were freed of fat and flesh are comminuted in a meat chopper and twice extracted with 5 L of acetone. The acetone was removed as far as possible by sucking off and the moist material is digested for 2.5 hours in 1.2 L of 1 N acetic acid and 2.8 L of 96% ethanol at 50°C. The filtrate containts about 230.000 inactivator units.

The alcoholic solution is concentrated to 1.2 L by evaporating in vacuo and shaken with an equal amount of ether. Dark coloring matters and residues of fat are thus dissolved. The aqueous phase is now mixed with acetone until a precipitate occurs and the dissolved in dilute acetic acid. The solution is brought to a weakly alkaline pH by addition of ammonia. It is then centrifuged and the inactivator is precipitated with five times the amount of ethanol. The yield amounts to about 180.000 kallikrein inactivator units in 0.4-0.5 g of substance.

References

Kraut H., Koerbel R.; US Patent No. 2,890,986; June 16, 1959; Assigned to Farbenfabriken Bayer Aktiengesellschaft, Leverkusen, Germany, a corporation of Germany

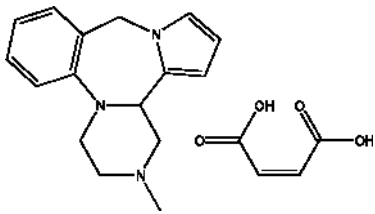
APTAZAPINE MALEATE

Therapeutic Function: Antidepressant

Chemical Name: 2H,10H-Parazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine, 1,3,4,14b-tetrahydro-2-methyl-, maleate (1:1)

Common Name: Aptazapine maleate

Structural Formula:



Chemical Abstracts Registry No.: 71576-40-4 (Base); 71576-41-5

Trade Name	Manufacturer	Country	Year Introduced
Aptazapine maleate	ZYF Pharm Chemical	-	-

Raw Materials

Diborane
N-Potassium phthalimide
Hydrazine hydrate
Chloroacetonitrile
Platinum oxide
Palladium on charcoal
Maleic acid
o-Nitrobenzyl chloride
2,5-Dimethoxytetrahydrofuran
N-Methylbenzylamine
Diethyl oxalate

Manufacturing Process

To the suspension of 12.8 g of 2-methyl-3,4-dioxo-1,3,4,14b-tetrahydro-10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine in 460 ml of tetrahydrofuran, 200 ml of 1-molar diborane in tetrahydrofuran are added while stirring and cooling with ice. The mixture is refluxed for one hour, again cooled and combined with 25 ml of acetic acid. It is evaporated, the residue taken up in 50 ml of 30% aqueous sodium hydroxide and the mixture extracted with methylene chloride. The extract is dried, evaporated, the residue dissolved in diethyl ether, the solution filtered and the filtrate evaporated, to yield the crude 2-methyl-1,3,4,14b-tetrahydro-10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine. It is triturated with ethyl acetate-diethyl ether, chromatographed on 70 g of silica gel and eluted with methanol-chloroform (1:9). The eluate is evaporated and the residue salified.

9.7 g thereof are dissolved in the minimum amount of isopropanol and the solution acidified with a concentrated solution of 4.45 g of maleic acid is isopropanol. The precipitate formed is collected and recrystallized from methanol-diethyl ether, to yield the corresponding mono-maleate melting at 180°-182°C.

The starting material is prepared as follows: the mixture of 54.0 g of N-potassium phthalimide, 50.0 g of o-nitrobenzyl chloride and 120 ml of dimethylformamide is refluxed for 3 hours and poured into 900 ml of ice-water while stirring. After 30 minutes, it is filtered, and the residue washed with water, to yield the N-o-nitrobenzyl-phthalimide melting at 190°-209°C.

The mixture of 70.0 g thereof, 14.6 g of hydrazine hydrate and 600 ml of ethanol is refluxed for 4 hours and combined with 50 ml of concentrated hydrochloric acid. After 30 minutes, it is cooled to room temperature, filtered and the residue washed with water. The filtrate is concentrated, the aqueous concentrate filtered and the filtrate basified with 3 N aqueous sodium hydroxide. It is extracted with diethyl ether, the extract dried and evaporated, to yield the o-nitrobenzylamine.

To the solution of 7.6 g thereof in 25 ml of glacial acetic acid, 6.6 g of 2,5-dimethoxytetrahydrofuran are added and the mixture is refluxed for one hour. It is evaporated, the residue poured into ice water and the mixture extracted with ethyl acetate. The extract is washed with saturated aqueous sodium bicarbonate, dried and evaporated. The residue is taken up in diethyl ether, the solution decolorized with charcoal, filtered and evaporated, to yield the 1-(o-nitrobenzyl)pyrrole.

Through the mixture of 13.42 g thereof, 140 ml of diethyl ether and 6.85 ml of chloroacetonitrile, hydrogen chloride is bubbled while stirring and cooling in

an ice-salt bath. The saturated mixture is stirred at room temperature overnight, filtered and the residue suspended in 100 ml of water. It is extracted 3 times with 100 ml of ethyl acetate, warmed on the steam bath while stirring until all is dissolved, and the solution evaporated, to yield the 1-o-nitrobenzyl-2-chloroacetylpyrrole.

To the solution of 16.2 g thereof in 450 ml of ethanol, 14.10 g of N-methyl-benzylamine are added and the mixture is refluxed for 3 hours. It is evaporated, the residue taken up in methylene chloride, the solution washed with saturated aqueous sodium carbonate dried, filtered and evaporated. The residue is triturated with diethyl ether, to yield the 1-(o-nitrobenzyl)-2-(N-methyl-N-benzylaminoacetyl)pyrrole.

The solution of 3.0 g thereof in 30 ml of glacial acetic acid is hydrogenated over 100 mg of platinum oxide at 2.7 atm and room temperature until the theoretical amount of hydrogen has been absorbed. It is filtered, the filtrate evaporated, the residue taken up in methylene chloride-diethyl ether and the solution washed with saturated aqueous sodium bicarbonate. It is dried, evaporated, the residue chromatographed on 30 g of silica gel and eluted with methanol-chloroform (1:9), to yield the 11-(N-methyl-N-benzylaminomethyl)-10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine melting at 147°-149°C.

The solution of 500 mg thereof in 35 ml of ethanol and 5 ml of glacial acetic acid is hydrogenated over 250 mg of 5% palladium on charcoal at 2.7 atm and 40°C for 7 hours. The mixture is filtered, the filtrate evaporated and the residue taken up in methylene chloride. The solution is washed with saturated aqueous sodium carbonate, the aqueous phase extracted with methylene chloride and the combined organic solutions dried and evaporated, to yield the 11-(N-methylaminomethyl)-10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine.

The mixture of 300 mg thereof and 232 mg of diethyl oxalate is slowly heated to 140°C during 45 minutes and to 180°C during 15 minutes, at which temperature it is maintained for 30 minutes. It is cooled, diluted with benzene, chromatographed on silica gel and eluted with methanol-chloroform (1:9), to yield the 2-methyl-3,4-dioxo-1,3,4,14b-tetrahydro-10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine melting at 178°-179°C.

In practice it is usually used as maleate salt.

References

Wasley J.W.F., Chatham; US Patent No. 4,316,900; February 23, 1982; Assigned to Ciba-Geigy Corporation, Ardsley, N.Y.

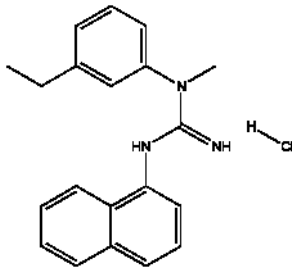
APTIGANEL HYDROCHLORIDE

Therapeutic Function: NMDA antagonist

Chemical Name: N-(3-Ethylphenyl)-N-methyl- N'-1-naphthalenylguanidine monohydrochloride

Common Name: Cerestat; Aptiganel hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 137160-11-3

Trade Name	Manufacturer	Country	Year Introduced
Aptiganel	Oregon State University	-	-
Cerestat	Cambridge NeuroScience	-	-

Raw Materials

m-Ethylphenylcyanamide	Sodium hydride
Methyl iodide	1-Aminonaphthalene
Sodium hydroxide	Hydrochloric acid

Manufacturing Process

A solution of m-ethylphenylcyanamide (1.46 g, 10 mmol) and sodium hydride (480 mg, 20 mmol, prewashed with hexane) in anhydrous THF (10 ml) was heated at 80-85°C for 2.5 hours. After it was allowed to cool to room temperature, methyl iodide (3.5 g, 25 mmol) was added and stirring continued at room temperature for 2 hours. Methanol (10 ml) followed by water (20 ml) was added and the reaction mixture was extracted with dichloromethane (3x25 ml). Concentration of the organic layer followed by flash chromatography on SiO_2 afforded N-(m-ethylphenyl)-N-methylcyanamide (960 mg, 60%) as a colorless liquid: IR (film): 2220, 3400cm-1.

A mixture of m-ethylphenyl-N-methylcyanamide (520 mg, 3.25 mmol) and 1-aminonaphthalene hydrochloride (508 mg, 3.25 mmol) was placed in a preheated oil bath at 160°C for 3 hours and then allowed to cool to room temperature. The resulting solid was taken into dichloromethane and washed with 10% sodium hydroxide solution. The organic layer was concentrated and the resulting residue was dissolved in absolute ethanol (2 ml) and treated with dilute hydrochloric acid. It was concentrated and the solid was twice

recrystallized from absolute ethanol-ether to give N-(1-naphthyl)-N'-(m-ethylphenyl)-N'-methylguanidine hydrochloride (403 mg, 37%) as off-white needles, melting point 223-225°C.

References

Weber Eckard, Keana John F. W.; US Patent No. 5,262,568; November 16, 1993; Assigned to State of Oregon (Portland, OR)

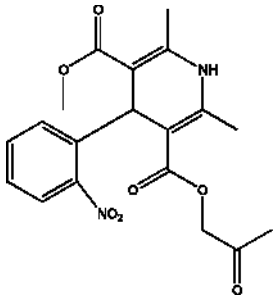
ARANIDIPINE

Therapeutic Function: Antihypertensive

Chemical Name: 3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, methyl 2-oxopropyl ester

Common Name: Aranidipine; Asanidipine

Structural Formula:



Chemical Abstracts Registry No.: 86780-90-7

Trade Name	Manufacturer	Country	Year Introduced
Aranidipine	Shiono Chemical Co., Ltd.	-	-
Aranidipine	INTER-CHEMICAL(chongqing) CO. LTD	-	-
Aranidipine	Verychem Co.	-	-
Sapresta	Taiho Pharmaceutical Co., Ltd.	-	-

Raw Materials

Sodium hydride	2,2-Ethylenedioxypropanol
Diketene	Methyl 2'-nitrobenzylidene acetoacetate
Ammonia	Hydrochloric acid

Manufacturing Process

100.0 mg of 50% sodium hydride was added to a mixture of 20.0 g of 2,2-ethylenedioxypropanol and 100 ml of benzene, and 20.0 g of diketene was added dropwise to the mixture while refluxing the mixture. After refluxing the mixture for 2 h, the solvent was distilled off and the resulting residue was distilled under reduced pressure to obtain 21.5 g (70% yield) of 2,2-ethylenedioxypropyl acetoacetate as a colorless oil, boiling point of 90°C (6 mm Hg).

Ammonia gas was passed through a mixture of 19.0 g of 2,2-ethylenedioxypropyl acetoacetate and 100 ml of methanol for 2.5 h under ice-cooling while stirring. The solvent was then distilled off and the residue was distilled under reduced pressure to obtain 16.0 g (84% yield) of 2,2-ethylenedioxypropyl 3-aminocrotonate as a pale yellow oil, boiling point of 120°C (5 mm Hg).

A mixture of methyl 2'-nitrobenzylidene acetoacetate, 2,2-ethylenedioxypropyl 3-aminocrotonate and ethanol was refluxed for 10 h. The resulting reaction solution was allowed to stand overnight, and the precipitated crystals were collected by filtration and recrystallized from ethanol to obtain methyl 2,2-ethylenedioxypropyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate.

Methyl 2,2-ethylenedioxypropyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate was refluxed in an ethanol solution containing 10% hydrochloric acid for 6 h. The solvent was then distilled off and the residue was crystallized from diethyl ether to give methyl 2-oxopropyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate as yellow prisms, melting point 155°C (recrystallized from a mixture of ethyl acetate and hexane).

References

Ohno S. et al.; US Patent No. 4,446,325; May 1, 1984; Assigned: Maruko Seiyaku Co., Ltd., Nagoya, Japan

ARAPROFEN

Therapeutic Function: Antiinflammatory, Analgesic

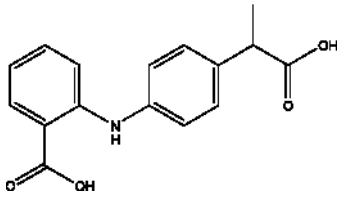
Chemical Name: (+/-)-4-[(2-Carboxyphenyl)amino]-α-methylbenzeneacetic acid

Common Name: Araprofen; Camprofen

Chemical Abstracts Registry No.: 15250-13-2

Trade Name	Manufacturer	Country	Year Introduced
Araprofen	Onbio Inc.	-	-

Structural Formula:



Raw Materials

Potassium carbonate
Copper
Sulfuric acid
2-(4-Aminophenyl)propionic acid
Potassium o-chlorobenzoate

Manufacturing Process

A mixture of 2-(4-aminophenyl)propionic acid (52.2 g), potassium o-chlorobenzoate (61.5 g), potassium carbonate (43.6 g) and copper powder (0.3 g) in amyl alcohol (620 ml) is heating under reflux for 16 h. The major proportion of the solvent is then removed by steam distillation. The residual aqueous solution is treated with decolorising charcoal (20.0 g) and acidified with 4 N sulfuric acid (220 ml). The cream product which crystallises is dissolved in diethyl ether (500 ml).

The aqueous mother liquors are extracted with methylene chloride (900 ml). The organic phases are combined, washed with water (800 ml) and dried over anhydrous sodium sulfate. After filtration, the filtrate is concentrated to dryness under a pressure of 20 mm Hg to give a semicrystalline paste (65.0 g) which is recrystallised from acetonitrile (550 ml). The crystals are filtered off, and the product recovered (32.0 g) is recrystallised from acetonitrile (600 ml). There is thus obtained 2-[4-(2-carboxyphenyl)aminophenyl]propionic acid (18.4 g) melting point 191°-192°C.

References

GB Patent No. 1,053,269; Dec. 30, 1966; Assigned: Rhone-Poulenc S.A., a French Body Corporate, 22, Avenue Montaigne, Paris, France

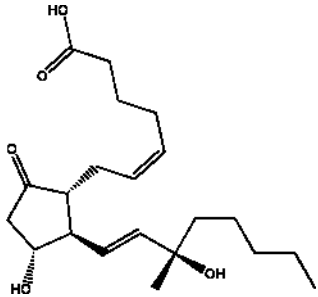
ARBAPROSTIL

Therapeutic Function: Gastric antisecretory; Antiulcer

Chemical Name: Prosta-5,13-dien-1-oic acid, 11,15-dihydroxy-15-methyl-9-oxo-, (5Z,11α,13E,15R)-

Common Name: Arbaprostil

Structural Formula:



Chemical Abstracts Registry No.: 55028-70-1

Trade Name	Manufacturer	Country	Year Introduced
Arbaprostil	ZYF Pharm Chemical	-	-

Raw Materials

Prostaglandin E_2
2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
Hexamethyldisilazane
Trimethylchlorosilane
Ammonium chloride
Methyl magnesium bromide
Potassium hydroxide
Hydrochloric acid
Diazomethane

Manufacturing Process

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone is added to a solution of PGF_{2a} [(5Z,11α,13E)-11,15-dihydroxy-9-oxoprosta-5,13-dien-1-oic acid or Prostaglandin E_2] in dioxane. The mixture is stirred 24 h at 50°C under nitrogen, and then is cooled to 20°C and filtered. The filtered solids are washed with dichloromethane. Evaporation of the combined filtrate and washings at reduced pressure gives a residue which is chromatographed on silica gel (Silicar CC-4; Malincrodt), eluting with 50% ethyl acetate in Skellysolve B (a mixture of isomeric hexanes). Evaporation of the eluates gives 15-oxo-PGF_{2a}.

A mixture of hexamethyldisilazane and tri-methylchlorosilane is added to a solution of 15-oxo-PGF_{2a} in tetrahydrofuran. This mixture is stirred 16 h at 25°C under nitrogen, and is then filtered. The filtrate is evaporated under reduced pressure. Xylene is added to the residue and the mixture is evaporated at 60°C under reduced pressure. This addition of xylene and evaporation is repeated twice. The resulting residue is the tris-(trimethylsilyl) derivative of 15-oxo-PGF_{2a}.

A 3 M diethyl ether solution of methylmagnesium bromide is added dropwise to a stirred solution of the tris-(trimethylsilyl) derivative of 15-oxo-PGF_{2a} in diethyl ether at 25°C.

The mixture is stirred 30 min at 25°C, after which an additional the methylmagnesium bromide solution is added and stirring is continued an additional 30 min. The resulting reaction mixture is poured into saturated aqueous ammonium chloride solution at 0°C. After stirring several minutes, the mixture is extracted repeatedly with diethyl ether. The combined diethyl ether extracts are washed with saturated aqueous sodium chloride solution and then dried with anhydrous sodium sulfate. Evaporation of the diethyl ether gives a yellow oil which is dissolved in ethanol. That solution is diluted with water, and the mixture is stirred 4 h at 25°C. The ethanol in the resulting solution is evaporated at reduced pressure, and the aqueous residue is saturated with sodium chloride and then extracted with ethyl acetate. Solution, dried with anhydrous sodium sulfate, and evaporated under reduced pressure to give a mixture of 15-methyl-PGF_{2a} and 15-methyl-15(R)-PGF_{2a}.

The 520.0 mg mixture of 15-methyl-PGF_{2a} and 15-methyl-15(R)-PGF_{2a} is dissolved in diethyl ether and cooled to 0°C. Excess diazomethane dissolved in diethyl ether is then added, and the mixture is maintained 5 min at 0°C and then 5 min at 25°C. The solution is evaporated in a stream of nitrogen, and the residue is chromatographed on 500.0 g of neutral silica (Merck), eluting successively with 20%, 40%, and of 50% ethyl acetate in Skellysolve B. The corresponding eluates emerging from the column are discarded. Elution is continued successively with gradients of 4 L of 50% and 4 L of 60% ethyl acetate in Skellysolve B, and 5 L of 60% and 5 L of 75% ethyl acetate in Skellysolve B, and then with 4 L of 75% ethyl acetate in Skellysolve B, collecting the corresponding eluates in 500 ml fractions. Elution is further continued successively with 5 L of 75% ethyl acetate in Skellysolve B and with 6 L of 100% ethyl acetate, collecting the corresponding eluates in 200 ml fractions. Eluate fractions 29-35 are combined and evaporated to give 109.0 mg of 15-methyl-15(R)-PGF_{2a} methyl ester.

Aqueous potassium hydroxide solution is added to a solution of 15-methyl-15(R)-PGF_{2a} methyl ester in a mixture of methanol and of water under nitrogen. The resulting solution is stirred 2 h at 25°C, and is then poured into several volumes of water. The aqueous mixture is extracted with ethyl acetate, acidified with 3 N hydrochloric acid, saturated with sodium chloride, and then extracted repeatedly with ethyl acetate. The latter ethyl acetate extracts are combined, washed successively with water and saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate, and evaporated under reduced pressure. The crystalline residue is recrystallized from a mixture of ethyl acetate and Skellysolve B to give 15-methyl-15(R)-PGF_{2a}.

References

Bundy G.L.; US Patent No. 3,804,889; April 16, 1974; Assigned: Upjohn Company, Kalamazoo, Mich.

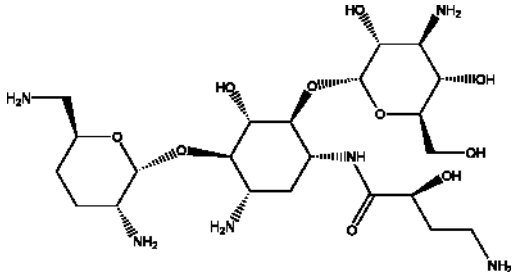
ARBEKACIN

Therapeutic Function: Antibiotic

Chemical Name: L-Streptamine, O-3-amino-3-deoxy-α-D-glucopyranosyl-(1-6)-O-(2,6-diamino-2,3,4,6-tetradeoxy-α-D-erythro-hexopyranosyl-(1-4))-N^1-(4-amino-2-hydroxy-1-oxobutyl)-2-deoxy-, (S)-

Common Name: Arbekacin; Habekacin

Structural Formula:



Chemical Abstracts Registry No.: 51025-85-5

Trade Name	Manufacturer	Country	Year Introduced
Habekacin	Meiji-Seika Co. Ltd.	-	-
Habekacin	Choong Wae Pharma. Co	-	-
Arbeka	Reyon Pharmaceutical Co. Ltd.	-	-

Raw Materials

3',4'-Dideoxykanamycin
Benzyloxycarbonyl chloride
Ammonia
Acetic acid
Hydrogen
Palladium on carbon
N-Hydroxysuccinimide ester of (S)-4-benzyloxycarbonylamino-2-hydroxybutyric acid

Manufacturing Process

13.53 g (30 mmole) of 3',4'-dideoxykanamycin (abbreviated as DKB) in the form of the free base was dissolved in 135 ml of water, and to this solution was added dropwise 5.61 g (33 mmole) of benzyloxycarbonyl chloride over 1 h under stirring and under ice-cooling (0°-5°C). After the addition, the mixture was further stirred for 1 h at room temperature and filtered to remove the precipitate.

The filtrate was washed with 135 ml of ethyl ether. The aqueous phase was neutralized by addition of aqueous ammonia and then concentrated under reduced pressure. The concentrated solution was passed through a column of 480 ml of a cation-exchange resin essentially consisting of a copolymer of methacrylic acid and divinylbenzene (available under a trade name "Amberlite

CG 50", a product of Rohm and Haas Co., U.S.A. the ammonium form) to effect the adsorption of the benzyloxycarbonylated DKB by the resin. The resin column was washed with water (1920 ml) and then eluted with 0.1 N aqueous ammonia. 960 ml of the first running of the eluate was discarded, and the subsequently running fraction of the eluate amounting to 780 ml was collected, concentrated and freeze-dried to give 5.43 g (yield 31%) of 6'-N-benzyloxycarbonyl DKB as a colorless powder, melting point 113°-115°C (dec.).

4.04 g (6.9 mmole) of the 6'-N-benzyloxycarbonyl DKB was dissolved in 26 ml of water, and to this solution was added a solution of 2.94 g (8 mmole) of N-hydroxysuccinimide ester of (S)-4-benzyloxycarbonylamino-2-hydroxybutyric acid in 45 ml of dimethoxyethane. The admixture was stirred at room temperature for 90 min and then the reaction mixture was concentrated to dryness. The residue was taken up in a volume of water and the aqueous solution was poured into a column of 560.0 g of silica gel. The elution was conducted using methanol-chloroform-17% aqueous ammonia (4:2:1), and such eluate fractions containing the unreacted materials were discarded. The fractions containing the mixed acylated products were collected and concentrated to give 5.63 g of the mixed acylated products. The mixed acylated products were dissolved in a mixture of 67 ml of glacial acetic acid, 63 ml of methanol and 17 ml of water, and the solution so obtained was admixed with 1.6 g of 5% palladium-carbon and hydrogenated with hydrogen at atmospheric pressure for 4 h to remove the benzyloxycarbonyl groups of the acylated products. The reaction mixture was filtered to remove the catalyst, and the filtrate was concentrated to under reduced pressure to give 5.20 g of a powder of the acetate of the acylated products comprising 1-N-[(S)-4-amino-2-hydroxybutyryl] DKB acetate.

The aqueous solution of 1-N-[(S)-4-amino-2-hydroxybutyryl] DKB acetate was poured into a column of 250 ml of a cation-exchange resin made of a copolymer of methacrylic acid and divinylbenzene (commerically available as "Amberlite CG 50" ammonium form). The resin column was washed with water and eluted successively with aqueous ammonia (0.1 N 850 ml, 0.3 N 830 ml, 0.63 N 830 ml and 1 N 830 ml). The eluate was collected in 17 ml fractions. 320 ml of the fractions which were eluted by using 1 N aqueous ammonia and which showed high antibacterial activity to Bacillus subtilis PC 1219 and Escherichia coli JR 66/W 677 were combined together and concentrated to dryness to give 301.0 mg of a powder. This powder was rechromatographed again into a column of 11 ml of a cation-exchange resin made of a copolymer of methacrylic acid with divinylbenzene (commercially available as "Amberlite CG 50", ammonium form).

Thus, the resin column was at first washed with 40 ml of water and then with 90 ml of 0.5 N aqueous ammonia, and subsequently the elution was made using 0.75 N aqueous ammonia. Such fractions of the eluate were combined together to a total volume of 26 ml and concentrated to dryness to give 61.0 mg (yield 1.6%) of 1-N-[(S)-4-amino-2-hydroxybutyryl]DKB as a colorless crystalline powder, melting point 178°C (dec.).

References

Umezawa H. et al.; US Patent No. 4,107,424; August 15, 1978; Assigned: Zaidan Hojin Biseibutsu Kagaku Kenkyu Kal, Tokyo, Japan

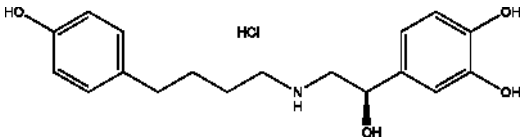
ARBUTAMIN HYDROCHLORIDE

Therapeutic Function: Cardiotonic

Chemical Name: 1,2-Benzenediol, 4-((1R)-1-hydroxy-2-((4-(4-hydroxyphenyl)butyl)amino)ethyl)-, hydrochloride

Common Name: Arbutamine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 125251-66-3; 128470-16-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Genesa	Genesia Automedics	UK	-

Raw Materials

3,4-Dihydroxybenzaldehyde
t-Butyldimethylsilyl chloride
Nitromethane
(S)-6,6'-Bis(triethylsilylethynyl)-1,1'-dihydroxy-2,2-binaphthalene
Butyl lithium
4-(4-Methoxymethoxyphenyl)butanoic acid
Diethylphosphorylcyanide
Triethylamine
Lithium aluminum hydride

Manufacturing Process

(R)-Arbutamin was produced as follows: 89.3 mg of (-)-1-di(t-butyldimethylsiloxy)phenyl)-2-aminoethanol, 50.0 mg of 4-(4-methoxymethoxyphenyl)butanoic acid, diethylphosphorylcyanide, and triethylamine were dissolved in N,N-dimethylformamide at 0°C, reacted at room temperature, so as to obtain 108.6 mg (in a yield of 82%) of amide compound. The amide compound obtained was reduced lithium aluminium hydride in an ether solvent at reflux temperature, so as to quantitative obtain amine. And 55.6 mg of (R)-arbutamin which is intended compound was obtained by deprotecting the hydroxyl-protecting group of amine in a methanol-THF solvent at room temperature using hydrochloric acid. $[\alpha]_D^{25}$ = -17 (c 1.15, EtOH).

(-)-1-(Dibutyldimethylsiloxy)phenyl)-2-aminoethanol was obtained by a hydrogenization of (R)-1-(3,4-di(t-butyldimethylsiloxyphenyl)-2-nitroethanol

on 10% Pd/C.

The last compound was prepared as follows: the hydroxyl groups of 3,4-dihydroxy-benzaldehyde was protected using t-butyldimethylsilylchloride (1). 100 mg (0.26 mmol) of 3,4-di(t-butyl-methylsiloxy)benzaldehyde was dissolved in 1 ml tetrahydrofurane under atmosphere of argon at -40°C, and 0.30 ml of metal complex from (S)-6,6'-bis(triethylsilylethynyl)-1,1-dihydroxy-2,2'-binaphtalene (2) mixed with a solution of n-butyllitium in hexane.After stirring for 30 minutes, 79.4 mg (1.3 mmol) of nitromethane was added dropwise to the mixture. After 67 hour reaction time, 2 ml of 1 N aqueous solution of hydrochloric acid added to stop the reaction. Product was extracted with 50 ml ethyl acetate, dehydrated with anhydrous sodium sulfate and concentrated within evaporator followed by silica gel chromatography (n-hexane/acetone = 10/1), after which (R)-1-(3,4-di(t-butyldimethylsiloxy) phenyl)-2-nitroethanol with an optical purity of 92% e.e. was obtained in a yield of 93%.

References

Aldrich, Catalogue Handbook of Fine Chemicals, 2000, p.312
Shibasaki et al.; US Patent No. 6,632,955B1; Oct. 14, 2003
Monte W.T. et al.; US Patent No. 5,874,601; Feb. 23, 1999; Assigned: Abbott Laboratories (Abbott Park, IL)

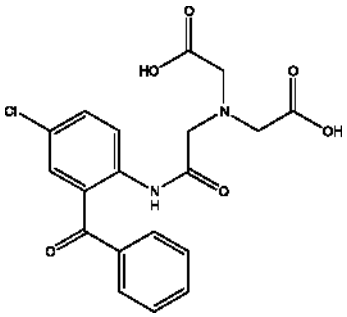
ARCLOFENIN

Therapeutic Function: Diagnostic aid

Chemical Name: Glycine, N-(2-((2-benzoyl-4-chlorophenyl)amino)-2-oxoethyl)-N-(carboxymethyl)

Common Name: Arclofenin

Structural Formula:



Chemical Abstracts Registry No.: 87071-16-7

Trade Name	Manufacturer	Country	Year Introduced
Arclofenin	ZYF Pharm Chemical	-	-

Raw Materials

Acetic anhydride
Pyridine
Nitrilotriacetic acid
Sodium hydroxide
2-Amino-5-chlorobenzophenone

Manufacturing Process

A round bottom flask is charged with dimethylformamide 72.0 g, acetic anhydride 25.0 g, pyridine 2.0 g, and nitrilotriacetic acid (NTA) 38.2 g and the suspension is nitrogen purged for several minutes. The flask is stoppered and the mixture is stirred at room temperature for 3 days. A small amount of unreacted NTA is filtered out. The bulk of the solvent 79 ml is removed in vacuo at a bath temperature of 60°-70°C. The resulting viscous solution is twice roto-vacued after two successive additions of 40 ml dimethylformamide. So the 2,6-diketo-N-carboxymethyl morpholine (NTA anhydride) is prepiared.

To the viscous solution of NTA anhydride is added 300 ml toluene. The mixture is stirred at room temperature until uniform. Then 46.3 g of 2-amino-5-chlorobenzophenone dissolved in 300 ml toluene is added to the stirred solution of NTA anhydride and heated at 90°-100°C for 1 h. After cooling, the reaction mixture is flashed to dryness. The residue is taken up in 400 ml of 1N sodium hydroxide and filtered. The filtrate is extracted with chloroform, ether and charcoaled. The charcoal is removed by filtration. The product is precipitated from the filtrate by the careful addition of 6 N HCl. The precipitate is removed by filtration to give the N-[N'-(2-benzoyl-4-chlorophenyl)carbamoylmethyl]iminodiacetic acid, melting point 180°-186°C (dec., recrystallized from hot methanol/water).

References

Roleston R.E.; US Patent No. 4,454,107; June 12, 1984; Assigned: Merck and Co., Inc., Rahway, N.J.

ARFENDAZAM

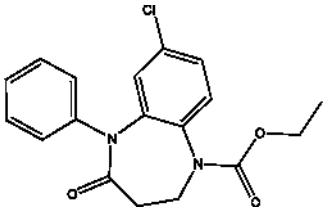
Therapeutic Function: Tranquilizer

Chemical Name: 1H-1,5-Benzodiazepine-1-carboxylic acid, 7-chloro-2,3,4,5-tetrahydro-4-oxo-5-phenyl-, ethyl ester

Common Name: Arfendazam

Chemical Abstracts Registry No.: 37669-57-1

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Arfendazam	ZYF Pharm Chemical	-	-

Raw Materials

Phosgene
Ethanol
8-Chloro-1-phenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-2-one

Manufacturing Process

A phosgene was mixed with ethanol, then cooling by ice-water the solution of 8-chloro-1-phenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-2-one in chloroform was added dropwise, mixed and allowed to stand. Then the reaction mixture was concentrated, and crystals was filtered off. So the 7-chloro-2,3,4,5-tetrahydro-4-oxo-5-phenyl-1H-1,5-benzodiazepine-1-carboxylic acid ethyl ester was obtained, melting point 172°-173°C (dec.).

References

Bub O. et al.; SU 474,986; Oct. 25, 1975; Assigned: Knol AG, FRG.
Karrer, Lehrbuch der organischen chemie, 1959

ARGATROBAN HYDRATE

Therapeutic Function: Anticoagulant

Chemical Name: (2R,4R)-4-methyl-1-[N2-3-methyl-1,2,3,4-tetrahydro-8-quinolinsulfonyl-L-arginyl]-2-piperidinecarboxylicacid hydrate

Common Name: Argatroban; Argipidine

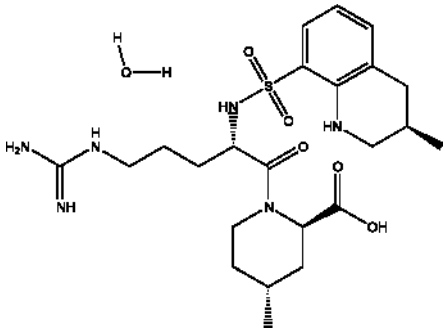
Chemical Abstracts Registry No.: 141396-28-3; 74863-84-6 (Base)

Raw Materials

Triethylamine
$N^{(G)}$-Nitro-$N^{(2)}$-(tert-butoxycarbonyl)-L-arginine
Isobutyl chloroformate

Ethyl 4-methyl-2-piperidinecarboxylate
Palladium
3-Methyl-8-quinolinesulfonyl chloride

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Acova	SmithKline Beecham	-	-
Argatroban	Texas Biotechnology Corporation	-	-
Novastan	Mitsubishi Chemical Corp.	Japan	-
Slonnon	Mitsubishi Chemical Corp.	Japan	-

Manufacturing Process

To a stirred solution of 28.3 g of N^G-nitro-N^2-(tert-butoxycarbonyl)-L-arginine in 450 ml of dry tetrahydrofuran were added in turn 9.0 g of triethylamine and 12.2 g of isobutyl chloroformate while keeping the temperature at -20°C. After 10 minutes, to this was added 15.2 g of ethyl 4-methyl-2-piperidinecarboxylate and the mixture was stirred for 10 minutes at -20°C. At the end of this period, the reaction mixture was warmed to room temperature. The solvent was evaporated and the residue taken up in 400 ml of ethyl acetate, and washed successively with 200 ml of water, 100 ml of 5% sodium bicarbonate solution, 100 ml of 10% citric acid solution and 200 ml of water. The ethyl acetate solution was dried over anhydrous sodium sulfate. The solution was evaporated to give 31.5 g (75 %) of ethyl 1-[N^G-nitro-N^2-(tert-butoxycarbonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylate in the form of a syrup.

To a stirred solution of 30 g of ethyl 1-[N^G-nitro-N^2-(tert-butoxycarbonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylate in 50 ml of ethyl acetate was added 80 ml of 10% dry HCl-ethyl acetate at 0°C. After 3 hours, to this solution was added 200 ml of dry ethyl ether to precipitate a viscous oily product. This was filtered and washed with dry ethyl ether to give ethyl 1-[N^G-nitro-L-arginyl]-4-methyl-2-piperidinecarboxylate hydrochloride as an amorphous solid.

To a stirred solution of ethyl 1-(N^G-nitro-L-arginyl)-4-methyl-2-piperidinecarboxylate hydrochloride in 200 ml of chloroform were added in turn 18.5 g of triethylamine, and 14.7 g of 3-methyl-8-quinolinesulfonyl chloride at 5°C, and stirring was continued for 3 hours at room temperature. At the end of this period, the solution was washed twice with 50 ml of water. The chloroform solution was dried over anhydrous sodium sulfate. Upon evaporation of the solvent, the residue was chromatographed on 50 g of silica gel packed in chloroform, washed with chloroform and eluted with 3% methanol-chloroform. The fraction eluted from 3% methanol-chloroform was evaporated to give 32.1 g (91%) of ethyl 1-[N^G-nitro-N^2-(3-methyl-8-quinolinesulfonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylate in the form of an amorphous solid.

A solution of 30 g the above product in 100 ml of ethanol and 100 ml of 1 N sodium hydroxide solution was stirred for 24 hrs at room temperature. At the end of this period, the solution was neutralized with 1 N hydrochloric acid and then concentrated to 70 ml. The solution was adjusted to pH=11 with 1 N sodium hydroxide solution, washed three times with 100 ml of ethyl acetate, acidified with 1 N hydrochloric acid and then extracted three times with 100 ml of chloroform. The combined chloroform solution was dried over anhydrous sodium sulfate and evaporated to give 28.0 g (97%) of 1-[N^G-nitro-N^2-(3-methyl-8-quinolinesulfonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylic acid as an amorphous solid. IR (KBr): 3,300, 1,720, 1,630 cm^{-1}.

To a solution of 3.00 g of 1-[N^G-nitro-N^2-(3-methyl-8-quinolinesulfonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylic acid in 50 ml of ethanol was added 0.5 g of palladium black and then the mixture was shaken under 10 kg/cm^2 H_2 pressure at 100°C for 8 hrs. At the end of this period, the ethanol solution was filtered to remove the catalyst and evaporated to give 2.50 g (90%) of 1-[N^2-(3-methyl-1,2,3,4-tetrahydro-8-quinolinesulfonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylic acid as an amorphous solid. IR (KBr): 3,400, 1,620, 1,460, 1,380 cm^{-1}.

References

Okamoto S. et al.; US Patent No. 4,201,863; May 6, 1980; Assigned: Mitsubishi Chemical Industries, Limited (Tokyo, JP)
Mano T. et al.; US Patent No. 5,506,241; Apr. 9, 1996; Assigned: Mitsubishi Chemical Corporation (Tokyo, JP)

ARGININE ASPARTATE

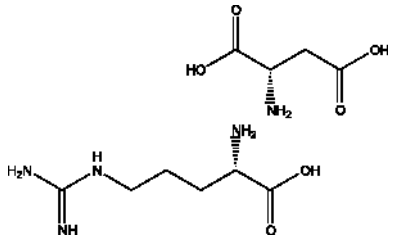
Therapeutic Function: Tonic, Stimulant, Hepatoprotectant

Chemical Name: L-Aspartic acid, compound with L-arginine (1:1)

Common Name: Arginine aspartate; Asparginininum

Chemical Abstracts Registry No.: 7675-83-4

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Arginine aspartate	Microbase Biotech Co., Ltd.	-	-
Arginine aspartate	Flamma S.P.A.	-	-
Asparten	Euro-Labor' Grunenthal	-	-
Bio-Energol	Medicum	-	-
Bio-Energol	Yamanouchi	-	-
Desfatigan	IMA	-	-
Dynamisan	Mipharm S.p.A	-	-
Dynamisan	Novartis Santé Familiale SAS	-	-
Dynamisan	Famar, S.A.	-	-
Eubiol	Chephasaar	-	-
Lacorene	Spedrog Caillon	-	-
Pargine	Viatris	-	-
Pargine	Asta Medica	-	-
Potenciator	Valderrama	-	-
Sangenor	Roche	-	-
Sargenor	Viatris S.p.A	-	-
Sorbenor	Casen Fleet, SA.	-	-
Targifor	Aventis Pharma	-	-
Targifor	Silva Araujo Roussel S.A.	-	-
Taurargin	Laboratorios Baldacci S.A.	-	-

Raw Materials

Calcium aspartate
Arginine dihydrochloride

Manufacturing Process

1000 ml of polystyrene-trimethylbenzylammonium ion exchange resin were converted into the chloride form by passing aqueous hydrochloride acid over the resin. The resin was washed with distilled water to remove all traces of

hydrochloric acid and a 1 N aqueous solution of calcium aspartate was then passed over the resin. A 10% excess of the calcium aspartate solution over the theoretical ion-exchange capacity of the resin was used and the resin was then washed with water until the wash water was free of chloride ions. At the end of this treatment, the resin was in the aspartic acid form.

An aqueous solution containing 168.56 g of calcium aspartate and 49.44 g of arginine dihydrochloride per litre was prepared, and this solution was passed slowly over the aspartic acid form resin. The effluent liquid was collected in fractions of 200 ml, then of 100 ml, and towards the end, in fractions of 50 ml. After about 1000 ml of eluate had been collected, the succeeding fractions were examined very carefully for the presence of chloride ion. All the eluate fractions prior to the first one containing traces of chloride, i.e. all the chloride-free eluate fractions, were combined; the combined chloride eluates amounted to about 1300 ml. The arginine present was determined by Sakaguchis method and the total nitrogen in the combined eluates was also determined. These determinations showed that the eluates contained from 270 to 300 g of arginine aspartare per litre. The combined eluates were evaporated to a volume of about 500 ml and allowed to crystallize at a low temperature (0°-4°C). After seeding with a crystal of arginine aspartate, colourless crystals were obtained; they were filtered off, washed with aqueous ethanol, and then dried. About 210 g, i.e. 70% of the theoretical yield, of crystals having a decomposition point of 220°C was obtained. The mother liquor from the first crystallization was evaporated down to a volume of about 150 ml. Ethanol was added to the solution until cloudiness which persisted was obtained, the solution was cooled to 0°C and a second crop of crystals was obtained. The size of this second crop was increased by adding further ethanol after the major portion of the second crop had crystallized and allowing the mixture to stand for 48 hours at 0°C. After separation, the second fraction consisted of 75 g of a crystalline mass which had the same physico-chemical and chemical properties as the main fraction.

References

GB Patent No. 1,045,060; Sept. 15, 1965; Assigned to Mundipharma S.A.

ARGININE GLUTAMATE

Therapeutic Function: Ammonia detoxicant (hepatic failure)

Chemical Name: Glutamic acid compound with L-arginine

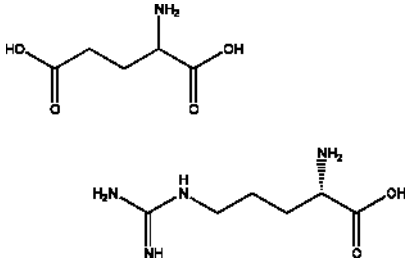
Common Name: -

Chemical Abstracts Registry No.: 4320-30-3

Raw Materials

L-Arginine
L-Glutamic acid

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Modamate	Abbott	US	1960
Eucol	Lefranco	France	1970

Manufacturing Process

This salt may be prepared by mixing L-arginine with L-glutamic acid in water and crystallizing the resulting salt from the water by the addition of a polar water miscible organic solvent to the water. For instance, when 17.2 g of L-arginine and 14.5 g of L-glutamic acid were dissolved in 155 g of water, a clear homogeneous solution resulted which had a pH of 5.3. This solution was filtered and the filtrate was evaporated at 50°C under reduced pressure to a solution having a solids content of about 45%. Absolute methanol (220 g) was added to the concentrated solution of the salt and this mixture cooled to 5°C for one hour. The resulting solid salt was removed from the mixture by filtration and washed with absolute methanol. After being dried preliminarily in the air, the salt was further dried in a vacuum oven at 60°C for 3 hours. The resulting salt, L-arginine-L-glutamate, weighed 30 g (94.6% of the theoretically possible yield based on the amount of L-arginine and L-glutamic acid employed) and melted at 193-194.5°C with decomposition.

References

Merck Index 798
DFU 3 (1) 10 (1978)
DOT 17 (3) 87 (1981)
I.N. p.98
Barker, N.G. and Chang, R.W.H., US Patent 2,851,482; September 9, 1958; Assigned to General Mills, Inc.

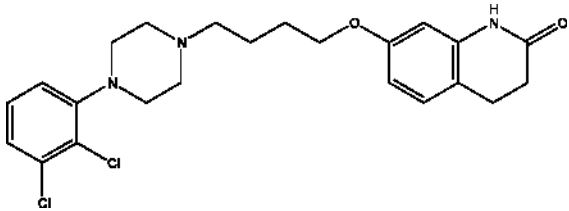
ARIPIPRAZOLE

Therapeutic Function: Antipsychotic

Chemical Name: 2(1H)-Quinolinone, 7-(4-(4-(2,3-dichlorophenyl)-1-piperazinyl)butoxy)-3,4-dihydro-

Common Name: Aripiprazole

Structural Formula:



Chemical Abstracts Registry No.: 129722-12-9

Trade Name	Manufacturer	Country	Year Introduced
Abilify	Bristol-Myers Squibb	USA	-
Abilify	Otsuka America Pharmaceutical, Inc.	USA	-
Abilitat	Bristol-Myers Squibb	USA	-
Aripiprazole	Bristol-Myers Squibb	USA	-
Aripiprazole	Otsuka Pharmaceutical Company, Ltd.	Japan	-

Raw Materials

2,3-Chloroaniline
7-Hydroxy-3,4-dihydrocarbostyril
1,4-Dibromobutane
Di(2-bromethyl)amine
Triethylamine

Manufacturing Process

To a solution of 4.06 g of K_2CO_3 with 400 ml of water was added 40 g of 7-hydroxy-3,4-dihydrocarbostyril [1] and 158 g of 1,4-dibrombutane. The mixture was refluxed for 3 hours. Then it was extracted with dichloremethane, dried with anhydrous $MgSO_4$, the solvent was removed by evaporation. The residue was purified by means of silica gel chromatography (eluent: dichloromethane) and recrystallized from n-hexane-ethanol to yield 50 g of 7-(4-bromobutoxy)-3,4-dihydrocarbostyril, mp 110.5°-110.0°C.

47 g of 7-(4-bromobutoxy)-3,4-dihydrocarbostyril, 35 g of NaJ in 600 ml of acetonitrile was refluxed for 30 minutes. To this suspension was added 40 g of 1-(2,3-dichlorophenyl)piperazine (it was prepareted from 2,3-chloroaniline and di(2-bromoethyl)amine [1]) and 33 ml of triethylamine. The mixture was refluxed for 3 hours. After removing of the solvent, the residue was dissolved in chloroform, washed with water and dried with anhydrous $MgSO_4$. The solvent was removed by evaporation, and residue was recrystallized from ethanol twice to yield 57.1 g of 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydrocarbostyril. Melting point: 139.0°-139.5°C.

References

J. Pharmacol. Exp. Ther., 277, 137-143 (1996)
Banno K. et al.; US Patent No. 4,734,416; March 29, 1988; Assigned: Otsuka Pharmaceutical Co., Ltd. (JP)
Oshiro Y. et al.;. US Patent No. 5,006,528; April 9, 1991; Assigned: Otsuka Pharmaceutical Co., Ltd. (Tokyo, JP)

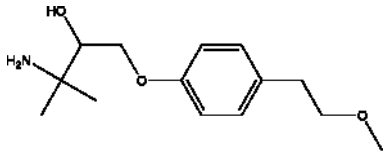
ARNOLOL

Therapeutic Function: Beta-adrenergic blocker (ophthalmic)

Chemical Name: 2-Butanol, 3-amino-1-(4-(2-methoxyethyl)phenoxy)-3-methyl-

Common Name: Arnolol

Structural Formula:



Chemical Abstracts Registry No.: 87129-71-3

Trade Name	Manufacturer	Country	Year Introduced
Arnolol	ZYF Pharm Chemical	-	-

Raw Materials

Palladium on charcoal
1-[4-(2-Methoxyethyl)phenoxy]-3-nitro-3-methylbutan-2-ol
Acetic acid
Sodium hydroxide
Zinc
Hydrochloric acid

Manufacturing Process

2 methods of producing of 1-[4-(2-methoxyethyl)-phenoxy]-3-amino-3-methyl-butan-2-ol:

1). 19.0 g of 1-[4-(2-methoxyethyl)phenoxy]-3-nitro-3-methylbutan-2-ol are hydrogenated at 60°C and under a pressure of 6 bar in a mixture of 250 ml of ethanol and 50 ml of glacial acetic acid in the presence of 4.0 g of palladium-on-charcoal (10% Pd). After the mixture has been filtered and the solvent has been evaporated off, the residue is rendered alkaline with 2 N NaOH and the

mixture is extracted with CH_2Cl_2. The organic phase is washed with water and dried with Na_2SO_4 to give, after evaporation, 15.0 g of the 1-[4-(2-methoxyethyl)phenoxy]-3-amino-3-methylbutan-2-ol, melting point 120°-122°C (dec.).

2). 18.3 g of zinc dust are gradually added to 20.0 g of 1-[4-(2-methoxyethyl) phenoxy]-3-nitro-3-methylbutan-2-ol in 400 ml of ethanol and 60 ml of concentrated hydrochloric acid at 50°-60°C. The mixture is stirred at this temperature for 1 h and filtered and the solvent is evaporated off. After 200 ml of 40% strength NaOH have been added, the product is extracted with methylene chloride. Solvent is distilled and the 1-[4-(2-methoxyethyl) phenoxy]-3-amino-3-methylbutan-2-ol is produced, melting point 120°-122°C (dec.).

References

Cohnen E., Heilwigstrasse, Fed. Rep. of Germany

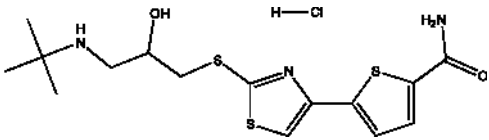
AROTINOLOL HYDROCHLORIDE

Therapeutic Function: Beta-adrenergic blocker

Chemical Name: 2-Thiophenecarboxamide, 5-(2-((3-((1,1-dimethylethyl) amino)-2-hydroxypropyl)thio)-4-thiazolyl)-, monohydrochloride

Common Name: Arotinolol hydrochloride; Tarotiolol hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 68377-92-4 (Base); 68377-91-3

Trade Name	Manufacturer	Country	Year Introduced
Arotinolol hydrochloride	ZYF Pharm Chemical	-	-

Raw Materials

2-Mercapto-4-(5'-carbamoyl-2'-thiophenyl)thiazole
Sodium hydroxide
1-Chloro-3-t-butylaminopropanol

Manufacturing Process

To a solution of 2-mercapto-4-(5'-carbamoyl-2'-thiophenyl)thiazole, 3.2 g in 20 ml of 0.3 % aqueous sodium hydroxide solution, 1-chloro-3-t-butylaminopropanol, 12.64 g in 20 ml of methanol was added, while the temperature was maintained at 20°C.

The reaction solution was stirred at room temperature for 4 h, and then condensed to a half volume in vacuo. The residual solution, added with 100 ml of water, was extracted with chloroform. The chloroform extract was washed with water, dried over anhydrous magnesium sulfate and evaporated in vacuo to give 4.8 g of 2-(3'-t-butylamino-2'-hydroxypropylthio)-4-(5'-carbamoyl-2'-thiophenyl)thiazole, as crystals, melting point 234°-235.5°C (dec., recrystallized from methanol/water).

In practice it is usually used as hydrochloride.

References

Hibino T. et al.; US Patent No. 3,932,400; January 13, 1976; Assigned: Sumitomo Chemical Company, Limited, Japan

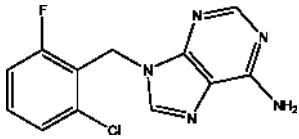
ARPRINOCID

Therapeutic Function: Coccidiostatic

Chemical Name: 9H-Purin-6-amine, 9-((2-chloro-6-fluorophenyl)methyl)-

Common Name: Arprinocid

Structural Formula:



Chemical Abstracts Registry No.: 55779-18-5

Trade Name	Manufacturer	Country	Year Introduced
Arprinocid	NANJING PHARMA CHEMICAL PLANT	-	-
Arprinocid	Hallochem Pharma Co., Ltd.	-	-
Arprinocid	Shanghai abochem chemical co., Ltd.	-	-

Raw Materials

Adenine
2-Chloro-6-fluorobenzyl chloride
Potassium t-butoxide

Manufacturing Process

To a solution of potassium t-butoxide in absolute ethanol slowly adding dry adenine. This mixture was stirred for about 2 h, and then 2-chloro-6-fluorobenzyl chloride was added over a period of about 4 h. The resulting mixture was heated to reflux with stirring and allowed to react for about 42 h, after which it was cooled to about 10°C. The crude product thus formed was isolated by filtration and then washed with ice cold ethanol and ice cold water to yield a 6-amino-9-(2-chloro-6-fluorobenzyl)purine.

References

Lira E.P. et al.; US Patent No. 3,846,426; Nov. 5, 1974; Assigned: International Minerals and Chemical Corporation, Libertyville, III.
G.B. Patent No. 1,123,457; 11 August 11, 1966; Warner Lambert Pharmaceutical Company, a Corporation of Delaware, USA

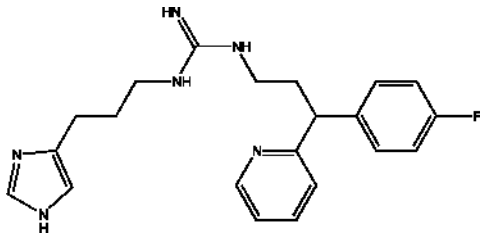
ARPROMIDINE

Therapeutic Function: Histamine H_2-receptor agonist

Chemical Name: Guanidine, N-(3-(4-fluorophenyl)-3-(2-pyridinyl)propyl)-N'-(3-(1H-imidazol-4-yl)propyl)-

Common Name: Arpromidine

Structural Formula:



Chemical Abstracts Registry No.: 106669-71-0

Trade Name	Manufacturer	Country	Year Introduced
Arpromidine	Onbio Inc.	-	-

Raw Materials

Sodium hydride
Sodium hydroxide
Sulfuric acid
Ammonia
Hydrochloric acid
(4-Fluorophenyl)-pyrid-2-yl acetonitrile
N-(2-Bromoethyl)phthalimide
3-(Imidazol-4-yl)-propylamine
N-Benzoyldiphenylimidocarbonate

Manufacturing Process

42.4 g (0.2 mol) of (4-fluorophenyl)-pyrid-2-yl-acetonitrile are dissolved in 50 ml of dimethylformamide and introduced dropwise into a suspension, cooled with ice, of 5.0 g of sodium hydride (put into the process as a dispersion in mineral oil) in 150 ml of dimethylformamide. The reaction mixture is then stirred at room temperature for 15 min and thereafter heated under reflux for 5 h after the addition of 53.4 g (0.21 mol) of N-(2-bromoethyl)phthalimide. When the resulting reaction mixture has cooled down, it is diluted with 500 ml of ether and the organic phase is washed with water until neutral, dehydrated over sodium sulfate and then concentrated by evaporation under vacuum. The N-[3-(cyano-3-(4-fluorophenyl)-3-(pyrid-2-yl)propyl]phthalimide, oily residue, melting point 154°C (crystallizing from methanol), yield: 48.5 g (63%).

46.25 g (0.12 mol) of N-[3-cyano-3-(4-fluorophenyl)-3-(pyrid-2-yl)propyl]phthalimide in 100 ml of 75% sulfuric acid are heated to 150°C for 5 h. When the reaction mixture is cold, it is poured out on ice, filtered through a glass filter, alkalized with sodium hydroxide solution and extracted with ether. The combined extracts are washed with water, dehydrated over sodium sulfate and concentrated by evaporation under vacuum, and the product obtained is isolated by distillation at 150°-155°C/0.8 mm Hg. 19.1 g (yield: 69%) of the 3-(4-fluorophenyl)-3-(pyrid-2-yl) propylamine are obtained.

1.15 g (5 mmol) of 3-(4-fluorophenyl)-3-(pyrid-2-yl)-propylamine and 1.59 g (5 mmol) of N-benzoyl-diphenylimidocarbonate are stirred together in 20 ml of methylene chloride for 15 min at room temperature. The solvent is distilled off under vacuum and the residue is taken up with 30 ml of pyridine and then heated under reflux for 60 min after the addition of 0.69 g (5.5 mmol) of 3-(imidazol-4-yl)-propylamine. The reaction mixture is concentrated by evaporation under vacuum and the residue is dissolved in dilute acid and extracted with ether to remove the phenol formed in the reaction. Alkalization of the aqueous phase with ammonia is followed by extraction with methylene chloride, and the organic phase is washed with water, dehydrated over sodium sulfate and concentrated by evaporation under vacuum. The crude product is purified by preparative layer chromatography (silica gel 60 PF_{254}, containing gypsum; solvent: chloroform/methanol 99+1, ammoniacal atmosphere). 1.4 g (yield 58%) of N-benzoyl-N'-[3-(4-fluorophenyl)-3-(pyrid-2-yl)propyl]-N"-[3-(imidazol-4-yl)propyl]-guanidine a non-crystalline solid (foam) are obtained (crystallisation from ethyl acetate).

0.97 g (2 mmol) of N-benzoyl-N'-[3-(4-fluorophenyl)-3-(pyrid-2-yl)propyl]-N"-[3-(imidazol-4-yl)propyl]-guanidine are heated under reflux in 45 ml of 18% hydrochloric acid for 6 h. When the reaction mixture has cooled down, the benzoic acid formed is removed by extraction with ether, the aqueous phase is evaporated to dryness under vacuum and the residue is dehydrated in a high vacuum: 0.9 g (yield 92%) of a hygroscopic, non-crystalline N-[3-(4-

fluorophenyl)-3-(pyrid-2-yl)propyl]-N'-[3-(imidazol-4-yl)propyl]-guanidine is obtained.

References

Buschauer A. et al.; US Patent No. 5,021,431; June 4, 1991; Assigned: Heumann Pharma GmbH and Co., Nuremberg, Fed. Rep. of Germany

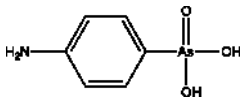
ARSANILIC ACID

Therapeutic Function: Antibacterial

Chemical Name: Arsonic acid, (4-aminophenyl)-

Common Name: Acidum arsanilicum; Arsanilic acid

Structural Formula:



Chemical Abstracts Registry No.: 98-50-0

Trade Name	Manufacturer	Country	Year Introduced
Arsanilic acid	Fleming Laboratories, Inc.	-	-
Arsanilic acid	AroKor Holdings Inc.	-	-
Arsanilic acid	Idea'l Nutrition Science And Development Co., LTD	-	-
Acidum arsanilicum	ZYF Pharm Chemical	-	-

Raw Materials

Arsenic acid
Aniline
Hydrochloric acid
Sodium hydroxide

Manufacturing Process

342.0 g (2 mol) of 83% arsenic acid were added during 75 min to a rapidly stirred mixture of 372.5 g (4 mol) aniline and 111.0 g chlorobenzene while the temperature of the mixture was kept at 147°-150°C. After the addition of arsenic acid was complete the mixture was stirred for an additional 8 h while being maintained at 149°-153°C. Water was continuously removed by distillation, and the organic phase of the distillate was continuously recycled

back into the reaction mixture. At the end of that time a total of 121.0 g of water, containing the condensation of aniline and arsenic acid has been removed. The mixture was then allowed to cool to 110°C. 562.0 g (2.81 mol) of 20% sodium hydroxide were added over a 2 h period while water, chlorobenzene and excess aniline were distilled off at a temperature of from 102°-113°C. The distillation was continued for an additional 2 h while the volume of the mixture was kept at about 700 ml by the addition of water.

The mixture was then diluted with water to a volume of 1400 ml and allowed to cool to 23°C. At this point, 52.0 g of by-product material, which was predominantly tri-(p-aminophenyl)-arsineoxide, were filtered out. The pH of the filtrate was then brought from 8.7 to 5.1 by the addition of 1.8 mol of hydrochloric acid while the volume of the mixture was increased to 2,200 ml by the addition of water. The mixture was stirred for 5 h at room temperature and again filtered. 108.0 g of by-product material comprising predominantly di-(p-aminophenyl)-arsinic acid was filtered off at this point.

The pH of the filtrate was lowered to 4.5 by the addition of 0.2 mole of hydrochloric acid, and an additional 5.0 g of by-products, the composition of which was not determined, was filtered off. The filtrate was then brought to a pH of 3.2 by addition of 0.6 mole of hydrochloric acid, and 128.0 g (29.5% based upon arsenic acid) of arsanilic acid were recovered as a precipitate.

The arsanilic acid filtrate was combined with the by-products filtered off during each of the three filtration steps. 2.8 mol of hydrochloric acid were added to the combined arsanilic acid filtrate and the mixture was heated at 80°C for 5 days. Arsanilic acid was then precipitated from the remaining hydrolyzed mixture in the manner described for the primary reaction product, and an additional 120.0 g (27.5% based on arsenic acid) were recovered. The filtrate contained 14.0 g (3.2%) of arsanilic acid which could be recovered at least partially in subsequent processing. Thus it can be seen from this example that an arsanilic acid yield of 59% was obtained.

References

Hoffmannn H., Green H.E.; US Patent No. 3,763,201; October 2, 1973

ARSTHINOL

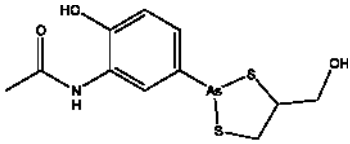
Therapeutic Function: Antiprotozoal

Chemical Name: 3-Hydroxypropylene ester of 3-acetamido-4-hydroxydithiobenzene-arsonous acid

Common Name: Arsthinenol; Arsthinol; Mercaptoarsenical; Mercaptoarsenol

Chemical Abstracts Registry No.: 119-96-0

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Arsthinol	ZYF Pharm Chemical	-	-

Raw Materials

4-Hydroxy-3-acetylaminophenyl-arsenoxide
2,3-Dimercaptopropanol

Manufacturing Process

0.1 mol of 4-hydroxy-3-acetylaminophenyl-arsenoxide is suspended in 50 times its weight of water, and to the suspension 3 mols of sodium carbonate and 11 ml (110 mmols) of 2,3-dimercaptopropanol are added with rapid stirringfor 60 min. The resulting precipitate is filtered off, washed with water and dried in vacuo.

So the N-[2-hydroxy-5-[4-(hydroxymethyl)-1,3,2-dithiarsolan-2-yl]phenyl] acetamide, melting point 163°-166°C is obtained.

References

Friedheim E.A.H.; US Patent No. 2,772,303; November 27, 1956

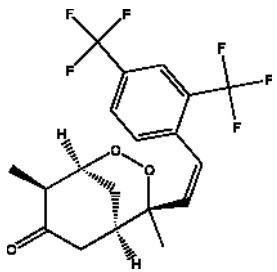
ARTEFLENE

Therapeutic Function: Antimalarial

Chemical Name: 2,3-Dioxabicyclo[3.3.1]nonan-7-one, 4-(2-(2,4-bis (trifluoromethyl)phenyl)ethenyl)-4,8-dimethyl- (1S-(1α,4β(Z),5α,8α))-

Common Name: Arteflene

Structural Formula:



Chemical Abstracts Registry No.: 123407-36-3

Trade Name	Manufacturer	Country	Year Introduced
Arteflene	Roche	-	-

Raw Materials

Carvone, (-)	3-Chloroperbenzoic acid
Sulfuric acid	Sodium hydroxide
Sodium sulfite	Sodium metaperiodate
Butyl lithium	Sodium bicarbonate
Zinc chloride	n-Butyltriphenylphosphonium bromide
Hydrogen bromide	Hydrogen peroxide
Sodium methanolate	Sodiumbis(trimethylsilyl)amide
Silver trifluoroacetate	2,4-Bis(trifluoromethyl)benzyltriphenyl-phosphonium bromide

Manufacturing Process

A solution of 3-chloroperbenzoic acid (55%) in methylene chloride is cooled in an ice bath. (5R)-(-)-Carvone are added dropwise thereto so that the temperature does not rise above 20°C. The reaction mixture is stirred at room temperature for 3.5 h, whereby a precipitate of 3-chlorobenzoic acid forms. This suspension is stirred for 30 min and cooled with ice in order to complete the precipitation. The precipitate is filtered off and washed with hexane/methylene chloride (9:1). The filtrate is evaporated carefully. The thus-obtained oil (epoxide) is suspended in ice-water and treated with 3 N sulfuric acid while cooling in an ice bath so that the temperature does not rise above 20°C. The mixture is stirred at room temperature for 15 h. The pH is adjusted to 6.5 by adding 3 N sodium hydroxide solution. A small amount of 3-chlorobenzoic acid is filtered off. The aqueous phase is cooled to 0°C, whereupon sodium (meta)periodate are added in portions over 30 min so that the temperature does not rise above 20°C. After stirring at room temperature for 2 h sodium sulfite and sodium bicarbonate are added in succession. The suspension is filtered and the filtrate is extracted three times with methylene chloride each time. The combined organic phases are dried over sodium sulfate and evaporated. There is obtained (5R)-5-acetyl-2-methyl-2-cyclohexen-1-one (crystallized from hexane/ethyl acetate at 0°C).

n-Butyltriphenylphosphonium bromide are suspended in dry tetrahydrofuran under argon and cooled to -50°C. 1.33 N n-butyl lithium in hexane are added thereto. The orange coloured suspension is warmed to room temperature and then again cooled to -50°C. (5R)-5-Acetyl-2-methyl-2-cyclohexen-1-one dissolved in dry tetrahydrofuran are added dropwise thereto over a period of 20 min. The cooling bath is then removed and the suspension is left to warm to room temperature. After stirring for 2 h the reaction mixture is filtered through siliceous earth. The filtrate is evaporated, the dark residue is dissolved in ethyl acetate and washed twice with water each time. The organic phase is dried over sodium sulfate and evaporated. The thus-obtained oil is purified by column chromatography on silica gel with hexane/ethyl acetate (95:5) as the elution agent. There is obtained (5R)-2-methyl-5-[(Z)-1-methyl-1-pentenyl]-2-cyclohexen-1-one.

(5R)-2-Methyl-5-[(Z)-1-methyl-1-pentenyl]-2-cyclohexen-1-one are dissolved

in methylene chloride and cooled to 0°C. After adding a catalytic amount zinc chloride the solution is saturated with hydrogen bromide gas. After 30 min the solution is filtered through silica gel and evaporated carefully. The resulting oily residue is dissolved in dry ether, cooled to 0°C and treated with 100% hydrogen peroxide. Silver trifluoroacetate dissolved in dry ether are added dropwise over a period of 30 min. The excess of silver ions is precipitated by adding 1 N hydrochloric acid and the suspension obtained is filtered through silica gel. In order to remove the excess hydrogen peroxide, the filtrate is washed 5 times with water each time. The ether phase is then evaporated carefully and the residue is taken up methanol. A catalytic amount of sodium methanolate is added to this solution, whereupon the mixture is left to stand at room temperature for 15 h. The methanol is distilled off and the residue is purified and separated into the two diastereomers (1:1) by chromatography on silica gel while eluting with hexane/ethyl acetate (7:3). There are obtained (1S,4R,5R,8S)-4-butyl-4,8-dimethyl-2,3-dioxabicyclo[3.3.1]nonan-7-one.

(1S,4R,5R,8S)-4-Butyl-4,8-dimethyl-2,3-dioxabicyclo[3.3.1]nonan-7-one is dissolved in methylene chloride. 2,4-Bis(trifluoromethyl) benzyltriphenylphosphonium bromide and sodium bis(trimethylsilyl)amide are added thereto and the solution is left to stand at room temperature for 24 h. The methylene chloride is distilled off and the (1S,4R,5R,8S)-4-[(Z)-2,4-bis(trifluoromethyl)styryl-4,8-dimethyl-2,3-dioxabicyclo[3.3.1]nonan-7-one, melting point 124°C is obtained.

References

Hofneinz W. et al.; US Patent No. 4,977,184; December 11, 1990; Assigned: Hoffmann-La Roche Inc., Nutley, N.J.

ARTILIDE FUMARATE

Therapeutic Function: Antiarrhythmic

Chemical Name: Methanesulfonamide, N-(4-(4-(dibutylamino)-1-hydroxybutyl)phenyl)-, (R)-, fumarate (2:1) (salt)

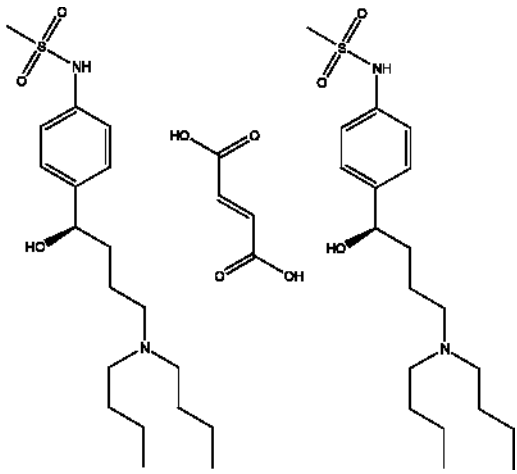
Common Name: Artilide fumarate

Chemical Abstracts Registry No.: 133267-19-3 (Base); 133267-20-6

Raw Materials

Aniline
Aluminum chloride
Sodium bicarbonate
1-Hydroxybenzotriazole
Lithium aluminum hydride
1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride
Methanesulfonyl chloride
Succinic anhydride
Hydrogen hydrochloride
Dibutylamine
Sodium potassium tartrate

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Artilide fumarate	Upjohn (Pharmacia)	-	-

Manufacturing Process

A mechanically stirred solution of aniline (139.7 g, 1.5 mol) in pyridine (2 L), under N2 is cooled in an icebath. Methanesulfonyl chloride (171.8 g, 1.5 mol) is added dropwise to this solution while the temperature is maintained at 15°-20°C, which results in a red-orange color change in the reaction mixture. After the addition is complete the ice bath is removed and the reaction is allowed to continue at room temperature for 2.5 h. The reaction mixture is concentrated in vacuo and the residue is combined with 700 ml of water which results in crystallization of a dark red material. This material is filtered and washed several times with water. The filtered material is dissolved in CH_2Cl_2, washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give four crops (157.37 g, 19.27 g, 26.55 g, 5.07 g) of methanesulfonanilide, melting point 93°C (decolorizing with Darco carbon and crystallization from ethyl acetate).

A mechanically stirred suspension of aluminum chloride (88.0 g, 0.66 mol) and 150 ml of carbon disulfide under N_2 is cooled in an ice bath. Methanesulfonanilide (30.0 g, 0.175 mol) and succinic anhydride (17.5 g, 0.175 mol) are combined and added rapidly to the cooled reaction mixture. The ice bath is removed and the mixture is stirred at room temperature for 6 h.

The reaction mixture is then heated to 55°C and allowed to continue for 18 h. The reaction mixture is separated into two layers the bottom of which solidifies. The upper layer is decanted and the remaining solid layer is decomposed with ice. The resulting suspension is filtered and the solid is washed several times with methylene chloride and dissolved in a mixture of saturated sodium bicarbonate (500 ml) and water (500 ml). This solution is

acidified (pH 2) with HCl and the resulting precipitate is collected by filtration, redissolved in $NaHCO_3$ and reprecipitated with HCl. The solid is collected by filtration and dried to give 4-[(methylsulfonyl)amino]-γ-oxobenzenebutanoic acid, melting point 198°-200°C.

A mixture of 4'-[(methylsulfonyl)amino]-γ-oxobenzenebutanoic acid and 1-hydroxybenzotriazole in dimethylformamide (DMF) under nitrogen, is treated with dibutylamine in DMF. The mixture is cooled in an ice bath and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC) added in portions over 5 min. The mixture is stirred in the cold 1 h and overnight at room temperature. The solvent is removed in vacuo (bath temperature 35°C). The residue is treated with ice and ethyl acetate and the organic layer washed sequentially with 0.5 N monopotassium sulfate, cold 4% $NaHCO_3$, cold water and finally brine. The organic solution is dried (Na_2SO_4) and concentrated in vacuo. The N,N-dibutyl-γ-oxo-4-[(methylsulfonyl)amino]benzenebutan-amide (crystallized from ethyl acetate-hexane) is obtained.

Lithium aluminum hydride is suspended in dry tetrahydrofuran (THF), under nitrogen and the mixture cooled in an ice bath. To this mixture is added N,N-dibutyl-γ-oxo-4-[(methylsulfonyl)amino]benzenebutanamide, (partly as a suspension in THF added over 10 min and partly as a solid added in portions over 30 min).

The mixture is stirred for 2.5 h in the cold. The cold reaction mixture is then treated cautiously with a saturated solution of sodium potassium tartrate in water and stirred for 10 min in the cold. This mixture is extracted with EtOAc. The pooled ethyl acetate extracts are washed with brine, dried (Na_2SO_4) and concentrated in vacuo to give a solid. The aqueous residue from the above extractions is diluted with 10 ml of water and extracted with ethyl acetate. The pooled extract is washed with brine, dried (Na_2SO_4) and concentrated to give solid. The two solids are recrystallized separately from EtOAc to give N-4-[4-(dibutylamino)-1-hydroxybutyl]phenyl]methanesulfonamide (recrystallized from EtOAc-hexane).

By recrystallyzation of stereo-isomers of N-4-[4-(dibutylamino)-1-hydroxybutyl]phenyl]methanesulfonamide may be obtained the (R)-N-4-[4-(dibutylamino)-1-hydroxybutyl]phenyl]methanesulfonamide, melting point 179°-180°C.

References

Boling H.J.; EU Patent No. 0,164,865; May 1, 1985; Assigned: Perry, Robert Edward et al., GILL JENNINGS and EVERY 53-64 Chancery Lane London WC2A 1HN (GB)

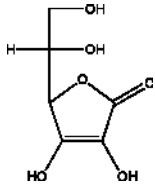
ASCORBIC ACID

Therapeutic Function: Vitamin

Chemical Name: 3-Keto-L-gulofuranolactone

Common Name: Acide ascorbique; Acido ascorbico; Acidium ascorbicum; Acidum ascorbinicum; Ascorbic acid; Ascorbinsaure; Askorbinsyra; Cevitamic acid; C-Vitamin; Hexuronic acid; Hexuronsaure; Vitamin C; Witamina C

Structural Formula:



Chemical Abstracts Registry No.: 50-81-7

Trade Name	Manufacturer	Country	Year Introduced
Ascorbic acid	Natur Product	France	-
Cebion	Merck KGaA	Germany	-
Celin Chewable	Glaxo	India	-
Plivit C	Pliva	Croatia	-
Styptovit	Dr. Reddy's Laboratories Ltd.	India	-
Upsavit Vitamin C	UPSA	France	-
Vitamin C	Hemofarm	Serbia and Montenegro	-
Vitamin C-Injektopas	Pascoe Naturmedizin	Germany	-
Vitamin C Nycomed	Nycomed Pharma A/S	Norway	-
Vitrum Plus Vitamin C	Unipharm	USA	-

Raw Materials

Glucose
Nickel Raney
Acetone
Sodium hypochlorite

Manufacturing Process

D-Glucose was reduced to the D-sorbitol with a hydrogen over Ni Raney, then it was turned into the L-sorbose with the acetobacter suboxydans and the hydroxyl groups of L-sorbose were protected with acetone treatment yielded the diaceton-L-sorbose. Subsequent treatment with NaOCl/Raney Ni produced di-O-isopropylidene-2-oxo-L-gulonic acid. Partial hydrolysis with aqueous HCl gave deprotected 2-oxo-L-gulonic acid, which yielded ascorbinic acid by heating with HCl.

References

Reichstein T., Grusser A.; Helv. Chim. Acta, 17, 311 (1934)
Kirk-Othmer, Encyclopedia of Chemical Technology, 2 Aufl. Vol. 2, s.747 ff

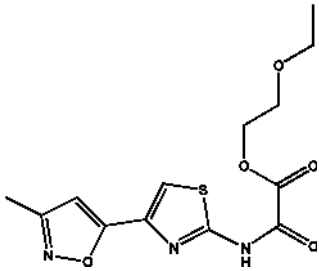
ASOBAMAST

Therapeutic Function: Antiallergic, Anti-asthmatic

Chemical Name: 2-Ethoxyethyl (4-(3-methyl-5-isoxazolyl)-2-thiazolyl) oxamate

Common Name: Asobamast; Sobamast

Structural Formula:



Chemical Abstracts Registry No.: 104777-03-9

Trade Name	Manufacturer	Country	Year Introduced
Asobamast	Onbio Inc.	-	-

Raw Materials

Bromine
3-Methyl-5-acetylisoxazole
Thiourea
2-Ethoxyethyloxalyl chloride

Manufacturing Process

1). 179 mmol of bromine in 20 ml of chloroform were added dropwise in 10 minutes to a solution of 172 mmol of 3-methyl-5-acetylisoxazole, (Gass. Chim. Ital. 72, 242, 194) containing 4.9 ml of glacial acetic acid while the reaction mixture was maintained under stirring at 48°-50°C. After 5 minutes the mixture was poured into 300 g of water and crushed ice. The organic layer was separated, washed with water, dried and evaporated to residual 3-methyl-5-bromoacetylisoxazole. Yield 87%; white crystalline compound, MP: 44°-46°C (isopropyl ether).

2). A mixture of 50 mmol of 3-methyl-5-bromoacetylisoxazole and 100 mmol of thiourea in 164 ml of ethyl alcohol was refluxed for 90 minutes and then cooled for 1 hour with an ice bath. The precipitate was collected by filtration and added to a mixture of 25 ml of a 10% aqueous solution of sodium hydroxide and 100 ml of ethyl acetate under vigorous stirring. The organic layer was separated, washed, dried and evaporated to dryness after recrystallization from acetonitrile the 2-amino-4-(3-methyl-5-isoxazolyl)thiazole melts at 208°-210°C. Yield, 57%.

3). To a mixture of 20.5 mmol of 2-amino-4-(3-methyl-5-isoxazolyl)thiazole in 37.4 ml of pyridine maintained under stirring at 5°C were added dropwise 23.6 mmol of 2-ethoxyethyloxalyl chloride. The reaction mixture was maintained under stirring overnight, then poured into 100 g of crushed ice, made acid with concentrate hydrochloric acid and extracted with chloroform. The chloroform extracts were washed with water, dried and evaporated to dryness. The residual 2-ethoxyethyl-4-(3-methyl-5-isoxazolyl)thiazole-2-oxamate was re-crystallized from 65 ml of acetonitrile. Yield, 91%; MP: 155°-156°C.

References

Carenzi A. et al.; US Patent No. 4,766,137; August 23, 1988; Assigned: Zambon S.p.A., Vicenza, Italy

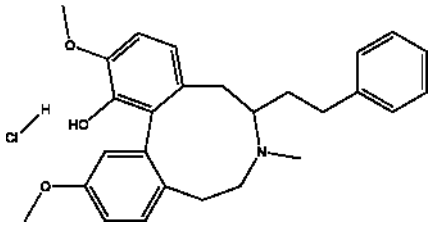
ASOCAINOL HYDROCHLORIDE

Therapeutic Function: Antiarrhythmic

Chemical Name: (+/-)-6,7,8,9-Tetrahydro-2,12-dimethoxy-7-methyl-6-(2-phenylethyl)-5H-dibenz[d,f]azonin-1-ol hydrochloride

Common Name: Asocainol hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 77400-65-8 (Base); 91574-89-9

Trade Name	Manufacturer	Country	Year Introduced
Asocainol hydrochloride	ZYF Pharm Chemical	-	-

Raw Materials

Phenethyl bromide
Activated magnesium turnings
Thebaine
Ammonium chloride

Manufacturing Process

A solution of a Grignard reagent is prepared from 5.5 g (0.23 mol) activated magnesium turnings and 41.5 g (0.24 mol) phenethyl bromide in 200 ml anhydrous diethyl ether. To this is added dropwise, at 35-40°C, a solution of 31.5 g (0.1 mol) thebaine in 0.4 liters dry benzene. After heating under reflux for 2 hours, the reaction mixture is decomposed with a solution of 48 g ammonium chloride in 200 ml water. The usual working up, after conversion of the base into the hydrochloride by means of hydrogen chloride in ethyl acetate, gives 7.3 g (21% of theory) (+/-)-2,12-dimethoxy-1-hydroxy-7-methyl-6-phenethyl-5,6,8,9-tetrahydro-7H-dibenz[d,f]azonine hydrochloride; melting point 227.6°C, after recrystallization from propan-2-ol.

References

Satzinger Gerhard, Herrmann Manfred, Fritschi Edgar, Bahrmann Heinrich, Ganser Volker, Wagner Bernd, Steinbrecher Wolfgang; US Patent No. 4,689,339; Nov. 15, 1983; Assigned to Godecke Aktiengesellschaft (Freiburg, DE)

ASPARAGINASE

Therapeutic Function: Antineoplastic (acute leukemia)

Chemical Name: See Structural Formula

Common Name: Colapase; L-Asnase

Structural Formula: L-Asparagine amidohydrolase (an enzyme of MW 133,000 ± 5,000 believed to consist of 4 equivalent subunits)

Trade Name	Manufacturer	Country	Year Introduced
Crasnitin	Bayer	W. Germany	1969
Crasnitin	Bayer	Italy	1971
Leunase	Kyowa Hakko	Japan	1971
Kidrolase	Specia	France	1971
Crasnitin	Bayer	UK	1971
Elspar	Merck Sharp and Dohme	US	1978
Kidrolase	Rhone Poulenc	Canada	-
Leucogen	Bayer	-	-

Chemical Abstracts Registry No.: 9015-68-3

Raw Materials

Erwinia bacteria
Nutrient medium

Manufacturing Process

Therapeutically active L-asparaginase is isolated from bacteria from the genus Erwinia, a known genus pathogenic towards plants. L-asparaginase is conveniently isolated from this genus by growing the bacteria upon a suitable nutrient medium until a desired quantity is obtained and then extracting the L-asparaginase either by conventional cell disruption methods, or preferably, by processes more fully described in US Patent 3,660,238.

References

Merck Index 849
Kleernan and Engel p. 62
PDR p. 1176
I.N. p. 102
REM p. 1143
Wade, H.E.; US Patent 3,660,238; May 2, 1972
Herbert, D. and Wade, H.E.; US Patent 3,686,072; August 22, 1972

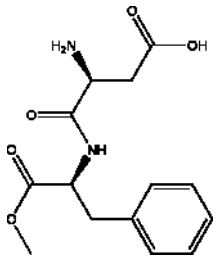
ASPARTAME

Therapeutic Function: Sugar supplement

Chemical Name: N-L-α-Aspartyl-L-phenylalanine 1-methyl ester

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 22839-47-0

Trade Name	Manufacturer	Country	Year Introduced
Canderel	Searle	France	1979
Canderel	Searle	Switz.	1981
Equal	Searle	US	1982
Canderel	Wander	W. Germany	1983
Canderel	Muro	US	-
Nutrasweet	Searle	US	-

Raw Materials

L-Phenylalanine methyl ester hydrochloride
N-Benzyloxycarbonyl-L-aspartic acid α-p-nitrophenyl, β-benzyl diester
Hydrogen

Manufacturing Process

A solution of 88.5 parts of L-phenylalanine methyl ester hydrochloride in 100 parts of water is neutralized by the addition of dilute aqueous potassium bicarbonate, then is extracted with approximately 900 parts of ethyl acetate. The resulting organic solution is washed with water and dried over anhydrous magnesium sulfate. To that solution is then added 200 parts of N-benzyloxycarbonyl-L-aspartic acid α-p-nitrophenyl, β-benzyl diester, and that reaction mixture is kept at room temperature for about 24 hours, then at approximately 65°C for about 24 hours. The reaction mixture is cooled to room temperature, diluted with approximately 390 parts of cyclohexane, then cooled to approximately -18°C in order to complete crystallization. The resulting crystalline product is isolated by filtration and dried to afford β-benzyl N-benzyloxycarbonyl-L-aspartyl-L-phenylalanine methyl ester, melting at about 118.5-119.5°C.

To a solution of 180 parts of β-benzyl N-benzyloxycarbonyl-L-aspartyl-L-phenylalanine methyl ester in 3,000 parts by volume of 75% acetic acid is added 18 parts of palladium black metal catalyst, and the resulting mixture is shaken with hydrogen at atmospheric pressure and room temperature for about 12 hours. The catalyst is removed by filtration, and the solvent is distilled under reduced pressure to afford a solid residue, which is purified by recrystallization from aqueous ethanol to yield L-aspartyl-L-phenylalanine methyl ester. It displays a double melting point at about 190°C and 245-247°C.

References

Merck Index 852
DOT 16 (2) 65 (1980)
I.N. p. 102
Schlatter, J.M.; US Patent 3,492,131; January 27, 1970; Assigned to G.D. Searle and Co.

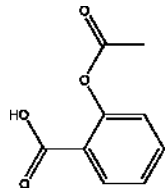
ASPIRIN

Therapeutic Function: Analgesic, Antipyretic, Antiinflammatory

Chemical Name: 2-(Acetyloxy)benzoic acid

Common Name: Acetylsalicylic acid

Structural Formula:



Chemical Abstracts Registry No.: 50-78-2

Trade Name	Manufacturer	Country	Year Introduced
Entab	Mayrand	US	1982
Easprin	WL/PD	US	1982
Ecotrin	Menley and James	US	1983
Zorprin	Boots	US	1983
Verin	Verex	US	1983
AAS	Sterwin Espanola	Spain	-
Acesal	Oranienbourg	E. Germany	-
Acetard	Benzon	Denmark	-
Acetisal	Alkaloid	Yugoslavia	-
Acetisal	Farmakos	Yugoslavia	-
Acetisal	Galenika	Yugoslavia	-
Acetical	Rekah	Israel	-
Acetophen	Merck-Frosst	Canada	-
Acetylin	Heyden	W. Germany	-
Acetylo	Chemedica	Switz.	-
Acetylosal	Maria Heil	Austria	-
Acetyl-Sal	Hartz	Canada	-
Acetysal	Jugoremedija	Yugoslavia	-
Acetysal	Krka	Yugoslavia	-
Acetysal	Zdravlje	Yugoslavia	-
Acimetten	Kwizda	Austria	-
Acisal	Pliva	Yugoslavia	-
Adiro	Bayer	-	-
Alaspine	Liba	Turkey	-
Albyl	AFI	Norway	-
Algo	Lokman	Turkey	-
Alka-Seltzer	Miles	Italy	-

Trade Name	Manufacturer	Country	Year Introduced
Ancasal	Anca	Canada	-
Antidol	Gebro	Austria	-
Apernyl	Bayer	Japan	-
Apyron	Lingner and Fischer	W. Germany	-
Asart	SK and F	US	-
Asatard	De Angeli	Italy	-
Asdol	Srbolek	Yugoslavia	-
Aspalgin	Krka	Yugoslavia	-
Aspec	Kempthorne Prosser	New Zealand	-
Aspegic	Egic	France	-
Aspercin	Otis Clapp	US	-
Aspermin	Buffington	US	-
Aspirin	Bayer	W. Germany	-
Aspirtab	Dover	US	-
Aspirvess	Miles	US	-
Aspisol	Bayer	W. Germany	-
Aspro	Nicholas	Italy	-
Aspro	Pan Quimica	Spain	-
Asrivo	Rivopharm	Switz.	-
Astrin	Medic	Canada	-
Ata spin	Atabay	Turkey	-
Babypyrin	Pfizer	US	-
Bebaspin	Deva	Turkey	-
Bi-Prin	Boots	UK	-
Breoprin	Izal	UK	-
Bufacyl	Teva	Israel	-
Buffaprin	Buffington	US	-
Buf fasal	Dover	US	-
Calmo Yer	Yer	Spain	-
Caprin	Sinclair	UK	-
Casprium	Liade	Spain	-
Catalgine	Theraplix	France	-
Cedrox	Cederroths	Sweden	-
Cemerit	Bayer	Italy	-
Claradin	Nicholas	UK	-
Claragine	Nicholas	France	-
Clariprin	Nicholas	-	-
Codalgina	Fass	Spain	-
Colfarit	Bayer	W. Germany	-
Contrheuma-Retard	Spitzner	W. Germany	-
Coryphen	Rougier	Canada	-
Diaforil	Maggioni	Italy	-
Domupirina	Medici Domus	Italy	-
Ecasil	Andromaco	Argentina	-

Trade Name	Manufacturer	Country	Year Introduced
Ecoprin	Sam-On	Israel	-
Ecotrin	SK and F	US	-
Empirin	Burroughs-Wellcome	US	-
Endospirin	Enila-Lotecia	Brazil	-
Endyol	Guidotti	Italy	-
Entericin	Bristol-Myers	US	-
Enterosarine	Sarein	France	-
Entrophen	Merck-Frosst	Canada	-
Eskotrin	SK and F	US	-
Extren	Vicks	US	-
Flectadol	Maggioni	Italy	-
Genasprin	Fisons	UK	-
Godamed	Pfleger	W. Germany	-
Globentyl	Nyegaard	Norway	-
Globoid	Nyegaard	Norway	-
Glucetyl	Technicopharm	Switz.	-
Hagedabletten	Hageda	W. Germany	-
Halgon	Togal	W. Germany	-
Idotyl	Ferrosan	Denmark	-
Juveprine	Sarget	France	-
Kilios	Farmitalia	Italy	-
Levius	Pharmitalia	UK	-
Levius	Montedison	W. Germany	-
Licyl	A.L.	Norway	-
Longasa	Squibb	US	-
Magnecyl	ACO	Sweden	-
Magnyl	DAK	Denmark	-
Measurin	Breon	US	-
Medisyl	Medica	Finland	-
Mejoral Infantil	Sterwin Espanola	Spain	-
Micristin	Gyogyert	Hungary	-
Neopirine	Casgrain and Charbonneau	Canada	-
Neutracetyl	Promedica	France	-
Nibol	Bosnalijek	Yugoslavia	-
Nova-Phase	Nova	Canada	-
Novasen	Novopharm	Canada	-
Pharmacin	Optrex	UK	-
Premaspin	Laake	Finland	-
Pyronoval	Hoechst	W. Germany	-
Rectosalyl	Bouty	Italy	-
Reunyl	Hassle	Sweden	-
Rhodine	Specia	France	-
Rhonal	Specia	France	-
Rhonal	Rhodia Iberica	Spain	-

Trade Name	Manufacturer	Country	Year Introduced
Rhusal	G.P.	Australia	-
Riphen	Riva	Canada	-
Rodina	Farmitalia	Italy	-
Sal Adult	Beecham	UK	-
Sal Infant	Beecham	UK	-
Sargepirine	Sarget	France	-
Saspryl	Teva	Israel	-
Seclopyrine	Seclo	France	-
Servisprin	Servipharm	Switz.	-
Solprin	Reckitt	UK	-
Solpyron	Beecham	UK	-
Solucetyl	Sarbach	France	-
Solusal	Hamilton	Australia	-
St. Joseph	Plough	US	-
Supasa	Nordic	Canada	-
Tasprin	Ticen	UK	-
Temagin	Beiersdorf	W. Germany	-
Triaphen	Trianon	Canada	-
Trineral	Beiersdorf	W. Germany	-
Winsprin	Winthrop	US	-

Raw Materials

Salicylic acid
Acetic anhydride
Ketene

Manufacturing Process

As described in US Patent 2,731,492, a glass-lined reactor of 1,500 gallons capacity, fitted with a water-cooled reflux condenser, thermometers with automatic temperature registers and an efficient agitator, is employed.

To start the process, a mother liquor is made by dissolving 1,532 kg of acetic anhydride (15 mols) in 1,200 kg of toluene. To this mother liquor, add 1,382 kg of salicylic acid (10 mols), heat the reaction mixture under an efficient reflux condenser, to 88-92°C and maintain within this temperature range for 20 hours.

The reaction mixture is now transferred to aluminum cooling tanks, and is allowed to cool slowly, over a period of 3 to 4 days, to a terminal temperature of 15-25°C (room temperature). The acetylsalicylic acid precipitates as large, regular crystals. The mother liquor is now filtered or centrifuged from the precipitated acetylsalicylic acid and the filter cake is pressed or centrifuged as free of mother liquor as possible. The crystals are washed with distilled water until completely free of acetic acid, pressed or centrifuged as dry as possible and the filter cake is then dried in a current of warm air at a temperature of 60-70°C.

The filtrate from this first batch will comprise a solution of 180 to 270 kg of unprecipitated acetylsalicylic acid (1.0 to 1.5 mols), 510 kg of acetic anhydride (5.0 mols), 600 kg of acetic acid (10.0 mols) (obtained as a by-product in the acetylation step) and 1,200 kg of the diluent toluene. Into this filtrate, at a temperature of 15° to 25°C, ketene gas is now passed through a sparger tube or diffuser plate, with good agitation, until a weight increase of 420.5 kg of ketene (10 mols) occurs. The reaction mixture will now contain 180-270 kg of unprecipitated acetylsalicylic acid (1.0-1.5 mols) and 1,532 kg of acetic anhydride (15 mols) in 1,200 kg of toluene. This mother liquor is recycled to the first step of the process for reaction with another batch of 1,382 kg of salicylic acid. On recirculating the mother liquor, the yield of pure acetylsalicylic acid is 1,780 to 1,795 kg per batch.

References

Merck Index 863
Kleeman and Engel p. 12
PDR (Many References)
DOT 16 (10) 359 (1980)
REM p. 1112
Kamlet, J.; US Patent 2,731,492; January 17, 1956
Hamer, W.E. and Phillips, G.V.; US Patent 2,890,240; June 9, 1959; Assigned to Monsanto Chemicals, Limited, England
Edmunds, R.T.; US Patent 3,235,583; February 15, 1966; Assigned to The Norwich Pharmacal Company

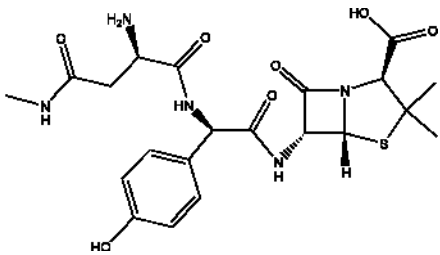
ASPOXICILLIN

Therapeutic Function: Antibiotic

Chemical Name: Glycinamide, N-methyl-D-asparaginyl-N-(2-carboxy-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-6-yl)-D-2-(4-hydroxyphenyl)-,(2S-(2-α,5-α,6-β))-

Common Name: Apaxicillin; Aspoxicillin; Doyle

Structural Formula:



Chemical Abstracts Registry No.: 63358-49-6

Trade Name	Manufacturer	Country	Year Introduced
Aspoxicillin	Shiono Chemical Co., Ltd.	-	-
Aspoxicillin	ZYF Pharm Chemical	-	-
Aspoxicillin	INTER-CHEMICAL(chongqing) CO. LTD	-	-

Raw Materials

D-2-Amino-3-N-methylcarbamoyl-propionic acid hydrochloride (D-N'-methylasparagine HCl)
Benzyloxycarbonyl chloride
Dicyclohexylcarbodiimide
N-Hydroxysuccinimide
p-Hydroxy-D-phenylglycine
Citric acid
6-Aminopenicillanic acid
Triethylamine
Palladium on barium carbonate

Manufacturing Process

1). 3 g (23.6 millimoles) of D-2-amino-3-N-methylcarbamoyl-propionic acid hydrochloride (D-N'-methylasparagine HCl), 4.5 g of benzyloxycarbonyl chloride, 30 g of water, 30 ml of tetrahydrofuran and 12 g of potassium carbonate are mixed at 5° to 10°C. Then, the mixture is stirred at the same temperature for 2 hours. During the reaction, the mixture is kept at a slightly alkaline pH (pH 8) with potassium carbonate. 10 ml of water are added to the reaction mixture, and insoluble materials are filtered off. The filtrate is washed twice with ethyl acetate, acidified with citric acid and then extracted three times with 50 ml of ethyl acetate. The ethyl acetate extracts are washed with water, dried and evaporated to remove solvent. 5.1 g of D-2-benzyloxycarbonylamino-3-N-methylcarbamoyl-propionic acid are obtained. MP: 142°-143°C.

2). 2.8 g (10 millimoles) of D-2-benzyloxycarbonylamino-3-N-methylcarbamoyl-propionic acid, 2.27 g of dicyclohexylcarbodiimide, 1.27 g of N-hydroxysuccinimide and 120 ml of tetrahydrofuran are mixed at 0° to 5°C, and the mixture is stirred at the same temperature for 16 hours. Insoluble materials are filtered off. Then, the filtrate is evaporated at 20°C under reduced pressure to remove the solvent, and the crystalline precipitates thus obtained are washed with a mixture of benzene-ether. 2.6 g of N-(D-2-benzyloxycarbonylamino-3-N-methylcarbamoyl-propionyloxy)succinimide are obtained. MP: 132°-134°C.

3). 3.75 g of N-(D-2-benzyloxycarbonylamino-3-N-methylcarbamoylpropionyloxy)succinimide are dissolved in 50 ml of tetrahydrofuran. 12.5 ml of an aqueous 1 N-sodium hydroxide solution containing 2.3 g of p-hydroxy-D-phenylglycine are added to the solution. The mixture is stirred at room temperature for 24 hours. 20 ml of ethyl acetate and 20 ml of water are added to the reaction mixture, and said mixture is shaken. Then, the aqueous layer is separated, adjusted to pH 3 with citric acid

and extracted with a mixture of 20 ml of tetrahydrofuran and 10 ml of ethyl acetate. The extract is washed with water, dried and evaporated to remove solvent. The residue thus obtained is washed with ether. 3.0 g of D-2-(D-2-benzyloxycarbonylamino-3-N-methylcarbamoylpropionamido)- 2-p-hydroxyphenylacetic acid are obtained as colorless crystalline powder. MP: 154°-156°C(decomp.).

4). 429 mg of D-2-(D-2-benzyloxycarbonylamino-3-N-methylcarbamoylpropionamido)-2-p-hydroxyphenylacetic acid and 382 mg of 6-aminopenicillanic acid triethylamine salt are dissolved in 10 ml of dimethylformamide. 303 mg of diphenylphosphoric azide [$N_3PO(OC_6H_5)_2$] and 110 mg of triethylamine are added to the solution at -5°C, and the mixture is stirred at -5°C for 15 hours. After the reaction, the mixture is adjusted to pH 3 with an aqueous 5% citric acid solution and extracted with a mixture of 15 ml of tetrahydrofuran and 10 ml of ethyl acetate. The extract is washed with water, dried and then evaporated at below 40°C to remove the solvent. Ether is added to the residue obtained, and precipitates are collected by filtration. 509 mg of 6-[D-2-(D-2-benzyloxycarbonylamino-3-N-methylcarbamoylpropionamido)-2-p-hydroxyphenylacetamido]penicillanic acid are obtained as a colorless powder.

5). 627 mg of 6-[D-2-(D-2-benzyloxycarbonylamino-3-N-methylcarbamoyl-propionamido)-2-p-hydroxyphenylacetamido]penicillanic acid and 400 mg of 30% palladium-$BaCO_3$ are suspended in 10 ml of methanol. The suspension is shaken at room temperature for 30 minutes. Said shaking step is carried out in a hydrogen gas atmosphere under atmospheric pressure. After the reaction is completed, the catalysts are removed by filtration. The filtrate is evaporated at below 40°C to remove the solvent, and ether is added to the residue. Then, a colorless crystalline powder is collected by filtration and washed with tetrahydrofuran. 443 mg of 6-[D-2-(D-2-amino-3-N-methylcarbamoyl-propionamido)-2-p-hydroxyphenylacetamido]penicillanic acid are obtained. MP: 198°-201°C(decomp.).

References

Kawazu M. et al.; US Patent No. 4,053,609; October 11, 1977; Assigned to Tanabe Seiyaku Co., Ltd., Osaka, Japan

ASTEMIZOLE

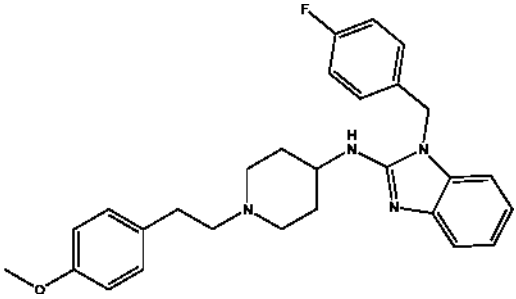
Therapeutic Function: Antiallergic, Antihistaminic

Chemical Name: 1-[(4-Fluorophenyl)methyl]-N-[1-[2-(4-methoxyphenyl) ethyl]-4-piperidinyl]-1H-benzimidazol-2-amine

Common Name: -

Chemical Abstracts Registry No.: 68844-77-9

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Hismanal	Janssen	UK	1983

Raw Materials

2-(4-Methoxyphenyl)ethyl methane sulfonate
1-[(4-Fluorophenyl)methyl]-N-(4-piperidinyl)-1H-benzimidazol-2-amine dihydrobromide
Sodium carbonate

Manufacturing Process

A mixture of 2.3 parts of 2-(4-methoxyphenyl)ethyl methanesulfonate, 4.9 parts of 1-[(4-fluorophenyl)methyl]-N-(4-piperidinyl)-1H-benzimidazol-2-amine dihydrobromide, 3.2 parts of sodium carbonate, 0.1 part of potassium iodide and 90 parts of N,N-dimethylformamide is stirred overnight at 70°C. The reaction mixture is poured onto water. The product is extracted with methylbenzene. The extract is washed with water, dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from 2,2'-oxybispropane, yielding 2.2 parts (48%) of 1-(4-fluorophenylmethyl)-N-[1-[2-(4-methoxyphenyl)ethyl]-4-piperidinyl]-1H-benzimidazol-2-amine; MP 149.1°C.

References

Merck Index A-1
DFU 7 (1) 10 (1982)
OCDS Vol. 3 p. 177
DOT 19 (7) 412 (1983)
I.N.p. 102
Janssens, F., Stokbroekx, R., Torremans, J. and Luyckx, M; US Patent 4,219,559; August 26, 1980; Assigned to Janssen Pharmaceutica N.V.

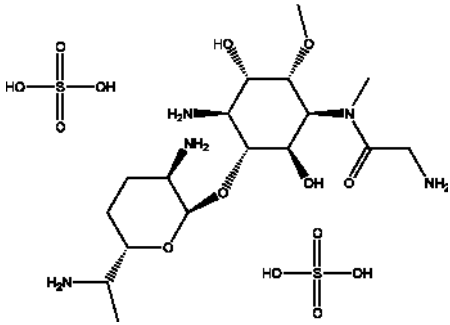
ASTROMICIN SULFATE

Therapeutic Function: Antibiotic

Chemical Name: L-chiro-Inositol, 4-amino-1-((aminoacetyl)methylamino)-1,4-dideoxy-3-O-(2,6-diamino-2,3,4,6,7-pentadeoxy-β-L-lyxo-heptopyranosyl)-6-O-methyl-, sulfate (1:2)

Common Name: Astromicin sulfate; Fortimicin A

Structural Formula:



Chemical Abstracts Registry No.: 55779-06-1 (Base); 72275-67-3

Trade Name	Manufacturer	Country	Year Introduced
Fortimicin sulfate	Youngjin Pharma	-	-
Astromicin sulfate	AroKor Holdings Inc.	-	-
Astromicin sulfate	ZYF Pharm Chemical	-	-
Abbott-44747	Abbott	-	-
Fortimicin A	Kyowa Hakko Kogyo Co., Ltd.	-	-

Raw Materials

Micromonospora olivoasterospora MK-70 (ATCC 21819)	Glucose
Yeast extract	Peptone
Starch	Calcium carbonate
Corn steep liquor	Soybean meal
Magnesium sulfate heptahydrate	Potassium phosphate, dibasic
Calcium carbonate	Potassium chloride
Amberlite	Radiolite No. 600
	Dowex

Manufacturing Process

Aminoglycoside antibiotic complex produced by Micromonospora

olivoasterospora.

Micromonospora olivoasterospora MK-70 (ATCC 21819) (FERM-P No. 1560) is used as a seed strain. One loopful of the seed strain is inoculated into 10 ml of a seed medium containing 2% glucose, 0.5% peptone, 0.5% yeast extract and 0.1% calcium carbonate (pH 7.5 before sterilization) in a 50 ml large test tube. Culturing is carried out at 30°C for 5 days. 10 ml of the seed culture broth is then inoculated into 30 ml of a second seed medium in a 250 ml Erlenmeyer flask. The composition of the second seed medium is the same as that of the first seed medium. The second seed culturing is carried out at 30°C for 2 days with shaking. Then 30 ml of the second seed culture broth is inoculated into 300 ml of a third seed medium in a 2 L Erlenmeyer flask provided with baffles. The composition of the third seed medium is the same as that of the first seed medium. The third seed culturing is carried out at 30°C for 2 days with shaking and 1.5 L of the third seed culture broth (corresponding to the content of five flasks) is inoculated into 15 L of a fourth seed medium in a 30 L glass jar fermenter. The composition of the fourth seed medium is the same as that of the first seed medium. Culturing in the jar fermenter is carried out at 37°C for 2 days with aeration and stirring (revolution: 350 r.p.m.; aeration: 15 L/min). Thereafter, 15 L of the fourth seed culture broth is inoculated into 150 L of a main fermentation medium in a 300 L fermenter. The main fermentation medium comprises 4% soluble starch, 2% soybean meal, 1% corn steep liquor, 0.05% K_2HPO_4, 0.05% $MgSO_4 \cdot 7H_2O$, 0.03% KCl and 0.1% $CaCO_3$ (pH 7.5 before sterilization). Culturing in the fermenter is carried out at 37°C for 4 days with aeration and stirring (revolution: 150 r.p.m.; aeration: 80 L/min).

After the completion of culturing, the resulting fermentation broth is adjusted to a pH of 2.5 with concentrated sulfuric acid, and stirred for 30 minutes. Then, about 7 kg of a filter aid, Radiolite No. 600 (product of Showa Kagaku Kogyo Co., Ltd., Japan) is added thereto and the microbial cells are removed by filtration. The filtrate is adjusted to a pH of 7.5 with 6 N sodium hydroxide and passed through a column packed with about 20 L of a cation exchange resin, Amberlite IRC-50 (ammonium form), and the effluent is discarded. Active substances are adsorbed on the resin. After washing the resin with water, the adsorbed active substances are eluted out with 1 N aqueous ammonia. Activity of the eluate is determined by a paper disc method, using an agar plate of Bacillus subtilis No. 10707. The active fractions are collected and the mixture is concentrated to about 1 L under reduced pressure. The concentrate is passed through a column packed with 500 ml of an anion exchange resin, Dowex 1x2 (OH^- form). Then, about 2 L of water is passed through the column, whereby impurities are removed and active substances are eluted out. The thus obtained active fractions are collected, and concentrated to about 100 ml under reduced pressure, and the resulting concentrate is passed through a column packed with about 50 ml of active carbon powder. The active substances are adsorbed onto the carbon powders. Then, the column is washed with water and the effluent and the washing water are discarded. Then, the adsorbed active substances are eluted out with 0.2 N sulfuric acid. Activity of the eluate is determined by the paper disc method using Bacillus subtilis, and the active fractions are collected. The thus obtained fractions are passed through a column of Dowex 44 (OH^- form), and active substances are eluted out with water. The active fractions are again collected and concentrated to about 50 ml. The thus obtained concentrate is lyophilized, whereby about 32 g of a crude powder containing Fortimicin A is

obtained. The crude powder exhibits an activity of 575 unit/mg (the activity of 1 mg of a pure product corresponds to 1000 units).

Then 10 g of the crude powder is placed as a thin and uniform layer on 500 ml of silica gel packed in a glass column. The glass column is prepared by suspending the silica gel in a solvent of the lower layer of a mixture comprising chloroform, isopropanol and 17% aqueous ammonia (2:1:1 by volume), and then packing the suspension tightly in the column as a uniform layer, and thereafter washing with the same solvent. After placing the crude powder at the head of the column, elution is carried out with the above-described solvent by gradually pouring into the column from its top, and thereafter elution is carried out at a flow rate of about 50 ml/hour. The eluate is obtained as fractions of 20 ml each, and the activity of each fraction is determined by a paper disc method. Fortimicin B is eluted out at first. Thereafter, fractions containing Fortimicin A are obtained. The active fractions are subjected to paper chromatography, and the fractions containing Fortimicin A are collected and concentrated under reduced pressure to completely remove the solvent. The concentrate is then dissolved in a small amount of water. After freeze-drying the solution, about 1.8 g of purified preparate of the free base of Fortimicin A is obtained. The activity of the preparate is about 970 unit/mg. White amorphous powder, MP: >200° (dec.). $[\alpha]_D^{25}$ +87.5° (c = 0.1 in water); solves in water and lower alcohols, insoluble in organic solvents.

References

Nara T. et al.; US Patent No. 3,946,768; August 24, 1976; Assigned to Abbott Laboratories, North Chicago Ill.

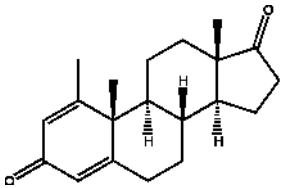
ATAMESTANE

Therapeutic Function: Aromatase inhibitor

Chemical Name: Androsta-1,4-diene-3,17-dione, 1-methyl-

Common Name: Atamestane

Structural Formula:



Chemical Abstracts Registry No.: 96301-34-7

Trade Name	Manufacturer	Country	Year Introduced
Atamestane	Schering AG	-	-

Raw Materials

17β-Hydroxy-1-methylandrosta-1,4-dien-3-one
Chromic acid

Manufacturing Process

6.01 g of 17β-hydroxy-1-methylandrosta-1,4-dien-3-one is dissolved in 100 ml of acetone. At room temperature, 22 ml of a chromic acid solution (prepared from 6.67 g of CrO_3, 6 ml of concentrated sulfuric acid, replenished with water to 100 ml) is added dropwise to this solution. The mixture is stirred for one hour and then precipitated into ice water; the product is suctioned off and dried, thus obtaining after recrystallization from acetone/hexane 5.25 g of 1-methylandrosta-1,4-diene-3,17-dione, melting point 165-166°C.

References

Kerb Ulrich, Sauer Gerhard, Wiechert Rudolf, Henderson David, Nishino Yukishige, Beier Sybille; US Patent No. 4,591,585; May 27, 1986; Assigned to Schering Aktiengesellschaft (Berlin and Bergkamen, DE)

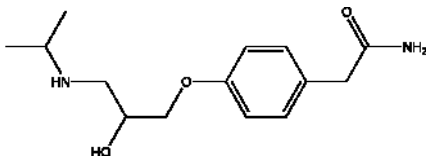
ATENOLOL

Therapeutic Function: Beta-adrenergic blocker

Chemical Name: 4-[2-Hydroxy-3-[(1-methylethyl)amino]propoxy] benzeneacetamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 29122-68-7

Trade Name	Manufacturer	Country	Year Introduced
Tenormin	Stuart	UK	1976
Tenormin	I.C.I.	W. Germany	1976

Trade Name	Manufacturer	Country	Year Introduced
Tenormin	I.C.I.	Switz.	1978
Tenormin	I.C.I.	Italy	1979
Tenormin	I.C.I.	France	1979
Tenormin	Stuart	US	1981
Atenol	C.T.	Italy	-
Blokium	Prodes	Spain	-
Ibinolo	I.B.I.	Italy	-
Myocord	Szabo-Kessler	Argentina	-
Normiten	Abic	Israel	-
Seles Beta	Farmitalia	Italy	-
Tenoretic	Stuart	US	-
Vericordin	Lazar	Argentina	-

Raw Materials

p-Hydroxyphenylacetamide
Epichlorohydrin
Isopropylamine

Manufacturing Process

1 gram of 1-p-carbamoylmethylphenoxy-2,3-epoxypropane and 10 ml of isopropylamine in 25 ml of methanol is heated in a sealed tube at 110°C for 12 hours. The mixture is evaporated to dryness and the residue is partitioned between 50 ml of chloroform and 50 ml of aqueous 2 N hydrochloric acid. The aqueous acidic layer is separated, made alkaline with sodium carbonate and extracted twice with 50 ml of chloroform each time. The combined extracts are dried and evaporated to dryness and the residue is crystallized from ethyl acetate. There is thus obtained 1-p-carbamoylmethyiphenoxy-3-isopropylamino-2-propanol, MP 146-148°C.

The 1-p-carbamoylmethylphenoxy-2,3-epoxypropane used as starting material may be obtained as follows: a mixture of 3.2 grams of p-hydroxyphenylacetamide, 25 ml of epichlorohydrin and 6 drops of piperidine is heated at 95-100°C for 6 hours. The mixture is cooled and filtered and the solid product is crystallized from methanol. There is thus obtained 1-p-carbamoylmethylphencxy-2,3-epoxypropane, MP 158-160°C.

References

Merck Index 868
DFU 1 (1) 7 (1976)
Kleeman and Engel p. 62
PDR pp. 1786, 1788
OCDS Vol. 2 p. 109 (1980)
DOT 13 (2) 49 (1977) and 16 (1) 30 (1980)
I.N. p. 103
REM p. 904
Barrett, A.M., Carter, J., Hull, R., Le Count, D.J. and Squire, C.J.; US Patent 3,663,607; May 16, 1972; Assigned to Imperial Chemical Industries Limited, England

Barrett, A.M., Carter, J., Hull, R., Le Count, D.J. and Squire, C.J.; US Patent 3,836,671; September 17, 1974; Assigned to Imperial Chemical Industries Limited, England

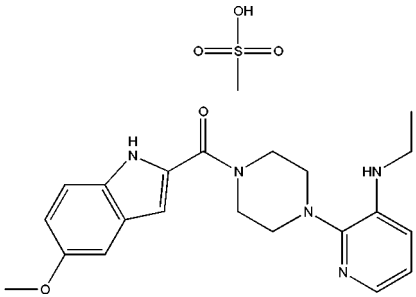
ATEVIRDINE MESYLATE

Therapeutic Function: Antiviral

Chemical Name: Piperazine, 1-(3-(ethylamino)-2-pyridinyl)-4-((5-methoxy-1H-indol-2-yl)carbonyl)-, monomethanesulfonate

Common Name: Atevirdine mesylate

Structural Formula:



Chemical Abstracts Registry No.: 136816-75-6 (Base); 138540-32-6

Trade Name	Manufacturer	Country	Year Introduced
Atevirdine mesylate	Upjohn	-	-

Raw Materials

1,1'-Carbonyldiimidazole
Chlorotrimethylsilane
Methanesulfonic acid
5-Methoxyindole-2-carboxylic acid
1-(3-N-Ethylamino-2-pyridinyl)piperazine

Manufacturing Process

1-[5-Methoxyindolyl-2-carbonyl]-4-[3-(ethylamino)-2-pyridinyl]piperazine:

1,1'-Carbonyldiimidazole (0.55 g) is added to a 20°-25°C solution of 5-methoxyindole-2-carboxylic acid (0.59 g) in tetrahydrofuran (7.0 ml). After stirring 1 hour, the reaction is transferred via cannnula into a solution of 1-(3-N-ethylamino-2-pyridinyl)piperazine (0.70 g) in tetrahydrofuran (7 ml) at -12°C (ice/acetone bath). The reaction is stirred at -10°C for 30 minutes, then slowly warmed to 20°-25°C and stirred a further 18 hours. After diluting with

ether (60 ml), the mixture is washed with saturated aqueous sodium bicarbonate (70 ml), saline (70 ml) and dried over anhydrous sodium sulfate. The mixture is concentrated under reduced pressure to a residue which is purified by flash chromatography (2 cm x 20 cm) eluting with methanol/chloroform (2/98) to give the title compound, mp 153°-154°C.

1-[5-Methoxyindolyl-2-carbonyl]-4-[3-(ethylamino)-2-pyridinyl]piperazine hydrochloride:

1-(Ethyl)-3-(dimethylaminopropyl)carbodiimide (1.25 g) is added to a solution of 1-(3-ethyl-2-pyridinyl)piperazine (1.12 g) in THF (15 ml). The reaction is stirred at 20°-25°C for 3 hr; then it is dissolved in chloroform (50 ml) and extracted with saturated aqueous sodium bicarbonate, saline, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash column chromatography (200 g silica) eluting with ethyl acetate/hexane (50/50), the appropriate fractions are pooled and concentrated to give the title compound, The product is dissolved in methanol (150 ml) with heating, cooled to 20°-25°C and chlorotrimethylsilane (4.70 mmol) is added. The mixture is concentrated to half-volume, ether is added until cloudy and the flask is stored at 0°C overnight. Filtration gives the hydrochloride salt, MP: 194°-195°C.

The mesylate salt is formed by dissolving the free base in methanol and by adding methanesulfonic acid (1 eq). The solution is diluted with diethyl ether until the salt crystallizes out of solution. The crystals are collected and dried to afford the mesyl salt of the title compound, MP: 215°-216°C.

References

Allen M.M. et al.; WO Patent No. 91/09849; 1991/07/11; Pharmacia and Upjohn Company, U.S.

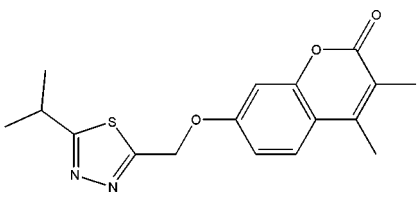
ATIBEPRONE

Therapeutic Function: Antidepressant

Chemical Name: 7-((5-Isopropyl-1,3,4 thiadiazol-2-yl)methoxy)-3,4-dimethylcoumarin

Common Name: Atibeprone

Structural Formula:



Chemical Abstracts Registry No.: 153420-96-3

Trade Name	Manufacturer	Country	Year Introduced
Atibeprone	BASF	-	-

Raw Materials

7-Methoxy-3,4-dimethylcoumarin
Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide)

Manufacturing Process

10 mmol of 7-methoxy-3,4-dimethylcoumarin were stirred with 10 mmol (4.04 g) of Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide) in 20 ml of toluene at 90°C for 1-2.5 h. After cooling, the solvent was distilled off, the residue was taken up in DMF, and water was added. The precipitate was filtered off with suction and the crude 3,4-dimethyl-7-(2-isopropyl-1,3,4-thiadiazol-5-ylmethoxy)-2-thiocoumarin was purified by recrystallization from methanol or by column chromatography (silica gel, methylene chloride). Yield: 98%, melting point: 134-135°C.

References

Rendenbach-Mueller Beatrice, Karl Ulrich, Weifenbach Harald; US Patent No. 5,414,006; May 9, 1995; Assigned to BASF Aktiengesellschaft (Ludwigshafen, DE)

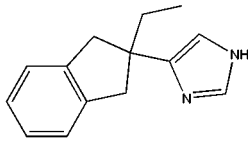
ATIPAMEZOLE

Therapeutic Function: Antihypertensive

Chemical Name: 4-(2-Ethyl-2,3-dihydro-1H-inden-2-yl)-1H-imidazole

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 104054-27-5

Trade Name	Manufacturer	Country	Year Introduced
Antisedan	Novartis	-	-
MPV 1248	Orion Farmos Group Ltd.	-	-

Raw Materials

2-Acetyl-1-indanone	Ethyl bromide
Sodium carbonate	Sodium borohydride
Bromine	Hydrochloric acid
Palladium on carbon	

Manufacturing Process

(a). 2-Acetyl-1-indanone (Liebigs Ann. Chem. 1906, 347, 112) is alkylated with ethylbromide in acetone in the presence of sodium carbonate to 2-acetyl-2-ethyl-1-indanone. The acetyl group is brominated with bromine in methanol and to imidazole by heating in formamide as before. The melting point of the 4(5)-(2,3-dihydro-2-ethyl-1-oxo-1H-inden-2-yl)imidazole is 126-127°C (from ethyl acetate).

(b). The carbonyl group of 4(5)-(2,3-dihydro-2-ethyl-1-oxo-1H-inden-2-yl)imidazole is reduced to the alcohol group with sodium borohydride in ethanol. The product is the mixture of cis-trans stereoisomers, the purification of which is accomplished by liquid chromatography: cis-isomer as hydrochloride (melting point 184-185°C); ^{1}H NMR (80 MHz, MeOH-d_4): 0.73 (3H, t), 1.86 (2H, m), 3.36 (2H, m), 3.61 (3H, s), 5.15 (1H, s), 7.06 (1H, d), 7.2-7.4 (4H, m), 8.69 (1H, d), and trans-isomer as hydrochloride; ^{1}H NMR (80 MHz, MeOH-d_4): 0.80 (3H, t), 1.84 (2H, m), 3.15 (2H, m), 3.24 (3H, s), 5.15 (1H, s), 6.87 (1H, d), 7.2-7.4 (4H, m), 8.54 (1H, d).

The oxo derivative prepared in step (a) or the hydroxy derivative prepared in step (b) is hydrogenated in 2 N hydrochloric acid in the presence of 10% palladium on carbon at 70°C. When the uptake of hydrogen ceases, the reaction mixture is filtered and made alkaline. The product is extracted with methylene chloride which is washed with water, dried and evaporated to dryness. From the residue, which is the product as base, is made the hydrochloride of 4(5)-(2,3-dihydro-2-ethyl-1H-inden-2-yl)imidazole using dry hydrogen chloride in ethyl acetate. It has melting point 211-215°C.

References

Karjalainen Arto J., Virtanen Raimo E., Karjalainen Arja L., Kurkela Kauko O.A.; US Patent No. 4,689,339; August 25, 1987; Farmos Yhtyma oy (Turku, FI)

ATOLIDE

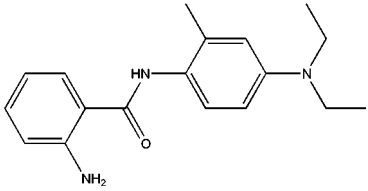
Therapeutic Function: Anticonvulsant

Chemical Name: 2-Amino-N-[4-(diethylamino)-2-methylphenyl]benzamide

Common Name: Atolide

Chemical Abstracts Registry No.: 16231-75-7

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Atolide	ZYF Pharm Chemical	-	-

Raw Materials

2-Amino-5-diethylaminotoluene
Isatoic acid anhydride

Manufacturing Process

0.8 kg (4.5 moles) of freshly distilled 2-amino-5-diethylaminotoluene is mixed thoroughly with 0.75 kg (4.5 moles) of isatoic acid anhydride and the mixture heated to 100°C with stirring for three hours. The product formed is taken up before cooling in 2.5 liters of boiling ethyl acetate and the solution filtered. On cooling the filtrate 1.1 kg (83% of theory) of 2-amino-4'-(diethylamino)-2'-methylbenzanilide precipitates out. After re-crystallzation from n-propanol the colorless crystalline product obtained melts at 152°C.

References

G.B. Patent No. 1,123,457; 11 August 11, 1966; Warner Lambert Pharmaceutical Company, a Corporation of Delaware, USA

ATORVASTATIN CALCIUM

Therapeutic Function: Anticholesteremic

Chemical Name: (βR,δR)-2-(4-Fluorophenyl)-β,δ-dihydroxy-5-[(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1)

Common Name: Atorvastatin calcium

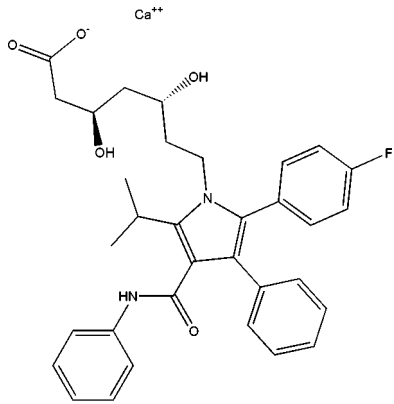
Chemical Abstracts Registry No.: 134523-03-08; 134523-00-5 (Base)

Raw Materials

n-Butyl diisopropyl amine
t-Butylcarboxylic acid
Sodium borohydride
Butyl lithium

Triethylborane
Bromine
Magnesium
S-(+)-2-Acetoxy-1,1,2-triphenylethanol
5-(4-Fluorophenyl)-2-(1-methylethyl)-1-(3-oxopropyl)-N,4-diphenyl-1H-pyrrole-3-carboxamide

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Cardyl	Pfizer	Spain	-
Citalor	Pfizer Pharmaceuticals	Ireland	-
Lipibec	IVAX Arg.	-	-
Lipibec	Syncro	Argentina	-
Lipitor	Parke Davis	-	-
Lipitor	Pfizer	-	-
Xarator	Pfizer Italy S.p.A.	Italy	-

Manufacturing Process

285 ml 2.2 M n-butyl lithium in hexane was added dropwise to 92 ml diisopropylamine at -50-60°C under nitrogen. The well stirred solutions warmed to about -20°C, then it was cannulated into a suspension of 99 g of S(+)-2-acetoxy-1,1,2-triphenylethanol in 500 ml absolute tetrahydrophuran (THF) at -70°C and the reaction mixture was allowed to warm to -10°C for 2 hours. A suspension of $MgBr_2$ was made from 564 ml (0.63 mol) of bromine and 15.3 g of magnesium (0.63 mol) in 500 ml THF cooled to -78°C. The enolate solution was cannulated into this suspension within 30 min and was stirred for 60 min at -78°C. 150 g 5-(4-fluorophenyl)-2-(1-methylethyl)-1-(3-oxopropyl)-N,4-diphenyl-1H-pyrrole-3-carboxamide in 800 ml absolute THF was added dropwise over 30 min; stirred 90 min at -78°C, then was added 200 ml acetic acid, this is removed to a cool bath, 500 ml of H_2O was added and the mixture concentrate in vacuo at 40-50°C. After adding of 500 ml of 1:1 EtOAc/heptane the mixture was filtered. The filtrate was washed extensively with 0.5 N HCl, then several times with H_2O and finally

EtOAc/heptane (3:1) and cooled with dry ice to -20°C. The light brown crystalline product was dried in vacuum oven at 40°C. The yield was 194 g. 112 g of the same product was produced by evaporation of mother liquor after recrystallization and chromatographic purification on a silicagel.

162 g of this substance was suspended in methanol/THF (5:3) and was stirred with 11.7 g of sodium methoxide until everything was dissolved and kept in the freezer overnight. Later it was quenched with AcOH concentrated in vacuo, was added to 500 ml H_2O and extracted twice with EtOAc (300 ml). The combined extracts was washed with saturated $NaHCO_3$ brine and dried over anhydrous $MgSO_4$, purified on silica-gel and gave 86.1 g of white crystals m.p. 125-126°C, α_D^{20}=4.23° (1.17 M, CH_3OH).

81 g of the last product in 500 ml absolute THF was added as quickly as possible to the mixture of 77 ml THF at diisopropylamine, 200 ml 2.2 M of n-butyl lithium and 62 ml of t-butylacetate in 200 ml THF -40-42°C under nitrogen. Stirring was continued for 4 hours at -70°C. The reaction mixture was concentrated in vacuo, the residue was taken up in EtOAc, washed with water, then saturated NH_4Cl, $NaHCO_3$ (saturated), dried over anhydrous $MgSO_4$, filtred and the solvent evaporated.

The organic phase was dried and concentrated in vacuo to yield 73 g crude product, that was dissolved in 500 ml absolute THF, 120 ml triehtylborane and 0.7 g t-butylcarboxylic acid, 70 ml methanol and 4.5 g sodium borohydride was added. The mixture was stirred at -78°C under a dry atmosphere for 6 hours, poured slowly into 4:1:1 mixture of ice/30%H_2O_2/H_2O and stirred overnight. $CHCl_3$ (400 ml) was added and organic layer washed extensively with H_2O until no peroxide could be found, was dried over $MgSO_4$, filtered and was treated by chromatography on silica gel to yield 51 g. The product was dissolved in THF/methanol and saponificated with NaOH and, concentrated to remove organic solvents at room temperature, added 100 ml H_2O, and extracted with Et_2O twice. Organic layer was thoroughly dried and it was left at room temperature for the next 10 days, then concentrated. Chromatography on silica gel yielded 13.2 g racemate of lactone - trans-(+/-)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-di-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide. This racemate was divided by chiral synthesis which was made analogously the method in US Pat. No. 4,581,893. Then each isomer was saponificated with NaOH and purificated by HPLC. The calcium salt corresponding acid was prepared by reaction with 1 eq. of $CaCl_2 \cdot 2H_2O$ in water.

References

Roth B.D.; US Patent No. 5,273,995; Dec. 28, 1993; Assigned: Warner-Lambert Company (Morris Plains, NJ)

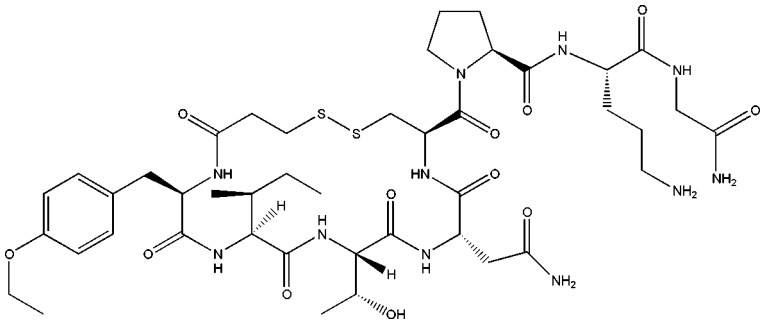
ATOSIBAN

Therapeutic Function: Oxytocin antagonist

Chemical Name: Oxytocin, 1-(3-mercaptopropanoic acid)-2-(O-ethyl-D-tyrosine)-4-L-threonine-8-L-ornithine-

Common Name: Atosiban; Tractotile

Structural Formula:



Chemical Abstracts Registry No.: 90779-69-4

Trade Name	Manufacturer	Country	Year Introduced
Tractocile	Ferring srl	-	-
Antocin	Ortho	-	-
Antocin	Ferring	-	-
Tractotile	Ferring	-	-
Atosiban	ASI Bio-tech's products	-	-

Raw Materials

BocGly resin
O-Ethyl-D-tyrosine
Boc-L-ornithine
Ammonia sodium
BOC-L-Asparagine
Diisopropylethylamine
Dicyclohexylcarbodiimide
3-Mercaptopropanoic acid
Boc-L-threonine
4-Ethoxyphenyl-D-alanine
Boc-L-cysteine
Boc-isoleucyne
Hydroxybenzotriazole

Manufacturing Process

BocGly resin (3.0 g, 3 meq) was placed in the reaction vessel of a Vega Model 50 semiautomatic peptide synthesizer. The peptide was built up by increments on the resin in accordance with Tables 1 and 2.

TABLE 1

Solid phase synthesis

Step	Solvent/Reagent	Vol. [ml]	Time [min]	Number of cycles
1	Dichloromethane	70	3	2
2	50% trifluoroacetic acid/dichloromethane	70	15	2
3	Isopropanol	70	3	2
4	Dichloromethane	70	3	2
5	10% diisopropylethylamine in dichloromathane	70	3	2
6	Dichloromethane	70	3	2
7	Activated amino acid	70	120*	1
8	Isopropanol	70	3	2
9	Dichloromethane	70	3	2

*30 for BocAsn and BocGln

TABLE 2

Termination procedure

Step	Solvent/Reagent	Vol. [ml]	Time [min]	Number of cycles
1	1 M Imidazole: dichloromethane + acetic acid anhydride	70 + 7	30	1
2	Isopropanol	70	3	2
3	Dichloromethane	70	3	4

Activation of the amino acid was carried out by dissolving 10 meq of a suitably protected amino acid, 15 meq of hydroxy benzotriazole and 10 meq of dicyclohexylcarbodiimide in DMF (70 ml), whereupon the mixture was left at room temperature for 1 h (asparagine and glutamine were activated at 0°C for 15 min), whereupon the precipitate was filtered off, and the filtrate was treated the activated amino acid in Table 1 (step 7). The completion of the coupling step was checked by the method of Kaiser (Anal. Biochem. 34, 595 (1970)) after the cycle had been completed (step 9). If the test was positive (coupling yield below 99%), the cycle was repeated starting from step 7. If the test was negative, the termination procedure was performed according to Table 2. When the whole sequence had been coupled, the resin was placed on a filter and washed repeatedly with methanol. The dried product was placed in a glass vessel and cooled in an ethanol-dry ice bath and suspended in methanol (about 100 ml). The mixture was then saturated with sodium-dried ammonia to achieve approximately 50% concentration. Then the vessel was placed in a steel cylinder and left at room temperature for two days. After the pressure had been relieved, the product was filtered, and the residue was extracted with hot (about 100°C) DMF (2x100 ml). The filtrate and the extract were combined and evaporated. The residue was dissolved in a small amount of hot DMF, and methanol was added to the coupling point. The precipitate was collected by filtration and washed on the filter with methanol. After drying in vacuum, the purity was checked by thin-layer chromatography. Yield about 2.8 g.

100 mg of the above described protected peptide were placed in a 100 ml

round-bottom flask, and dry nitrogen was flushed through for about 15 min. 50 ml of sodium-dried ammonia were distilled in, and the protective group was removed from the product by adding sodium until blue color remained in the solution for 15 sec. The excess of sodium was destroyed by adding of ammonium chloride. Ammonia was removed in a nitrogen stream, and the residue was dissolved in 1 liter of methanol. The pH of the solution was adjusted to about 4 with concentrated acetic acid, and the solution was then titrated with 0.1 mM of iodine in methanol to brownish color. The mixture was stirred with 3 g of Dowex 50x2 ion exchanger in chloride form for 10 min at room temperature. The ion exchanger was removed by filtration, and the filtrate was evaporated to dryness. The residue was dissolved in 3 ml of 20% acetic acid and purified by chromatography on Sephadex G-25 with 20% acetic acid as eluent. The final purification was achieved by reverse phase HPLC. The purity of the product was determined on a HPCL column μ-Bondapak C-18 in 45% ethanol and 55% 5 mM trifluoroacetic acid in water. The column was supplied by Water Associates, Inc., Millford, Mass., U.S.A. The purity of the product was also shown by amino acid analysis.

References

Per O.R. Melin et al.; US Patent No. 4,504,469; March 12, 1985; Assigned to Ferring AB, Malmo, Sweden

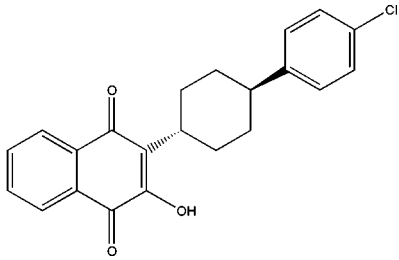
ATOVAQUONE

Therapeutic Function: Antiprotozoal

Chemical Name: 2-(trans-4-(p-Chlorophenyl)cyclohexyl)-3-hydroxy-1,4-naphthoquinone

Common Name: Atovaquone

Structural Formula:



Chemical Abstracts Registry No.: 95233-18-4

Trade Name	Manufacturer	Country	Year Introduced
Atovaquone	GlaxoSmithKline	-	-
Mepron	GlaxoSmithKline	USA	-

Trade Name	Manufacturer	Country	Year Introduced
Tropine	Neon Laboratories Ltd.	India	-
Wellvone	GlaxoSmithKline	USA	-
Wellvone Suspension	GlaxoSmithKline Australia Pty Ltd.	Australia	-

Raw Materials

2-Chloro-1,4-napthohinone
Acetyl chloride
Carbon disulfide
Aluminum chloride
Silver nitrate
Cyclohexene
Ammonium persulfate
Bromine
Sodium metabisulphite

Manufacturing Process

Preparation of intermediate 4-(4-chlorophenyl)cyclohexane-1-carboxylic acid was needed at first. It was made as follows: acetyl chloride (30 g), aluminium chloride (60 g) in carbon disulfide (120 ml) were stirred at -50°C. Cyclohexen (30 g) previously cooled to -50°C was added dropwise during 10 minutes and the mixture was stirred for 60 minutes at -50°C. The solvent was decanted and 300 ml chlorobenzene was added, the so-obtained solution heated at 40°C for 3 hours with stirring, poured onto a mixture of ice and concentrated hydrochloric acid and the organic layer washed with 2 M HCl, 2 M NaOH and water, dried over anhydrous Na_2SO_4. The product was distilled in vacuo, the fraction boiling at 140°-154°C (0.1 mm Hg) collected, diluted with an equal volume of petroleum ether, cooled to -6°C and a stream of nitrogen gas bubbled through.

3.1 g above obtained hexahydroacetophenone was dissolved in dioxan (15 ml) and the fresh preparated hypobromite (8 ml) in a solution of NaOH (6.2 g) in water (42 ml) at 0°C was added at below 20°C. The mixture was stirred at ambient temperature for 6 hours then allowed to stand overnight. Excess hypobromite was destroyed with sodium metabisulphite, cooled and then acidified to give a colourless solid. It was filtered off, washed with water, dried and recrystallysed from ethanol to give 4-(4-chlorophenyl)cyclohexane-1-carboxylic acid, m.p. 254°-256°C. A mixture of this acid, 2-chloro-1,4-naphthoquinone and silver nitrate was added to ammonium persulfate to give the corresponding naphthoquinone which was saponificated with KOH and was yielded 2-trans-4-(p-chlorophenyl)cyclohexyl)-3-hydroxy-1,4 naphthoquinone, m.p. 216°-219°C, shown by NMR to be the pure trans isomer.

References

Hudson A.T. et al.; US Patent No. 5,053,432; Oct. 1, 1991; Assigned: Burroughs Wellcome Co. (Research Triangle Park, NC)

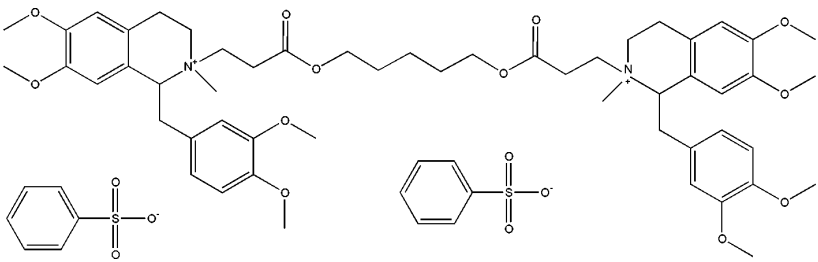
ATRACURIUM BESYLATE

Therapeutic Function: Neuromuscular blocker

Chemical Name: N,N'-4,10-Dioxa-3,11-dioxotridecylene-1,13-bis-tetrahydropapaverine dibenzenesulfonate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 64228-81-5

Trade Name	Manufacturer	Country	Year Introduced
Tracrium	Burroughs-Wellcome	US	1983
Tracrium	Burroughs-Wellcome	UK	1983
Tracrium	Burroughs-Wellcome	Switz.	1983

Raw Materials

Acryloyl chloride
Tetrahydropapaverine
Pentane-1,5-diol
Methyl benzene sulfonate

Manufacturing Process

Acryloyl chloride (0.2 mol) in dry benzene (60 ml) was added over 0.5 hour with mechanical stirring to pentane-1,5-diol (0.1 mol), triethylamine (0.2 mol) and pyrogallol (0.1 g) in dry benzene (100 ml). Further dry benzene (ca 100 ml) was added followed by triethylamine (10 ml), and the mixture stirred at 50°C for 0.5 hour. The triethylamine hydrochloride was filtered off and the solvent removed in vacuum to leave a yellow oil which was distilled in the presence of a trace of p-methoxyphenol, excluding light, to give 1,5-pentamethylenediacrylate (12.9 g; 61%; BP 90° to 95°C/0.01 mm Hg).

A solution of tetrahydropapaverine (4.43 g) and 1,5-pentamethylene diacrylate (1.30 g) in dry benzene (15 ml) was stirred under reflux for 48 hours excluding light. The solvent was removed in vacuum and the residual pale red oil dissolved in chloroform (10 ml). Addition of ether (ca 400 ml), followed by saturated ethereal oxalic acid solution (ca 500 ml) gave a flocculent white precipitate, which was filtered off, washed with ether and

dried. Crystallization (twice) from ethanol gave N,N'-4,10-dioxa-3,11-dioxotridecylene-1,13-bis-tetrahydropapaverine dioxalate as a white powder (3.5 g; 51%; MP 117° to 121°C).

The free base, N,N'-14,10-dioxa-3,11-dioxotridecylene-1,13-bis-tetrahydropapaverine, was obtained by basifying an aqueous solution of the dioxalate with sodium bicarbonate solution, followed by extraction with toluene and evaporation of the solvent, to give a colorless viscous oil.

Scrupulously dried base (0.5 g) in spectroscopically pure acetonitrile (8 ml) was treated with methyl benzene sulfonate at room temperature for 22 hours. The filtered reaction mixture was added dropwise to mechanically stirred, filtered, dry ether (ca 450 ml). The flocculent white precipitate was filtered off, washed with dry ether, and dried in vacuum over P_2O_5 at 50°C to yield the product, an off-white powder melting at 85° to 90°C.

In practice it is usually used as dibenzenesulfonate.

References

Merck Index A-2
DFU 5 (11) 541 (1980)
PDR p.766
DOT 19 (2) 111 (1983)
I.N. p.104
REM p.925
Stenlake, J.B., Waigh, R.D., Dewar, G.H., Urwin, J. and Dhar, N.C.; US Patent 4,179,507 December 18,1979; Assigned to Burroughs Wellcome Company

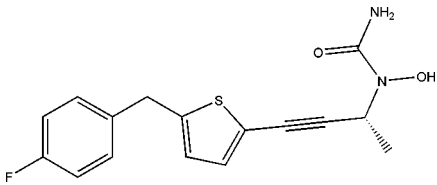
ATRELEUTON

Therapeutic Function: Antiallergic, Anti-asthmatic

Chemical Name: 1-((R)-3-(5-(p-Fluorobenzyl)-2-thienyl)-1-methyl-2-propynyl)-1-hydroxyurea

Common Name: Atreleuton; ABT 761

Structural Formula:



Chemical Abstracts Registry No.: 154355-76-7

Trade Name	Manufacturer	Country	Year Introduced
Abbott-85761	Abbott	-	-

Raw Materials

Thiophene	tetrakis(Triphenylphosphine)palladium(O)
Butyl lithium	Bis(acetonitrile)palladium(II) chloride
N-Iodosuccinimide	4-Fluorobenzylbromide
Sodium thiosulfate	p-Toluenesulfonyl chloride
Triethylamine	(S)-3-Butyn-2-ol
Hydroxylamine	Hydrogen chloride
Sodium hydroxide	Potassium cyanate
Triphenylphosphine	(R)-N-Hydroxy-N-(3-butyn-2-yl)urea
Copper (I) iodide	Diethylamine

Manufacturing Process

A solution of thiophene (12.6 g, 0.15 mol) in a mixture of anhydrous ether (230 ml) and anhydrous THF (70 ml) was treated dropwise at 0°C with a 2.5 M solution of n-butyl lithium in hexane (54.0 ml, 0.134 mol). The mixture was stirred at 0°C for 1.5 h and then transferred by cannula into a -78°C solution of 4-fluorobenzylbromide (23.6 g, 0.125 mol) containing tetrakis(triphenylphosphine)palladium(O) (1.25 g) in anhydrous THF (200 ml). The reaction mixture was stirred for 17 h at room temperature and then quenched with saturated aqueous NH_4Cl solution (100 ml) and partitioned between ether and additional NH_4Cl solution. The ether layer was dried over $MgSO_4$, concentrated in vacuum and the residue subjected to vacuum distillation to give 19.4 g (81%) of 2-(4-fluorophenylmethyl)thiophene, boiling point 74°-83°C at 0.6-0.7 mm of Hg.

A mixture of 2-(4-fluorophenylmethyl)thiophene (3.85 g, 20.0 mmol) and N-iodosuccinimide (4.50 g, 20.0 mmol) in 1:1 chloroform-acetic acid (40 ml) was stirred at room temperature for 1 h and then diluted with an equal volume of water. The organic layer was washed with saturated aqueous $NaHCO_3$ solution (2 times 50 ml), 10% aqueous sodium thiosulfate solution (2 times 50 ml) and once with brine. After drying over $MgSO_4$, the organic layer was concentrated in vacuum to give 6.07 g (95%) of 2-iodo-5-(4-fluorophenylmethyl)thiophene as a gold colored oil.

To a solution of (S)-O-p-toluenesulfonyl-3-butyn-2-ol (11.2 g, 50.0 mmol), prepared by addition of p-toluenesulfonyl chloride and triethylamine to (S)-3-butyn-2-ol, in methanol (100 ml), was added 55% aqueous hydroxylamine (30 ml, 0.50 mol) and the reaction mixture was stirred at room temperature for 40 h. The reaction mixture was cooled to 10°C and concentrated HCl (50 ml) was added dropwise. The reaction mixture was concentrated in vacuum and the residue was partitioned between H_2O (50 ml) and ethyl acetate (200 ml). The 2-phase mixture was cooled to 10°C and taken to pH 8 with 50% aqueous NaOH solution (60 ml). After stirring for 15 min the layers were separated and the aqueous phase was extracted twice with 200 ml of ethyl acetate. The combined ethyl acetate extracts were cooled to 10°C and a solution of KOCN (8.1 g, 0.10 mmol) in H_2O (30 ml) was added, followed by dropwise addition of 11 ml of concentrated HCl, and the reaction mixture was

stirred for 30 min. The ethyl acetate layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuum to give 5.9 g (92% yield) of (R)-N-hydroxy-N-(3-butyn-2-yl)urea, melting point 129°C.

To a solution of 2-iodo-5-(4-fluorophenylmethyl)thiophene (5.30 g, 16.6 mmol), in anhydrous DMF (5.0 ml) was added (R)-N-hydroxy-N-(3-butyn-2-yl)urea (2.12 g, 16.6 mmol), triphenylphosphine (84.0 mg, 0.32 mmol), bis(acetonitrile)palladium(II) chloride (40.0 mg, 0.16 mmol), copper(I) iodide (16.0 mg, 0.08 mmol), and diethylamine (5.6 ml). The mixture was stirred under nitrogen at room temperature for 22 h and concentrated in vacuum at 32°C. The residue was subjected to chromatography on silica eluting with 2-7% MeOH in CH_2Cl_2, crystallization from ethyl acetate-hexane and trituration in CH_2Cl_2 to afford (R)-N-{3-[5-(4-fluorophenylmethyl)thien-2-yl]-1-methyl-2-propynyl}-N-hydroxyurea as a cream-colored solid 0.94 g (18%), melting point 135°-136°C, (dec).

References

Brooks D.W. et al.; US Patent No. 5,506,261; April 9, 1996; Assigned: Abbott Laboratories, Abbott Park, Ill.

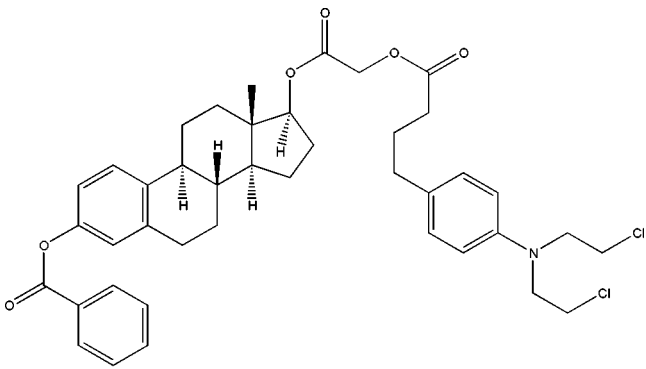
ATRIMUSTINE

Therapeutic Function: Antineoplastic

Chemical Name: Estra-1,3,5(10)-triene-3,17-diol, (17β)-, 3-benzoate, 17-((4-(4-(bis(2-chloroethyl)amino)phenyl)-1-oxobutoxy)acetate)

Common Name: Atrimustine; Busramustine

Structural Formula:



Chemical Abstracts Registry No.: 75219-46-4

Trade Name	Manufacturer	Country	Year Introduced
Atrimustine	Onbio Inc.	-	-

Raw Materials

1,3,5(10)-Estratriene-3,17β-diol
Monobromoacetyl bromide
Dimethyl sulfoxide

Manufacturing Process

Preparation of 3-hydroxy-1,3,5(10)-estratriene-17β-[4-{p-[bis(2-chloroethyl)amino]phenyl}butyryloxy]acetate:

Preparation of 3-hydroxy-1,3,5(10)-estratriene-17β-monobromoacetate. 10 g of 1,3,5(10)-estratriene-3,17β-diol was dissolved in 400 ml of anhydrous tetrahydrofuran (THF), and then, 8.8 g of pyridine was added. A solution of 22.5 g of monobromoacetyl bromide in 74 g of carbon tetrachloride was added dropwise to the resulting solution at about -5°C to -7°C. The mixture was kept for one night. After the reaction, the resulting precipitate was separated by a filtration. The solvent was distilled off from the filtrate. The residue was dissolved in ether and recrystallized from ether to obtain 1,3,5(10)-estratriene-3,17β-bis(monobromoacetate). 2 g of the product was dissolved in 900 ml of methanol and the solution was cooled to -5°C. A solution of 0.24 g of K_2CO_3 in 20 ml of water was added dropwise to the resulting solution. After the reaction for 30 minutes, 1000 ml of water was added and the resulting precipitate was separated and dried. It was confirmed that the product was 3-hydroxy-1,3,5(10)-estradiene-17β-monobromoacetate by the elementary analysis and the IR spectrum.

Preparation of 3-hydroxy-1,3,5(10)-estratriene-17β-[4{p-[bis(2-chloroethyl)amino]phenyl}butyryloxy]acetate:

200 mg of silver [4-{p-[bis(2-chloroethyl)amino]phenyl}butyrate (silver salt of Chlorambucil) was added in 10 ml of DMSO to form a white colloidal solution. Then, 190.8 mg of 3-hydroxy-1,3,5(10)-estratriene-17β-monobromoacetate was added and the mixture was stirred at room temperature for 64 hours in the dark. The precipitate was changed to yellowish green color. A small amount of acetone was added and the precipitate was separated by a filtration through G-4 filter. The precipitate was changed from yellowish green color to blackish green color by the irradiation of light. The filtrate was colorless and transparent. DMSO was distilled off under a reduced pressure on a water bath at 80°C and 100 ml of water was added to precipitate white crystals. The crystals were kept for 1 hour to remove DMSO and the crystals were separated through G-4 filter and thoroughly washed with distilled water and dried under a reduced pressure in a desiccator. A crude yield was 330.5 mg.

Purification of the product 330.5 mg of crude crystals were dissolved in a mixed solvent of 50 vol. parts of cyclohexane and 10 vol. parts of ethyl acetate. The solution was slowly passed through a column filling 40 g of silica gel and the product was gradually separated to obtain 188.2 mg (yield: 62.86%) of pure product. It was confirmed that the product was 3-hydroxy-

1,3,5(10)-estratriene-17β-[4{p-[bis(2-chloroethyl)amino]phenyl} butyryloxy]acetate by the elementary analysis and the IR spectrum.

References

Asano K. et al.; US Patent No. 4,332,797; June 1, 1982; Assigned to Kureha Kagaku Kogyo Kabushiki Kaisha, Tokyo, Japan

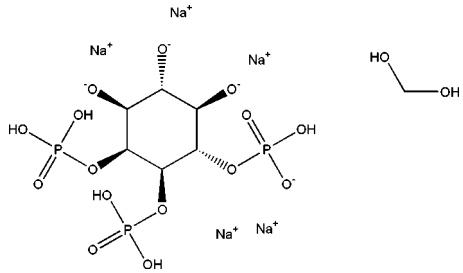
ATRINOSITOL SODIUM

Therapeutic Function: Neuropeptide antagonist, Antiinflammatory

Chemical Name: D-myo-Inositol 1,2,6-tris(dihydrogen phosphate) pentasodium salt

Common Name: Atrinositol sodium; Minosifate sodium; α-Trinositol sodium

Structural Formula:



Chemical Abstracts Registry No.: 136033-48-2

Trade Name	Manufacturer	Country	Year Introduced
Atrinositol sodium	Perstorp (Sweden)	-	-

Raw Materials

Borane-methyl sulphide complex
4-Toluenesulfonyl chloride
cis-3,5-Cyclohexadiene-1,2-diol
1'-Dynamax 83,123-6 column
Silver oxide
Sodium hydride
Palladium on charcoal
Tetrabenzylpyrophosphate
Mandelic acid, (S)-,(+)-
Lithium aluminum hydride
m-Chloroperbenzoic acid
Benzyl bromide
Cyclohexene
N,N,N',N'-Tetramethylenediamine
Diisopropylamine
Butyl lithium

Manufacturing Process

Pseudomonas putida oxidation of benzene affords cis-3,5-cyclohexadiene-1,2-diol which is used as a novel precursor for the synthesis of D- and L-myo-inositol trisphosphates, which was prepared in 11 steps:

1). (R)-(+)-sec-Phenethyl alcohol:

Borane-methyl sulfide complex (68 ml, 0.71 mol) was added dropwise to a solution of (S)-(+)-mandelic acid (98.5 g, 0.65 mol) in THF (900 ml) at room temperature (RT) under a flow of argon over 3 h. The reaction was stirred for 6 h. Then methanol was added dropwise and stirring continued for a further 13 h. The volatiles were then removed in vacuum, the residue stirred in methanol, and the process repeated 3 times. Column chromatography (MeOH-ethyl acetate-petrol, gradient elution) of the residue afforded the diol (57.3 g, 64%). p-Toluenesulphonyl chloride (80 g, 98% 0.41 mol) was then added portionwise to a solution of the diol in pyridine (700 ml) at 0°C over 8 h. The reaction was stirred at RT for 13 h, then the volatiles removed in vacuum.

The residue was washed with water, dried ($MgSO_4$), and the residual pyridine removed in vacuum to afford the tosylate as an orange oil. A solution of the tosylate in ether/THF (500 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (15.6 g, 0.41 mol) in ether (500 ml) at RT under argon. The reaction was stirred for 16 h, then water (15.6 ml), aqueous sodium hydroxide solution (15.6 ml), and water (46.8 ml) were successively added dropwise. After 4 h, sodium sulfate was added and stirring continued. The mixture was filtered through a pad of celite, washed with dichloromethane, and the solvents evaporated in vacuum. Column chromatography (0-100% ether-petrol, gradient elution) followed by distillation (b.p. 96°C/20mmHg) afforded the title alcohol (24.1 g, 48%) as a colourless liquid, $[\alpha]_D^{27}$+41.48°.

2). (3aα,6α,7α,7aα)-6,7-Epoxy-3a,6,7,7a-tetrahydrobenzo[d]-1,3-dioxol-2-one and (3aα,6β,7β,7aα)-6,7-Epoxy-3a,6,7,7a-tetrahydrobenro[d]-1,3-dioxol-2-one:

Freshly prepared sodium methoxide (0.1 ml of a 1 M solution in methanol, 10 mmol) was added dropwise to a solution of cis-3,5-cyclohexadiene-1,2-diol (112 mg, 1 mmol) in dimethyl carbonate (1.7 ml) and methanol (0.2 ml) at RT under argon, and stirred for 20 min. A small aliquot was removed, solvent evaporated in vacuum (bath T 22°C) and the resulting solid was washed with a small volume of chilled (-20°C) ether and chilled (-20°C) petrol (b.p. 30°-40°C) to afford the 3a,7a-dihydrobenzo[1,3]dioxol-2-one (cyclic carbonate) as a beige-coloured solid, mp 90°C (dec.).

The remaining solution was diluted with DCM (2 ml), and m-chloroperbenzoic acid (mCPBA) (0.30 g, 2.0 mmol) was added portionwise. After stirring at RT for 40 h, the mixture was extracted with DCM and washed successively with aqueous sodium sulfite solution, aqueous sodium bicarbonate solution and water, dried ($MgSO_4$) and evaporated in vacuum. Column chromatography (45-70% ether-petrol, gradient elution) of the residue afforded the title epoxides (3aα,6α,7α,7aα)-6,7-epoxy-3a,6,7,7a-tetrahydrobenzo[d]-1,3-dioxol-2-one (73 mg, 47%) mp 87°-89°C and (3aα,6β,7β,7aα)-6,7-epoxy-3a,6,7,7a-

tetrahydrobenro[d]-1,3-dioxol-2-one, (16 mg 10%) mp 107.5°-108.5°C.

3). [3aR-[3aα,4α,5β(R),7aα]-3a,4,5,7a-Tetrahydro-4-hydroxy-5-(1-phenylethoxy)benzo[d]-1,3-dioxol-2-one and [3aS-[3aα,4α,5β(R),7aα]-3a,4,5,7a-tetrahydro-4-hydroxy-5-(1-phenylethoxy)benzo[d]-1,3-dioxol-2-one:

Tetrafluoroboric acid-diethyl ether complex (catalytic amount) was added to a stirred solution of epoxide (+/-)-(3aα,6α,7α,7aα)-6,7-epoxy-3a,6,7,7a-tetrahydrobenzo[d]-1,3-dioxol-2-one (32 mg, 0.2 mmol) and (R)-(+)-sec-phenethyl alcohol (0.048 ml, 0.4 mmol) in DCM at RT under argon. After 30 min, water was added and the mixture extracted with DCM (3 times). The combined organic phase was dried ($MgSO_4$) and evaporated in vacuum. Column chromatography (30-75% ether-petrol, gradient elution) of the residue afforded the alcohols [3aR-[3aα,4α,5β(R),7aα]-3a,4,5,7a-tetrahydro-4-hydroxy-5-(1-phenylethoxy)benzo[d]-1,3-dioxol-2-one and [3aS-[3aα,4α,5β(R),7aα]-3a,4,5,7a-tetrahydro-4-hydroxy-5-(1-phenylethoxy)benzo[d]-1,3-dioxol-2-one. (37 mg, 67%) as a thick oil and a 1:1 mixture of diastereomers. Subsequent HIPLC (1'-Dynamax 83,123-6 column; 6% isopropanol-petrol, 15 ml/min) effected separation of the diastereomers. Less polar [3aR-[3aα,4α,5β(R),7aα]-3a,4,5,7a-tetrahydro-4-hydroxy-5-(1-phenylethoxy)benzo[d]-1,3-dioxol-2-one had retention time 16.3 min; $[\alpha]_D^{20}$ +90.1° (c 1.1, $CHCl_3$).

4. [3aS-[3aα,6β(R),7α,7aα]-7-Benzyloxy-3a,6,7,7a-tetrahydro-6-(1-phenylethoxy)benzo[d]-1,3-dioxol-2-one):

Freshly prepared silver oxide (88 mg, 0.38 mmol) was added to a stirred solution of the alcohol [3aR-[3aα,4α,5β(R),7aα]-3a,4,5,7a-tetrahydro-4-hydroxy-5-(1-phenylethoxy)benzo[d]-1,3-dioxol-2-one (53 mg, 0.19 mmol) and benzyl bromide (0.080 ml, 0.67 mmol) in DMF (2 ml) at RT under argon and the mixture stirred vigorously in the dark for 64 h. The mixture was diluted with ether, filtered through a pad of silica which was then washed copiously with ether and DCM, and the filtrate evaporated in vacuum. The residue was dissolved in ether, washed with water and brine, dried ($MgSO_4$) and evaporated in vacuum. Column chromatography (30-100% ether-petrol, gradient elution) of the residue afforded the title benzyl erher. (70 mg, 100%) as needles, m.p. 97°-99°C; $[\alpha]_D^{20}$ +102.9° (c 1.0, $CHCl_3$).

5). [1S-[1α,2α,5α(R),6β]-6-Benzyloxy-5-(1-phenylethoxy)-3-cyclohexene-1,2-diol:

The carbonate (0.459 g, 1.25 mmol) was stirred in 1:5:1 triethylamine/methanol/water (12 ml) at RT. After 72 h, the volatiles were removed in vacuum and the residue freeze-dried. The crude product was purified by column chromatography (50-100% ethyl acetate-petrol, gradient elution) to afford the title diol (0.421 g, 99%) as a white solid, mp 46°-47°C; $[\alpha]_D^{20}$ +82.4° (c 2.5, $CHCl_3$).

6. [1R-[1α,2α,3β,4α(R),5α,6α)-3-Benzyloxy-5,6-epoxy-4-(1-phenylethoxy) cyclohexane-1,2-diol:

mCPBA (2.68 g, 80% 12.4 mmol) was added to a stirred solution of olefin

(2.111 g, 6.2 mmol) in DCM (30 ml) at RT under argon. After stirring for 48 h, cyclohexene was added dropwise (excess) and the mixture stirred for 90 min. The solvents were removed in vacuum to afford the title epoxydiol (1.93 g, 92%) as a foam and a 17:1 mixture of epoxide stereoisomers. Column chromatography (10-50% ethyl acetate-petrol, gradient elution) yielded the major epoxide (1.928 g, 87%) as a foam, $[\alpha]_D^{20}$ +98.9° (c 0.92, $CHCl_3$).

7). [3aR-[3aα,4α,5β(R),6β,7β,7aα)-4-Benzyloxy-6,7-epoxy-5-(1-phenylethoxy) hexahydro-2,2-dimethylbenzo[d]-1,3-dioxole:

Camphorsulphonic acid monohydrate (catalytic amount) was added to a stirred solution of [1R-[1α,2α,3β,4α(R),5α,6α)-3-benzyloxy-5,6-epoxy-4-(1-phenylethoxy)cyclohexane-1,2-diol (0.321 g, 0.9 mmol) in 2,2-dimethoxypropane (10 ml) at RT under argon. After 16 h, the mixture was poured into DCM and washed with aqueous sodium bicarbonate solution and water. The aqueous layers were reextracted with DCM and the combined organic extracts dried ($MgSO_4$) and evaporated in vacuum column chromatography (50% ether-petrol) of the residue afforded the title epoxy acetonide (0.317 g, 89%) as needles, m.p. 114°-115°C (recrystallized from ether-petrol); $[\alpha]_D^{20}$+134.1° (c 1.00, $CHCl_3$).

8). [2(R)]-L-3-O-Benzyl-4,5-O-isopropylidene-6-O-[2-(5,5-dimethyl-1,3-dioxan-2-yl)ethyl]-2-O-(1-phenylethyl)-muco-inositol and [S(R)]-D-4-O-Benzyl-2,3-O-isopropylidene-6-O-[2-(5,5-dimethyl-1,3-dioxan-2-yl)ethyl]-5-O-(1-phenylethyl)-myo-inositol:

The 1,3-dioxane-2-ethanol (2 ml) was added dropwise to sodium hydride (396 mg of 60% dispersion, 10 mmol) at RT under argon. When the effervescence had ceased, N,N,N',N'-tetramethylenediamine (TMEDA) (1 ml) was added, the mixture stirred for a further 4 h and then a solution of the epoxide (396 mg, 1.0 mmol) in TMEDA (1.0 ml) was added dropwise. The mixture was stirred at 100-110°C for 3 days and then allowed to cool to RT. Water was added and, after 5 min the mixture extracted with ether. The extract was washed with water and the aqueous phase reextracted with ether. The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuum column chromatography (4% MeOH-10% ether-86% petrol) of the residue afforded [2(R)]-L-3-O-Benzyl-4,5-O-isopropylidene-6-O-[2-(5,5-dimethyl-1,3-dioxan-2-yl)ethyl]-2-O-(1-phenylethyl)-muco-inositol (176 mg, 31%), $[\alpha]_D^{20}$ +63.4° (c 1.4, $CHCl_3$); and [S(R)]-D-4-O-Benzyl-2,3-O-isopropylidene-6-O-[2-(5,5-dimethyl-1,3-dioxan-2-yl)ethyl]-5-O-(phenylethyl)-myo-inositol (273 mg, 48%), mp 108°-110°C, $[\alpha]_D^{20}$+29.3° (c 0.76, $CHCl_3$) as a thick oil and a white solid respectively, and starting epoxide (65 mg, 16%).

9). D-6-O-[2-(5,5-Dimethyl-1,3-dioxan-2-yl)ethyl]-2,3-O-isopropylidene-myo-inositol:

10% Palladium on activated charcoal (Fluka) (catalytic amount) was added to a solution of [S(R)]-D-4-O-benzyl-2,3-O-isopropylidene-6-O-[2-(5,5-dimethyl-1,3-dioxan-2-yl)ethyl]-5-O-(phenylethyl)-myo-inositol (105 mg, 0.18 mmol) in ethanol (10 ml) at RT under argon. The flask was flushed through with hydrogen and the mixture stirred vigorously under a hydrogen atmosphere. After 16 h, the flask was refluxed with argon and the mixture filtered through a pad of celite, which was washed copiously with ether and then DCM.

Evaporation of the solvents in vacuum afforded. D-6-O-[2-(5,5-Dimethyl-1,3-dioxan-2-yl)ethyl]-2,3-O-isopropylidene-myo-inositol (65 mg, 100%) as a white solid, mp 96.5°-97.5°C; $[\alpha]_D^{20}$ +24.7° (c 0.45, $CHCl_3$).

10). D-6-O-[2-(5,5-Dimethyl-1,3-dioxan-2-yl)ethyl]-2,3-O-isopropylidene-myo-inositol 1,4,5-tris(dibenqylphosphate):

n-Butyl lithium (0.172 ml of a 2.5 M solution in hexanes, 0.43 mmol) was added dropwise to a solution of the above compound (45 mg, 0.12 mmol) in THF (4 ml) at -30°C under argon. Diisopropylamine (0.073 ml, 0.52 mmol) was then added and the mixture stirred at -30°-(-25)°C for 20 min. Tetrabenzylpyrophosphate (242 mg, 0.45 mmol) was added in one portion and the reaction allowed to warm gradually to +2°C over 4 h. The precipitated lithium dibenzylphosphate was filtered off, the cake washed with THF and the solvent evaporated in vacuum. Column chromatography (30-100% ethyl acetate-petrol, gradient elution) of the residue afforded the triphosphate (95 mg, 67%) as a thick oil, $[\alpha]_D^{20}$ -4.5° (c 1.13, $CHCl_3$).

11). D-(-)-myo-Inositol 1,4,5-trisphosphate:

10% Palladium on activated charcoal (Fluka) (catalytic amount) was added to a solution of the protected trisphosphate (243 mg, 0.21 mmol) in ethanol (10 ml) at RT under argon. The flask was flushed through with hydrogen and the mixture stirred vigorously under a hydrogen atmosphere. After 48 h, the flask was refluxed with argon, the mixture filtered and washed with ethanol. The volatiles were removed in vucuo and the residue freeze-dried to afford fully debenzylated material. This was stirred in 80% aqueous trifluoroacetic acid (cu. 6 ml) at RT for 4 h. After removing the volatiles in vacuum, the residue was again freeze-dried. Purification of the crude product by HPLC (Spherisorb S5SAX column, 202 mm x 250 mm; 0.2 M ammonium formate buffer at pH 4, 12 ml/min) afforded atrinositol (64 mg, 88%), retention time 42 min, $[\alpha]_D^{20}$ 22°-24° (c 0.15, H_2O, pH 6.9). UR, ^{1}H-NMR, ^{31}P-NMR spectra confirmed the structure of described compounds.

References

Ley S.V. et al.; Tetrahedron; vol. 46, No 13/14, pp. 4995-5026; 1990

ATROPINE

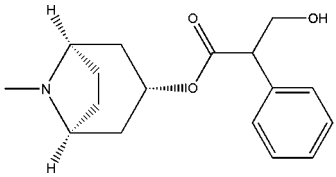
Therapeutic Function: Anticholinergic

Chemical Name: 1-α-H,5-α-H-Tropan-3-α-ol (+/-)-tropate (ester)

Common Name: Atropine; DL-Hyoscyamine

Chemical Abstracts Registry No.: 51-55-8

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Atromed	Promed Exports	India	-
Atropen	Meridian	USA	-
Atropinol	Wenzer	Denmark	-

Raw Materials

Plants from botanic family *Slanaceae: Atropa belladonna, Atropa acminata, Atropa boetica, Hyocyamus niger*
Chloroform

Manufacturing Process

Atropin was obtained from belladonna roots and by racemisation of L-hyoscyamine with dilute alkali or by heating in chloroform solution. The alkaloid was crystallised from alcohol on addition of water, or from chloroform on addition of light petroleum, or from acetone in long prisms, m.p. 118°C, sublimed unchanged when heated rapidly. It is soluble in alcohol or chloroform, less soluble in ether or hot water, sparingly so in cold water (in 450 L at 25°C) and almost insoluble in light petroleum. Atropine is optically inactive.

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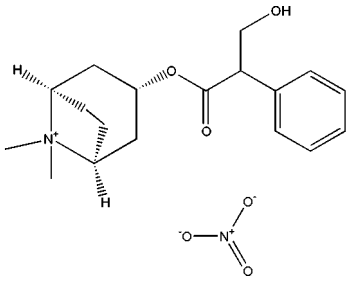
ATROPINE METHONITRATE

Therapeutic Function: Anticholinergic, Mydriatic, Spasmolytic

Chemical Name: 8-Azoniabicyclo[3.2.1]octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8,8-dimethyl-, (3-endo)-, nitrate (salt)

Common Name: Methylatropine nitrate; Atropine methonitrate

Structural Formula:



Chemical Abstracts Registry No.: 52-88-0

Trade Name	Manufacturer	Country	Year Introduced
Methylatropine nitrate	Paganfarma	-	-
Methylatropine nitrate	Yick-Vic Chemicals and Pharmaceuticals (HK) Ltd.	-	-
Atropine methyl nitrate	Sigma	-	-

Raw Materials

Atropine
Atropine sulfate
Methyl nitrate
Barium nitrate

Manufacturing Process

There are 2 methods of synthesis of methyl atropine nitrate:

1) To a solution of 28.9 g atropine of in 100 g of methanol was added at 110°C for 2 hours 7.7 g methyl nitrate. Methanol was evaporated and methyl atropine nitrate was crystallysed, M.P. 163°C.

2) To a solution of 70.4 g methyl atropine sulfate (prepared from methyl atropine chloride and silver nitrate) in water was added aqueous solution of 26.1 g barium nitrate. Barium sulfate was deleted by filtration. Filtrate was concentrated and the methyl atropine nitrate was obtained.

References

DE Patent No. 138,443; Nov. 28, 1901; Assigned to Farbenfabriken vorm. Friedr. Bayer and Company in Elberfeld
DE Patent No. 137,622; Nov.28, 1902; Assigned to Farbenfabriken vorm. Friedr. Bayer and Company in Elberfeld

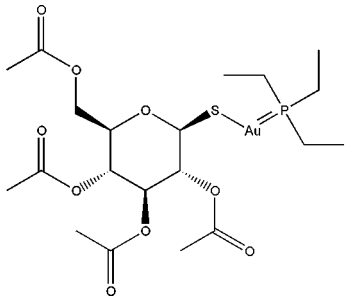
AURANOFIN

Therapeutic Function: Antiarthritic

Chemical Name: S-Triethylphosphine gold 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 34031-32-8

Trade Name	Manufacturer	Country	Year Introduced
Ridaura	SK and F	W. Germany	1982
Ridaura	SK and F	Switz.	1983

Raw Materials

Thiodiglycol
Triethylphosphine
S-(2,3,4,6-Tetra-O-acetylglucopyranosyl)thiopseudourea hydrobromide
Gold acid chloride trihydrate
Potassium carbonate

Manufacturing Process

(A) Triethylphosphine gold chloride: A solution of 10.0 g (0.08 mol) of thiodiglycol in 25 ml of ethanol is mixed with a solution of 15.76 g (0.04 mol) of gold acid chloride trihydrate in 75 ml of distilled water. When the bright orange-yellow solution is almost colorless, it is cooled to -5°C and an equally cold solution of 5.0 g (0.0425 mol) of triethylphosphine in 25 ml of ethanol is added dropwise to the stirred solution. After the addition is complete, the cooled mixture is stirred for ½ hour. Solid that separates is removed and the filtrate is concentrated to about 30 ml to yield a second crop. The combined solid is washed with aqueous-ethanol (2:1) and recrystallized from ethanol by adding water to the cloud point. The product is obtained as white needles, MP 85° to 86°C.

(B) Auranofin: A cold solution of 1.66 g (0.012 mol) of potassium carbonate in

20 ml of distilled water is added to a solution of 5.3 g (0.011 mol) of S-(2,3,4,6-tetra-O-acetylglucopyranosyl)-thiopseudourea hydrobromide [Methods in Carbohydrate Chemistry, vol 2, page 435 (1963)] in 30 ml of water at -10°C. A cold solution of 3.86 g (0.011 mol) of triethylphosphine gold chloride in 30 ml of ethanol containing a few drops of methylene chloride is added to the above mixture before hydrolysis of the thiouronium salt is complete. After the addition is complete, the mixture is stirred in the cold for ½ hour. The solid that separates is removed, washed first with aqueous ethanol then water and dried in vacuum. There is obtained colorless crystals, MP 110° to 111°C, of S-triethylphosphine gold 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside.

References

Merck Index 882
DFU 1 (10) 451 (1976)
PDR p. 1721
DOT 18 (9) 463 (1982)
I.N. p. 106
REM p. 1122
McGusty, E.R. and Sutton, B.M.; US Patent 3,708,579; January 2, 1973; Assigned to Smith Kline and French Laboratories
Nemeth, P.E. and Sutton, B.M.; US Patent 3,635,945; January 18, 1972; Assigned to Smith Kline and French Laboratories

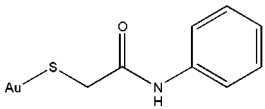
AUROTHIOGLYCANIDE

Therapeutic Function: Antiarthritic

Chemical Name: [[(Phenylcarbamoyl)methyl]thio]gold

Common Name: Aurothioglycollic acid anilide

Structural Formula:



Chemical Abstracts Registry No.: 16925-51-2

Trade Name	Manufacturer	Country	Year Introduced
Lauron	Endo	US	1945

Raw Materials

Potassium bromoaurate
Sulfur dioxide
Thioglycolic acid anilide

Manufacturing Process

The product is made preferably by reacting thioglycolic acid anilide with an aurous bromide (AuBr).

Prior art methods for making the starting material, $HSCH_2CONHC_6H_5$ are disclosed in an article by Beckurts et al. in Journ. Praktische Chemie (2) 66 p. 174, and in the literature referred to in the mentioned article.

Ten grams of the potassium salt of bromoauric acid are dissolved in 100 cc of 96% ethyl alcohol. This salt is also designated as potassium auribromide. Sulfur dioxide (SO_2) is then led through this solution, through a fine capillary tube, for several minutes. This reaction produces aurous bromide (AuBr). The solution of the aurous bromide is then allowed to stand for 2 to 3 hours until it is colorless. A precipitate of KBr is thus formed. This precipitate is separated from the solution of the aurous bromide which is added to a solution of three grams of the thioglycolic acid anilide in 50 cc of ethyl alcohol. This is done at about 20°C. Then 300 cc of water are added to this mixture, at 20°C. The water is then removed by decantation or any suitable method, and the mixture is repeatedly thus treated with water, in order to remove all impurities which can thus be removed. The product is then centrifuged twice with 96% ethyl alcohol. It is then centrifuged three times with 100% or absolute ethyl alcohol, and then centrifuged three times with water-free ligroin (petroleum ether), i.e., the 40-60°C fraction which is distilled from petroleum. After each centrifuging, the product is separated from the liquid which has been used during the centrifuging.

The product is then dried in a high vacuum with the use of phosphorus pentoxide (P_2O_5).

References

Merck Index 889
I.N. p. 106
Lewenstein, M.J.; US Patent 2,451,841; October 19, 1948

AVILAMYCIN

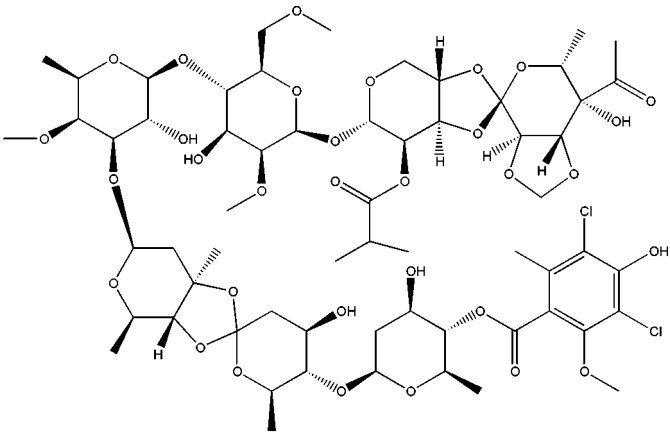
Therapeutic Function: Antibiotic

Chemical Name: Avilamycin A, mixture of small quantities of avilamycin B, C, D_1, D_2 and E

Common Name: Avilamycin; Maxus

Chemical Abstracts Registry No.: 11051-71-1

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Maxus	Eli Lilly	-	-
Avilamicina	Eli Lilly	-	-

Raw Materials

Meat meal	Salt extract
Peptone	Calcium carbonate
Glucose	Streptomyces viridochromogenes NRRL 2860
Meat extract	Sodium chloride

Manufacturing Process

Avilamycin is produced from Streptomyces viridochromogenes NRRL 2860:

A nutrient solution is prepared which contains 20.0 g of meat meal, 20.0 g of salt extract, 10.0 g of calcium carbonate and 1 L of tap water and adjusted to pH=7. This solution, or a multiple thereof, is charged into conical flasks of 500 ml capacity (100 ml of nutrient solution each) or into fermenters of 500 L capacity (300 L of nutrient solution each) and sterilized for 20-30 min under a pressure of 1 atm. The contents of the flasks are then inoculated with up to 10% of a partially sporulating vegetative culture of Streptomyces viridochromogenes NRRL 2860 and incubated at 27°C with thorough shaking or stirring, and in the fermenters with aerating with about 1 volume of sterile air per volume of nutrient solution per minute. The cultures are allowed to grow for 24-48 h, mixed with about 1.5% of a filtration assistant and then filtered depending on the volume, through a suction filter or a filter press or a rotary filter to free the antibiotically active aqueous solution from the mycelium and other solid constituents.

The medium described above is replaced the nutrient media: 10.0 g of crude glucose, 5.0 g of peptone, 3.0 g of meat extract (Oxo Lab- Lemco), 5.0 g of sodium chloride, 10.0 g of calcium carbonate and 1 L of tap water; pH - prior

to sterilization: 7.5, analogous sterilization, inoculation with Streptomnyces viridochromogenes NRRL 2860, incubation at 27°C and filtration likewise yield aqueous antibiotically active solutions.

90 L of culture filtrate are extracted with 20 L of ethyl acetate, and the extract is concentrated to 400 ml. When the concentrate is kept for 20 h at 2°C, avilamycin precipitates in the form of a dense floccular substance which is filtered off. After having been dried in an exsiccator, the practically colorless crystal cake consisting of strongly felted small needles weighs 3.07 g. The mother liquors are concentrated to about 200 ml and mixed with twice the amount of ether. When the concentrate is kept for 4 days at 0°C, a further 3.28 g of avilamycin crystallize out. 3.0 g of the crystallizate are dissolved in 50 ml of acetone, and a small amount of insoluble sludge is filtered off. The clear filtrate is mixed with ether and concentrated. On cooling, 2.0 g of colorless fine needles crystallize out. Concentration of the mother liquors to about one quarter their volume produces a further 0.48 g of crystals. For analysis a test portion of these crystals is recrystallized 4 times from acetone+ether and dried for 20 h in a high vacuum at 70°C. The analytically pure antibiotic avilamycin have a melting point 188°-189.5°C. Optical rotation $[\alpha]_D^{20} = +0.8°$ (c=1.165 in absolute ethanol).

References

Gaeumann E., Prelog V.; US Patent No. 3,131,126; April 28, 1964; Assigned: Ciba Corporation, a corporation of Delaware

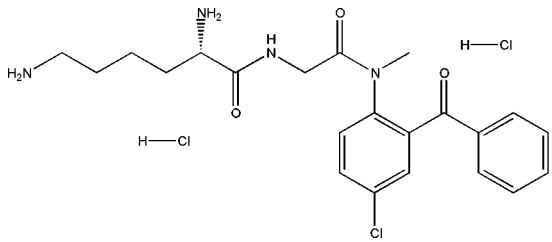
AVIZAFONE HYDROCHLORIDE

Therapeutic Function: Anxiolytic, Anticonvulsant

Chemical Name: 2'-Benzoyl-4'-chloro-2-((S)-2,6-diaminohexanamido)-N-methylacetanilide dihydrochloride

Common Name: Avizafone hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 65617-86-9 (Base); 60067-16-5

Trade Name	Manufacturer	Country	Year Introduced
Avizafone hydrochloride	Onbio Inc.	-	-
Avizafone hydrochloride	Roche Product Ltd.	-	-

Raw Materials

N-Benzyloxycarbonylglycine
Isobutylchloroformate
N-Methylmorpholine
5-Chloro-2-methylaminobenzophenone
Hydrogen bromide
$N^{(\alpha)}$,$N^{(\varepsilon)}$-Bisbenzyloxycarbonyl-L-lysyl N-hydroxysuccinimide ester
Amberlite

Manufacturing Process

(a) 20.9 g of N-benzyloxycarbonylglycine were suspended in 1500 ml of dry 1,2-dimethoxyethane and the suspension was cooled to -20°C. 10.1 g of N-methylmorpholine and 13.7 g of isobutylchloroformate were added, the resulting solution was stirred at -20°C for 1 hour and then filtered. The filtrate was added portion-wise over a period of several hours to a refluxing solution of 24.55 g of 5-chloro-2-methylaminobenzophenone in 200 ml of 1,2-dimethoxyethane, the resulting mixture was boiled overnight and then evaporated to dryness in vacuum. The yellow residue was dissolved in ethyl acetate, washed with two portions of water and one portion of saturated sodium chloride solution, dried over anhydrous magnesium sulfate and then evaporated. Column chromatography of the residue on Florisil (Trade Mark) using mixtures of benzene and chloroform yielded 35 g (80%) of pure 2-(N-benzyloxycarbonylamino)-N-(2-benzoyl-4-chlorophenyl)-N-methylacetamide as a pale yellow gum.

43.7 g of 2-(N-benzyloxycarbonylamino)-N-(2-benzoyl-4-chlorophenyl)-N-methylacetamide were dissolved in 200 ml of a 30% solution of hydrogen bromide in glacial acetic acid and the resulting solution was stirred overnight at room temperature. The mixture was added slowly to a large excess (2000 ml) of dry diethyl ether with vigorous stirring. The product, which separated was allowed to settle and the supernatant liquors were decanted off. The residue was triturated with 150 ml of acetone and the product filtered off, washed consecutively with the minimum amount of acetone and dry diethyl ether and dried in vacuum to give 29.5 g (77%) of 2-amino-N-(2-benzoyl-4-chlorophenyl)-N'-methylacetamide hydrobromide as a white hygroscopic powder of melting point 194°-195°C (decomposition).

(b) 84 g of N-benzyloxycarbonylglycine were suspended in 500 ml of alcohol-free chloroform and the suspension was cooled to -200°C. The stirred suspension was treated portion-wise over a period of 15 minutes with 90 g of phosphorus pentachloride and the stirring was continued until a clear solution was obtained. At this point, the cold mixture was added dropwise over a period of 30 minutes to a cold (-5°C) vigorously stirred emulsion consisting of 82 g of 5-chloro-2-methylaminobenzophenone, 347 g of potassium bicarbonate, 700 ml of chloroform and 1400 ml of water. The resulting

mixture was stirred for a further 1 hour at -5°C and then overnight at room temperature. The stirring was then discontinued and the liquid phases allowed to separate. The chloroform layer was washed three times with 500 ml of water each time and evaporated in VW to give 150.7 g of a viscous yellow gum which was shown by physical methods to be almost pure (above 95%) 2-(N-benzyloxycarbonylamino)-N-(2-benzoyl-4-chlorophenyl)-N-methylacetamide. The product above obtained was dissolved in 650 ml of a 30% solution of hydrogen bromide in glacial acetic acid and treated in an identical manner to that described in part (a) to give 2-amino-N-(2-benzoyl-4chlorophenyl)-N-methylacetamide hydrobromide in a 77% overall yield from 5-chloro-2-methylaminobenzophenone.

(c) 1 mole of $N^{\alpha},N^{\varepsilon}$-bisbenzyloxycarbonyl-L-lysyl N-hydroxysuccinimide ester was dissolved in 50 ml of dry dimethylformamide. The resulting solution was cooled to -20°C and there were added 1 mole of 2-amino-N-(2-benzoyl-4-chlorophenyl)-N-methylacetamide hydrobromide followed by the dropwise addition of 1 mole of N-ethylmorpholine. The resulting mixture was vigorously stirred for 1 hour at -20°C and then overnight at room temperature. The solvent was evaporated in vacuum and the residue dissolved in a mixture of dichloromethane and water. The organic and aqueous layers were separated and the aqueous phase extracted with further portions of dichloromethane. The combined organic phases (250 ml) were washed three times with 50 ml of water each time, dried over anhydrous magnesium sulfate and evaporated in vacuum to give a yellow oily residue, which was shown by physical methods to consist of $N^{\alpha},N^{\varepsilon}$-bisbenzyloxycarbonyl-L-lysyl-N-(2-benzoyl-4-chlorophenyl)-N-methylglycinamide as an almost colorless light-sensitive gum; $[\alpha]_D^{20}$= -9.3° (c=1 in ethanol).

$N^{\alpha},N^{\varepsilon}$-Bisbenzyloxycarbonyl-L-lysyl-N-(2-benzoyl-4-chlorophenyl)-N-methylglycinamide was converted using a 30% solution of hydrogen bromide in glacial acetic acid into L-lysyl-N-(2-benzoyl-4-chlorophenyl)-N-methylglycinamide dihydrobromide which was obtained as a hygroscopic powder of melting point 145°C (decomposition); $[\alpha]_D^{20}$= + 15.6° (c=1 in water).

Treatment of the foregoing dihydrobromide in aqueous solution by passage over an excess of an anion-exchange resin such as 'Amberlite' IRA-401 in the chloride form followed by lyophilisation of the eluate gave, in quantitative yield, L-lysyl-N-(2-benzoyl-4-chlorophenyl)-N-methylglycinamide dihydrochloride (avizafone) as a hygroscopic white light-sensitive powder of melting point 125°-145°C (slow decomposition); $[\alpha]_D^{20}$= +19.3° (c= 1 in water).

References

Hassall G.H. et al.; GB Patent No. 1,517,165; May 21, 1975; Roche Product Limited; a British Company

Hassall G.H. et al.; GB Patent No. 1,517,166; August 11, 1975; Roche Product Limited; a British Company

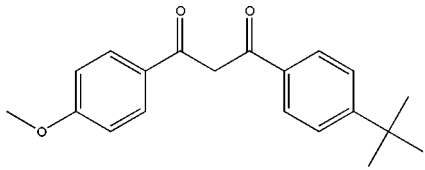
AVOBENZONE

Therapeutic Function: Sunscreen agent

Chemical Name: 1,3-Propanedione, 1-(4-(1,1-dimethylethyl)phenyl)-3-(4-methoxyphenyl)-

Common Name: Avobenzone; Episol

Structural Formula:



Chemical Abstracts Registry No.: 70356-09-1

Trade Name	Manufacturer	Country	Year Introduced
Avobenzone	AroKor Holdings Inc.	-	-
Avobenzone	Vivimed Labs Ltd	-	-
Clarins	Clarins	-	-
Episol	Schering-Plough	-	-

Raw Materials

p-t-Butylbenzoic acid
Sodium carbonate
Acetylanisole
Methanol
Sulfuric acid
Sodium amide
Hydrochloric acid

Manufacturing Process

356.0 g (2 mol) of p-t-butylbenzoic acid, 243.0 g (7.6 mol) of methyl alcohol and 35.0 g of sulfuric acid (96%) are added to a four-necked round flask which is provided with a stirrer and a condenser. The mixture is held for 8 h at reflux temperature with slight stirring. The condenser is then replaced by a distillation column and the excess methyl alcohol is distilled off, towards the end under a slight vacuum but without the temperature exceeding 100°C. The mixture is cooled and poured on to ice. The phases are left to separate, the organic phase is washed with ice-water, with a saturated sodium carbonate solution in the presence of ice and finally with ice until neutral. The organic phase is dried over sodium sulfate and there is thus obtained a precipitate. By distillation on a Widmer column (120 mm) there are obtained 345.0 g (90% yield) of the p-t-butylbenzoic acid methyl ester, boiling point 76°C/0.02 mmHg.

2 methods of producing of 4-(1,1-dimethylethyl)-4'-methoxydibenzoylmethane

from p-t-butylbenzoic acid methyl ester:

1). To a round flask which has been well dried and flushed with nitrogen are added 85.0 g (1.1 mol) of sodium amide (50% suspension in toluene) and 180.0 g of isopropyl ether and there are now added dropwise thereto at a temperature of 50°-60°C 150.2 g (1 mol) of acetylanisole in 180.0 g of isopropyl ether. Reaction sets in immediately and a white paste-like mass forms. After completion of the addition, the mixture is stirred for a further 0.5 h and then 192.3 g of p-t-butylbenzoic acid methyl ester are added rapidly at 25°-30°C. The mixture is stirred for 0.5 h at room temperature, then for 3 h at 60°-70°C and left to stand for 12 h. 200.0 g of ice are then added and the mixture is acidified with 128.0 g (1.1 mol) of technical hydrochloric acid and 200 ml of ice-water. The mixture is stirred until the sodium salt of the product has dissolved. The phases are separated and the organic phase is washed with ice-water until neutral. The organic phase is concentrated on a rotary evaporator and there are thus recovered 290.0 g of isopropyl ether. The yield of 4-(1,1-dimethylethyl)-4'-methoxydibenzoylmethane, melting point 83.5°C is 199.8 g (64.5%) (recrystallisation from methanol).

2). 36.0 g (1.2 mol) of 80% sodium amide and 300.0 g of dry toluene are added to a round flask which was flushed with nitrogen. The mixture is heated to 50°C and 150.2 g (1 mol) of acetylanisole in 309.0 g of toluene are added within 1.5 h. After completion of the addition, the mixture is held at 50°C for 15 min and there are then added thereto at this temperature within 1 h 50 min 192.3 g (1 mol) of p-t-butylbenzoic acid methyl ester. The mixture is stirred for a further 1 h at 50°C and then heated at 100°C for 1 h, after which time the product has separated out in the form of a solid precipitate. The mixture is left to stand for 12 h and there are then added thereto 300 ml of ice-water followed by a mixture of 100 ml of pure hydrochloric acid and 250 ml of ice-water. The phases are separated and the organic phase is washed twice with water. The organic phase is dried over sodium sulfate and treated simultaneously with 20.0 g of active carbon. After filtration, the filtrate is concentrated until crystallisation begins. 50 ml of hexane are added, the mixture is cooled and then filtered over a Buchner funnel. There is obtained a total yield of 220.91 g (71.2%) of the desired 4-(1,1-dimethylethyl)-4'-methoxydibenzoylmethane, of melting point 83.5°C (recrystallisation from 600 ml of methanol).

References

De Polo K.-F.; US Patent No. 4,387,089; June 7, 1983; Assigned: Givaudan Corporation, Clifton, N.J.

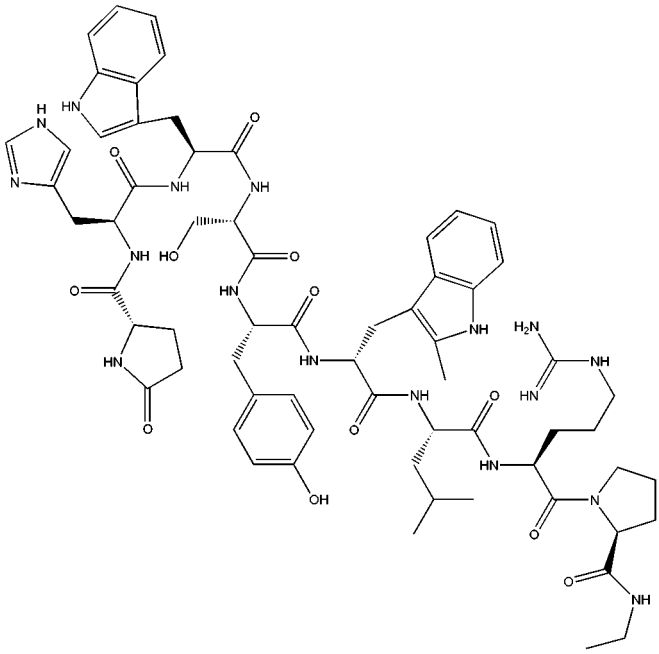
AVORELIN

Therapeutic Function: LHRH agonist

Chemical Name: 10-deglycinamideluteinizing hormone-releasing factor (pig), 6-(2-methyl-D-tryptophan)-9-(N-ethyl-L-prolinamide)-

Common Name: Avorelin

Structural Formula:



Chemical Abstracts Registry No.: 140703-49-7

Trade Name	Manufacturer	Country	Year Introduced
Avolerin	Mediolanum	-	-

Raw Materials

Benzhydrylamine resin
Diisopropylcarbodiimide
Aminoacids: 5-oxoproline, histidine, typthophan, serine, tyrosine, leucyne, arginine,N-ethyl proline amide
Trifluoroacetic acid
Hydrogen fluoride
Sephadex G-50 F column

Manufacturing Process

It is well known that the incorporation or substitution of a D-tryptophan residue into a biologically active peptide chain enhances the activity of that chain. Furthermore, such incorporation or substitution will prolong the biological activity. The prolonged and enhanced effectiveness of such peptides probably relates the increased resistance to degradation by peptidases.

[D-2-Methyl-Trp6] LHRH and [Des-Gly10-D-2-methyl-Trp6-Pro-ethylamide9]

LHRH.

2-Methyl-tryptophan is known (cf. H.N. Rydon, J. Chem. Soc. 1948, 705) and the homologous alkylated derivatives are conveniently prepared from the corresponding 2-alkyl indoles by well known methods (cf. J.P. Li et al., Synthesis (1), 73, 1988). The resolution of the racemic tryptophan derivatives to give the D-enantiomers can also be achieved by a variety of methods (cf. Amino Acids, Peptides and Proteins, Vol. 16, pages 18-20, The Royal Society of Chemistry, London, 1985). The both solution phase or the solid phase method of peptide synthesis can be used to make 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-2-methyl-D-tryptophyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide (cf. R. Geiger et al., "The Peptides", Academic Press, New York 1981). If the solid phase method is used, peptide synthesizers such as the Applied Biosystem 430A, Bioresearch Sam 9500 or the Beckman Model 990 are preferably used. According to this methodology, the first amino acid is linked to the benzhydrylamine resin and the remaining protected amino acids are then coupled in a stepwise manner using the standard procedures recommended by the manufacturers of the synthesizers.

For instance, amino acid couplings are performed by using symmetrical anhydrides in the Applied Biosystems Synthesizer and diisopropylcarbodiimide in the Bioresearch or Beckman machines. The amino acid derivatives are protected by the tertiary butoxy-carbonyl groups on the α-amino function during the synthesis. The functional groups present in the amino-acid in the side chain are previously protected. For instance, the functional groups of histidine are protected by benzyloxymethyl (His(Bom)), tosyl (His(Tos)), the functional groups of tryptophan by formyl (Trp(For)), those of serine by benzyl (Ser(Bzl)), those of tyrosine by 2-Br-benzyloxycarbonyl (Tyr(2-Br-Z)), those of arginine by tosyl (Arg(Tos)); those of proline by O-benzyl HCl (Pro(OBzl HCl)). The Boc protective groups on the α-aminic function are removed at each stage by treatment with 60% trifluoroacetic acid ("TFA") in dichloromethane. The crude peptides after HF cleavage are purified on a Sephadex G-50 F column in 50% acetic acid or by preparative reverse phase HPLC using gradients of acetonitrile and water containing 0.1% trifluoroacetic acid.

References

DEGHENGHI, Romano [It/CH]; Chesaux Dessus B1, CH-1264 S.-Cergue (CH); W.O. 91/18016

AVRIDINE

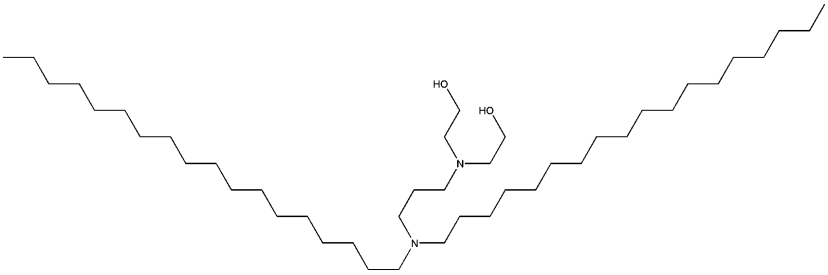
Therapeutic Function: Antiviral

Chemical Name: Ethanol, 2,2'-((3-(dioctadecylamino)propyl)imino)bis-

Common Name: Avridine

Chemical Abstracts Registry No.: 35607-20-6

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Avridine	Chemical Formulations, LLC	-	-

Raw Materials

Dioctadecylamine
Acrylonitrile
N-Propionyl chloride

Manufacturing Process

N,N-Dioctadecyl-1,3-propanediamine:

A). A two-gallon autoclave is charged with 3-(dioctadecylamino)propionitrile (100 g), ethanol (3750 ml) containing anhydrous ammonia (100 g) and Raney nickel (20 g dry basis) and purged with nitrogen, then with hydrogen. It is then sealed and the hydrogen pressure raised to 250 psi. The autoclave is agitated, the temperature raised to 70°C and the mixture held at this temperature for 1.5 hours at which time hydrogen absorption has ceased. The autoclave is cooled to 20°C, vented, and the contents removed. The catalyst is filtered off, washed with ethanol, and the combined washings and reaction mixture concentrated in vacuum to a viscous green-yellow oil (82 g) which solidified upon standing; MP: 39°-41°C.

3-(Dioctadecylamino)propionitrile is prepared by refluxing a mixture of dioctadecylamine (200 g) and acrylonitrile (1903.8 ml) for eighteen hours. The mixture is then concentrated to a waxy semi-solid which is slurried in acetone, filtered, and air dried overnight.

B). The monoacyl derivatives of N,N-dioctadecyl-1,3-propanediamine are prepared as follows:

To a solution of methylene chloride (500 ml per 0.1 mole of reactants) containing equimolar amounts of N,N-dioctadecyl-1,3-propanediamine and triethylamine and cooled in an ice-bath is added an equimolar amount of the appropriate acyl chloride in methylene chloride (25 ml per 0.1 mole of acyl chloride) over a period of 15 minutes. The mixture is stirred for ten minutes then brought to room temperature and stirred for one hour. The methylene chloride phase is separated and extracted with water (3x25 ml). The water is

in turn extracted with methylene chloride (2x25 ml) and the combined methylene chloride phases dried (Na_2SO_4) then evaporated under reduced pressure. The residue is taken up in benzene and the solution passed through a silica gel column. The column is eluted with benzene, then with benzene containing increasing amounts of ethyl acetate; e.g., 5, 10, 25, and 50 %. The eluate is subjected to thin layer chromatography (ethyl acetate) and those fractions, which show only one spot, combined and evaporated to give N,N-dioctadecyl-N',N'-bis(2-hydroxyethyl)propanediamine M.P. 48.5°-49°C.

References

GB Patent No. 1,369,247; August 7, 1970; Pfizer Inc. St Delaware, USA

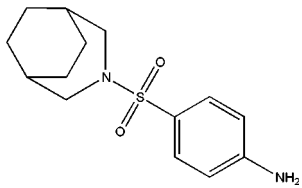
AZABON

Therapeutic Function: Central stimulant

Chemical Name: 3-[(4-Aminophenyl)sulfonyl]-3-azabicyclo[3.2.2]nonane

Common Name: Azabon

Structural Formula:



Chemical Abstracts Registry No.: 1150-20-5

Trade Name	Manufacturer	Country	Year Introduced
Azabon	ZYF Pharm Chemical	-	-

Raw Materials

Sodium hydroxide
1,4-Cyclohexane-bis(methylamine)
Nickel Raney
4-Nitrobenzenesulfonyl chloride
Hydrogen

Manufacturing Process

The 1,4-cyclohexane-bis(methylamine) feed line was connected to the top of the preheater in a pyrolysis tube. The pyrolysis section was heated by external electric heaters. For a typical run, the pyrolysis temperature was

maintained at 385°-395°C; the feed rate was 8.4 g per minute of 1,4-cyclohexanebis(methylamine) and 1.47 g per minute of nitrogen this is a ratio of 0.885 mole of nitrogen per mole of 1,4-cyclohexanebis(methylamine) per h. The crude reaction product was collected in a chilled flask and the nitrogen and reaction gases were vented to a hood. These conditions were maintained for 15.5 h, during which time 7,849 g (55 moles) of 1,4-cyclohexanebis(methylamine) was fed to the unit. Tile total crude product obtained weighed 7,269 g. Distillation of the crude product at atmospheric pressure to a base temperature of 260°-270°C yielded 1,480 g of 3-azabicyclo[3.2.2]nonane (recrystallized from an equal weight of acetone). Gas chromatography of the filtrates of this first fraction through a 6-foot column packed with 15% Carbowax 20M on white Chromosorb indicated 1,854 g of 1,4-cyclohexanebis(metnylamine) and 721.0 g of 3-azabicyclo[3.2.2]nonane present. The remainder of the crude product was distilled at 1-5 mm to a base temperature of 200°-225°C. Thus, a total of 2,201 g (17.6 moles, 62.1% yield) of 3-azabicycla[3.2.2]nonane was produced.

To a 3 L, three-neck flask equipped with a stirrer, thremometer, and condenser was charge 30.0 g (0.24 mole) of 3-azabicyclo[3.2.2]nonane, 44.3 g (0.2 mole) of p-nitrobenzenesulfonyl chloride and 2 L of water. The pH of the reaction mixture was adjusted to 14 with a 10% solution of sodium hydroxide; the reaction mixture was then slowly heated to 75°C and heating stopped. The reaction mixture was cooled to 20°C and 44.0 g (71% of theory) of crude 3-(p-nitrobenzenesulfonyl)-3-azabicyclo[3.2.2]nonane was collected by filtration.

The crude 3-(p-nitrobenzenesulfonyl)-3-azabicyclo[3.2.2]nonane (44.0 g, 0.14 mole), 5.0 g alcohol wet Raney nickel, and 400 ml methyl alcohol were charged to an autoclave and reduced at 70°C at 1000 p.s.i. hydrogen pressure until absorption of hydrogen had stopped. The crude reduced product was filtered hot to remove the Raney nickel catalyst. The filtrate was cooled to 20°C and the solid 3-(p-ammobenzenesulfonyl)-3-azabicyclo[3.2.2]nonane was collected by filtration (38.9 g 98% theory), melting point 149°-151°C.

References

Pircio A.W. et al.; US Patent No. 3,351,528; Nov. 7, 1967; Assigned: Bristol-Myers Company, New York, N.Y.

AZACITIDINE

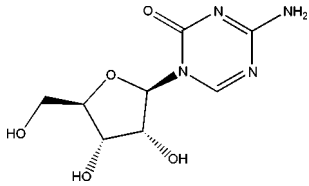
Therapeutic Function: Antineoplastic

Chemical Name: 1,3,5-Triazin-2(1H)-one, 4-amino-1β-D-ribofuranosyl-

Common Name: Azacitidine; 5-Azacytidine; Ladakamycin

Chemical Abstracts Registry No.: 320-67-2

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
5-Azacytidine	AroKor Holdings Inc.	-	-
5-Azacytidine	Xinxiang Tuoxin BiochemicTechnology and Science Co., Ltd.	-	-
Mylosar	Upjohn	-	-

Raw Materials

1-(2,3,5-tri-O-Benzoyl-β-D-ribofuranosyl)-4-methylthio-1,2-dihydro-1,3,5-triazin-2-one
Ammonia
Potassium hydroxide
Sodium methoxide

Manufacturing Process

A mixture of 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-4-methylthio-1,2-dihydro-1,3,5-triazin-2-one (0.5875 g), absolute methanol (5 ml) and a normal methanolic sodium methoxide solution (1.2 ml) is stirred at room temperature with the exclusion of atmospheric moisture (a guard tube filled with potassium hydroxide pellets is fitted to the reaction vessel). The starting compound passes into solution in the course of 5 min. The resulting solution is allowed to stand at room temperature for 45 min and then the cations are removed by passage of the solution through a column packed with 10 ml of a weakly acidic cation exchange resin in the H+ form prewashed with water and methanol. The methanolic effluent (60 ml) is evaporated under reduced pressure at 30°C, the residue is dissolved in methanol (20 ml) and the solution once again is evaporated and the 1-β-D-ribofuranosyl-4-methoxy-1,2-dihydro-1,3,5-triazin-2-one was obtained.

The residual crude crystalline 1β-D-ribofuranosyl-4-methoxy-1,2-dihydro-1,3,5-triazin-2-one is dissolved in a 10% solution of dry ammonia in absolute methanol (4 ml) and the whole reaction mixture is allowed to stand in a stoppered flask for 30 min at room temperature (the product begins to deposit in the course of 5 min) and for 12 h in a refrigerator at -10°C. The resulting 5-azacytidine is collected with suction, washed with methanol and dried under reduced pressure. A yield of 0.216 g (88.6%) of 5-azacytidine, that is [1-β-D-ribofuranosyl-4-amino-1,3,5-triazin-2(1H)-one], melting point 232°-234°C (dec.), is obtained.

References

GB Patent No. 1,227,691; April 7, 1971; Assigned: Ceskoslovenska akademie ved, a Corporation organized and existing under the law of Czechoslovakia of N 3 Narodni, Prague 1, Czechoslovakia

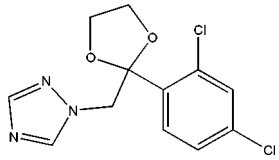
AZACONAZOLE

Therapeutic Function: Antifungal

Chemical Name: 1H-1,2,4-Triazole, 1-((2-(2,4-dichlorophenyl)-1,3-dioxolan-2-yl)methyl)-

Common Name: Azaconazolel; Azoconazole

Structural Formula:



Chemical Abstracts Registry No.: 60207-31-0

Trade Name	Manufacturer	Country	Year Introduced
Azaconazole	Chemical Formulations, LLC	-	-

Raw Materials

Hydrochloric acid
Acetic acid
Sodium hydroxide
1H-1,2,4-Triazole
Sodium
1-(2,4-Diaminopheny1)-1-ethanone
Sodium nitrite
Bromine
4-Methylbenzenesulfonic acid

Manufacturing Process

A stirred and cooled (0°C) solution of 1-(2,4-diaminophenyl)-1-ethanone in a concentrated hydrochloric acid solution, water and acetic acid was diazotated with a solution of sodium nitrite in water. After stirring at 0°C, the whole was poured onto a solution of copper (I) chloride in a concentrated hydrochloric acid solution while stirring. The mixture was heated at 60°C. After cooling to room temperature, the product was extracted twice with 2,2'-oxybispropane. The combined extracts were washed successively with water, a diluted sodium hydroxide solution and again twice with water, dried, filtered and evaporated, yielding 1-(2,4-dichlorophenyl)-1-ethanone.

1-(2,4-Dichlorophenyl)-1-ethanon were dissolved in 1,2-ethanediol at heating. While stirring bromine were added dropwise, without external heating. After stirring at room temperature, 4-methylbenzenesulfonic acid and benzene were added. The whole was stirred and refluxed overnight with water-separator. The reaction mixture was evaporated and the residue was taken up in 2,2'-oxybispropane. The resulting solution was washed successively once with a dilute sodium hydroxide solution and 3 times with water, dried, filtered and evaporated. The residue was distilled, yielding 2-(bromomethyl)-2-(2,4-dichlorophenyl)-1,3-dioxolane.

6.9 parts of 1H-1,2,4-triazole in 150 parts of dimethylformamide were added to a stirred solution of 2.3 parts of sodium in 120 parts of methanol. The methanol was removed at normal pressure until the internal temperature of 130°C was reached. Then, 25 parts of 2-(bromomethyl)-2-(2,4-dichlorophenyl)-1,3-dioxolane were added. The reaction-mixture was stirred and refluxed for 3 h. It was allowed to cool to room temperature and poured onto water. The precipitated product was filtered off, yielding 12 parts of 1-[2-(2,4-dichlorophenyl)-1,3-dioxolan-2-yl-methyl]-1H-1,2,4-triazole; melting point 109.9°C (crystallized from diisopropylether; activated charcoal).

References

GB Patent No. 1,522,657; August 23, 1978; Assigned: Janssen Pharmaceutica N.V., a Belgian Body Corporate, of Turnhoutsebaan 30, Beerse, Belgium

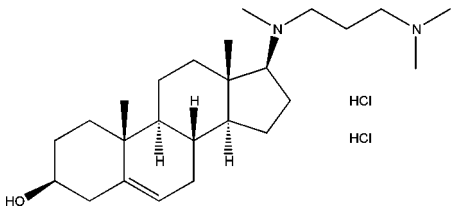
AZACOSTEROL HYDROCHLORIDE

Therapeutic Function: Hypocholesteremic

Chemical Name: Androst-5-en-3β-ol, 17β-((3-(dimethylamino)propyl) methylamino)-, dihydrochloride

Common Name: Azacosterol hydrochloride; Diazacholesterol dihydrochloride; Diazasterol hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 1249-84-9; 313-05-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Ornitrol	Avitrol Corporation	-	-

Raw Materials

3β-Hydroxyandrost-5-en-17-one
3-Dimethylaminopropylamine
Lithium aluminum hydride

Manufacturing Process

A solution of 15 parts of 3β-hydroxyandrost-5-en-17-one and 30 parts of 3-dimethylaminopropylamine in 36.6 parts of formic acid is heated in an oil bath at about 170-180°C for about 24 hours. The cooled mixture is diluted with about 500 parts of water, and the resulting aqueous mixture is extracted with chloroform, containing a small amount of methanol. The organic layer is separated, washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness under reduced pressure. The viscous residue is dissolved in a mixture of 80 parts of isopropyl alcohol and 420 parts of ether, and this solution is treated with isopropanolic hydrogen chloride. The resulting precipitate is collected by filtration and washed with acetone to afford 17β-[N-(3-dimethylaminopropyl)formamido-1-androst-5-en-3β-ol hydrochloride. A solution of this hydrochloride in aqueous methanol is made alkaline by the addition of dilute aqueous sodium hydroxide, and the resulting colloidal precipitate is extracted with chloroform. The chloroform extracts washed with water, dried over anhydrous sodium sulfate and concentrated to dryness to afford a residue, which is crystallized from acetone, resulting in 17β-[N-(3-dimethylaminopropyl)formamido]androst-5-en-3β-ol, which displays a double melting point at about 116-118°C and 143-148°C; $[\alpha]_D$= -67.5° (chloroform).

To a slurry of 4 parts of $LiAlH_4$ in 150 parts of dioxane is added dropwise with stirring, at the reflux temperature a solution of 10 parts of 17β-[N-(3-dimethylaminopropyl)
formamido]androst-5-en-3β-ol in 150 parts of dioxane. This reaction mixture is heated at reflux for about 18 hours longer, and then treated dropwise successively, at the reflux temperature, with a solution of 4 parts of water in 25 parts of dioxane, 3 parts of 20% aqueous sodium hydroxide, and 14 parts of water. The resulting mixture is clarified by filtration, and the residue on the filter is washed with fresh dioxane. The filtrates are combined, evaporated to dryness under reduced pressure, and the resulting residue is recrystallized from acetone-methanol to produce 17β-[N-methyl-N-(3-dimethylaminopropyl)amino]androst-5-en-3β-ol, M.P. about 146-148°C; $[\alpha]_D$= -54.5° (chloroform). A solution of this amine in ether-isopropyl alcohol is treated with isopropanolic hydrogen chloride to afford the corresponding dihydrochloride; $[\alpha]_D$= -32° (methanol).

References

Merck Index, Monograph number: 924, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Counsell R.E. et al.; US Patent No. 3,084,156; Apr. 2, 1963; Assigned to G.D. Searle and Co., Chicago, Ill., a corporation of Delawere

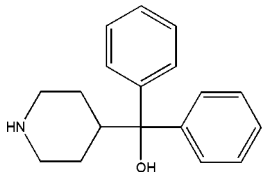
AZACYCLONOL

Therapeutic Function: Tranquilizer

Chemical Name: α,α-Diphenyl-4-piperidinemethanol

Common Name: γ-Pipradol

Structural Formula:



Chemical Abstracts Registry No.: 115-46-8; 1798-50-1 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Frenquel	Merrell	US	1955
Frenoton	Draco	Sweden	-
Frenquel	Inibsa	Spain	-
Frenquel	Merrell-Tourade	France	-
Frenquel	Shionogi	Japan	-

Raw Materials

α-(4-Pyridyl)-benzhydrol
Hydrogen

Manufacturing Process

A mixture of 26 g (0.1 mol) of α-(4-pyridyl)-benzhydrol, 1.5 g of platinum oxide, and 250 ml of glacial acetic acid is shaken at 50-60°C under hydrogen at a pressure of 40-50 lb/in^2. The hydrogenation is complete in 2 to 3 hours. The solution is filtered and the filtrate evaprated under reduced pressure. The residue is dissolved in a mixture of equal parts of methanol and butanone and 0.1 mol of concentrated hydrochloric acid is added. The mixture is cooled and filtered to give about 30 g of α-(4-piperidyl)benzhydrol hydrochloride, MP 283-285°C, as a white, crystalline substance.

The free base is readily obtained from the hydrochloride salt by treatment with ammonia and when so obtained has a melting point of 160-161°C.

References

Merck Index 898
Kleeman and Engei p. 65
OCDS Vol. 1 p. 47

I.N.p. 109
Schumann, E.L., Van Campen, M.G., Jr. and Pogge, R.C.; US Patent 2,804,422; August 27, 1957; Assigned to The Wm. S. Merrell Co.

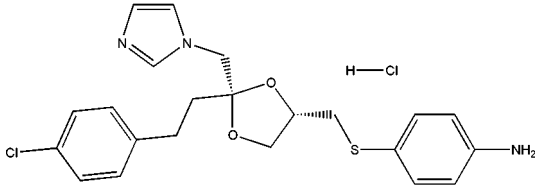
AZALANSTAT HYDROCHLORIDE

Therapeutic Function: Antihyperlipidemic

Chemical Name: Benzenamine, 4-(((2-(2-(4-chlorophenyl)ethyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl)methyl)thio)-, (2S,4S)-, hydrochloride

Common Name: Azalanstat hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 143393-27-5 (Base); 143484-82-6

Trade Name	Manufacturer	Country	Year Introduced
Azalanstat hydrochloride	Syntex	-	-

Raw Materials

4-Chlorophenethyl alcohol	Triphenylphosphine
N-Bromosuccinimide	Vinyl bromide
Peracetic acid	Sodium acetate
Potassium carbonate	Sodium hydride
Imidazole	Oxalyl chloride
Triethylamine	Glycerol
Sodium hydroxide	4-Toluenesulfonic acid monohydrate
Methanesulfonyl chloride	4-Aminothiophenol

Manufacturing Process

A stirred solution of 4-chlorophenethyl alcohol (131.0 g) and triphenylphosphine (241.3 g) in dry THF (500 ml) at 0°C was treated portion-wise over 30 min with N-bromosuccinimide (163.75 g). The resulting black solution was stirred overnight at room temperature, whereupon the THF was evaporated and the residue stirred with ether. The solution was filtered and the filtrate evaporated and treated with hexane. The stirred mixture was filtered, evaporated, and the residue distilled under reduced pressure to give 100.0 g of 4-chlorophenethyl bromide as a colorless liquid, boiling point 85°C

(3 mm Hg).

To a flame-dried flask containing magnesium turnings under ether was added 4-chlorophenethyl bromide in anhydrous ether at such a rate as to maintain a gentle reflux. When the addition was complete, the mixture was heated under reflux for an additional hour and then treated dropwise over 1 h with vinyl bromide in ether maintaining a gentle reflux. The resulting mixture was stirred overnight at room temperature and then poured onto ice-cold dilute sulfuric acid. The product was extracted with ethyl acetate and the combined extracts were washed with dilute aqueous potassium carbonate, dried $MgSO_4$ and evaporated. The resulting brown oil was distilled under reduced pressure to give 4-(4-chlorophenyl)but-1-ene.

To a solution of 4-(4-chlorophenyl)but-1-ene in dichloromethane was added dropwise with stirring a mixture of 40% peracetic acid and sodium acetate. The resulting mixture was heated under reflux, cooled, and stirred with water. The dichloromethane layer was separated, washed with dilute aqueous potassium carbonate until neutral, water, and dried ($MgSO_4$) and evaporated to give 4-(4-chlorophenyl)-1,2-epoxybutane as a colorless oil.

To a suspension of sodium hydride (50% dispersion in mineral oil) in dry DMF under nitrogen was added imidazole in dry DMF with stirring at such a rate as to keep the temperature below 65°C (ice bath). When the evolution of gas had ceased, 4-(4-chlorophenyl)-1,2-epoxybutane was added dropwise and the mixture stirred overnight at room temperature. The resulting brown solution was added water, extracted with ethyl acetate and the combined extracts were washed with water 3 times, dried ($MgSO_4$) and evaporated to give an oil which crystallized. Washing the solid with ether and filtration give 1-(4-(4-chlorophenyl)-2-hydroxybutyl)imidazole.

A solution of oxalyl chloride (74.8 g) in dry dichloromethane (1350 ml) at below -70°C under a nitrogen atmosphere was treated with dry dimethylsulfoxide (91.5 ml) in methylene chloride (270 ml) dropwise over 15-20 min while maintaining the temperature of the reaction mixture below -50°C. After an additional 5 min a solution of (+/)-1-(4-(4-chlorophenyl)-2-hydroxybutyl)imidazole (128.3 g) in a mixture of dimethylsulfoxide (50 ml) and methylene chloride (200 ml) was added over a period of 20 min keeping the reaction mixture at temperatures below -65°C. After a further 15 min dry triethylamine (300 ml) was added rapidly and after 15 min the reaction mixture was allowed to warm to 0°C. Water (20 ml) was then added to the reaction mixture, the methylene chloride then removed by evaporation and the resulting slurry was then treated with water and filtered. The filter cake was washed well with ice water, cold ethyl acetate and then dried in air to yield 118.0 g of 4-(4-chlorophenyl)-1-(imidazol-1-yl)butan-2-one.

A mixture of 4-(4-chlorophenyl)-1-(imidazol-1-yl)butan-2-one (50.0 g), p-toluenesulfonic acid monohydrate (42.07 g) and glycerol (37.0 g) in toluene (200 ml) was heated under reflux, with stirring, through a Dean-Stark trap for 6 h. The two layers were allowed to separate and the hot toluene (upper layer) decanted and discarded. The lower layer was poured into 2 N sodium hydroxide (500 ml), the transfer completed by washing the flask with 1 N sodium hydroxide and methylene chloride, and the product extracted with methylene chloride (4x200 ml). The extracts were dried ($MgSO_4$) evaporated

and the residue recrystallized from toluene to give 61.4 g of (cis/trans)-2-(2-(4-chlorophenyl)ethyl)-2-(imidazol-1-yl)methyl-4-hydroxymethyl-1,3-dioxolane, melting point 96°-110°C.

(cis/trans)-2-[2-(4-Chlorophenyl)ethyl]-2-(imidazol-1-yl)methyl-4-hydroxymethyl-1,3-dioxolane (39.7 g) in pyridine (150 ml) at 0°C was treated drop-wise with stirring with methanesulfonyl chloride (10.6 ml) and the mixture stirred overnight. The resulting solid mass was stirred with ether (500 ml) to break up the solid, filtered and washed well with ether to give (cis/trans)-2-[2-(4-chlorophenyl)ethyl]-2-(imidazol-1-yl)methyl-4-(methylsulfonyloxy)methyl-1,3-dioxolane hydrochloride, melting point 107°-110°C (recrystallized from dichloromethane/isopropanol).

The (cis/trans)-2-[2-(4-chlorophenyl)ethyl]-2-(imidazol-1-yl)methyl-4-(methylsulfonyloxy)methyl-1,3-dioxolane hydrochloride was basified with aqueous potassium carbonate solution, extracted with ethyl acetate (2x400 ml) and the extracts washed, dried ($MgSO_4$) and evaporated. The resulting semicrystalline mass was chromatographed on silica gel (900.0 g) eluting with dichloromethane, aqueous ethyl acetate (2.2% water) to give 25.4 g of (+/-)-cis-2-(2-(4-chlorophenyl)ethyl)-2-(imidazol-1-yl)methyl-4-(methylsulfonyloxy)methyl-1,3-dioxolane, as a snow white solid, melting point 93.5°-96°C. Further elution gave, after a small mixed fraction, pure (+/-)-trans-2-[2-(4-chlorophenyl)ethyl]-2-(imidazol-1-yl)methyl-4-(methylsulfonyloxy)methyl-1,3-dioxolane, as a white solid, melting point 93°-95°C.

A mixture of (+/-)-cis-2-[2-(4-chlorophenyl)ethyl]-2-(imidazol-1-yl)methyl-4-(methylsulfonyloxy)methyl-1,3-dioxolane (31.0 g), 4-aminothiophenol (12.6 g) and anhydrous potassium carbonate (23.1 g) in acetone (250 ml) was stirred overnight under reflux under nitrogen. The reaction mixture was then evaporated to dryness, and the resulting residue was extracted with methylene chloride (300 ml) and filtered. The solid filter cake was then washed with methylene chloride (200 ml). The methylene chloride extracts were then combined and concentrated and flash chromatographed on a silica gel eluting with methylene chloride followed by 30% acetone in methylene chloride. The pure product was dissolved in a minimum amount of hot ethyl acetate (125 ml), the solution diluted with an equal volume of hot hexane and seeded to give 30.0 g of (+/-)-cis-2-[2-(4-chlorophenyl)ethyl]-2-(imidazol-1-yl)methyl-4-(4-amino-phenylthio)methyl-1,3-dioxolane, melting point 121°-122.5°C.

In practice it is usually used as hydrochloride.

References

Walker K.A. et al.; US Patent No. 5,158,949; Oct. 27, 1992; Assigned: Syntex (U.S.A.) Inc., Palo Alto, Calif.

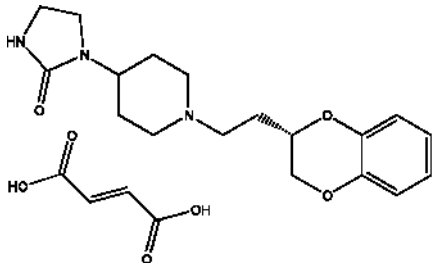
AZALOXAN FUMARATE

Therapeutic Function: Antidepressant

Chemical Name: (S)-1-[1-[2-(1,4-Benzodioxan-2-yl)-ethyl]-4-piperidyl]-2-imidazolidinone fumarate

Common Name: Azaloxan fumarate

Structural Formula:



Chemical Abstracts Registry No.: 72822-56-1 (Base); 86116-60-1

Trade Name	Manufacturer	Country	Year Introduced
Idulian	Unicet	-	-
CGS7135A	Ciba-Geigy	-	-
Azaloxan Fumarate	ZYF Pharm Chemical	-	-

Raw Materials

Bromine	Acetic acid
Catechol	4-Toluenesulfonyl chloride
Allyl cyanide	Sodium bis(2-methoxyethoxy)aluminum hydride
Sulfuric acid	Potassium carbonate
4-Aminopyridine	Sodium methanolate
Hydrogen	2-Chloroethylisocyanate
Furmaric acid	Ruthenium on carbon

Manufacturing Process

The producing of starting materials 1 and 2:

1). The solution of 16.0 g of bromine in 10 ml of petroleum ether is slowly added to the solution of 6.7 g of allyl cyanide in 30 ml of the same solvent, while stirring and keeping the temperature at about -15°C. After removal of the solvent the oily 3,4-dibromo-butyronitrile is obtained [J.A. C.S. 67, 400 (1945)].

227.0 g of 3,4-dibromobutyronitrile are added dropwise in 5 equal parts to the stirred mixture of 85.0 g of catechol and 50. g of anhydrous potassium carbonate in 100 ml of refluxing acetone each. Another 50.0 g of potassium carbonate are added, followed by a slow addition of another part of nitrile. After 3 more cycles, using 40.0 g of potassium carbonate, 1 part nitrile each and sufficient acetone to allow stirring, the mixture is refluxed for 20 h. It is

filtered, the filtrate evaporated, the residue distilled and the fraction boiling at 105°C/0.15 mm Hg collected, to yield the 1,4-benzodioxan-2-yl-acetonitrile [Belgium Pat. No. 643,853-Aug. 14, 1964].

The mixture of 111.0 g of 1,4-benzodioxan-2-yl-acetonitrile, 63.5 ml of sulfuric acid, 160 ml of acetic acid and 160 ml of water is refluxed for 48 h. It is poured on ice, the resulting solid collected to yield the 1,4-benzodioxan-2-yl-acetic acid, melting point 100°C, (recrystallized from benzene-petroleum ether) [Belgium Pat. No. 613,211-July 30, 1962].

The solution of 5.8 g of 1,4-benzodioxan-2-yl-acetic acid in 100 ml of benzene is added dropwise to 16.5 ml of a refluxing, 70% benzene solution of sodium bis(2-methoxyethoxy)aluminum hydride under nitrogen. When addition is complete, the mixture is refluxed for 4 h, cooled and poured slowly into 20 ml of 25% sulfuric acid. After filtration and removal of the solvent, the residue is taken up in methylene chloride, the solution washed several times with saturated aqueous sodium bicarbonate, dried and evaporated, to yield the oily 2-(2-hydroxyethyl)-1,4-benzodioxan.

The mixture of 3.6 g of 2-(2-hydroxyethyl)-1,4-benzodioxan, 5.7 g of p-toluenesulfonyl chloride and 20 ml of dry pyridine is stirred and cooled in an ice bath for 2 h. Ice is then added to the mixture, the resulting solid is filtered off to yield the 2-(2-tosyloxyethyl)-1,4-benzodioxan, melting point 82°-83°C (recrystallized from ethyl acetate-petroleum ether).

2). To the solution of 1.6 g of 4-aminopyridine in 7 ml of dimethylformamide 2.0 g of 2-chloroethylisocyanate are added while stirring and keeping the temperature below 40°C. After 2 h 28 ml of water are added and stirring is continued for 2 h at room temperature. The precipitate formed is filtered off, washed with water, dried to yield the 1-(4-pyridyl)-3-(2-chloroethyl)urea, melting point 120°-122°C, (recrystallized from aqueous ethanol).

To the suspension of 2.66 g of 1-(4-pyridyl)-3-(2-chloroethyl)urea in 4 ml of boiling methanol, 2.68 g of 30.8% methanolic sodium methanolate are added while stirring and the mixture is refluxed for 1 h. It is filtered hot, washed with hot methanol, the filtrate evaporated, to yield the 1-(4-pyridyl)-2-imidazolidinone, melting point 204°-207°C, (recrystallized from 90% aqeuous ethanol).

The solution of 5.0 g of 1-(4-pyridyl)-2-imidazolidinone in 45 ml of water is hydrogenated over 0.8 g of 10% ruthenium on carbon at 120°C and 120 atm until the hydrogen absorption ceases. It is filtered, the filtrate evaporated, the residue taken up in chloroform, the solution dried, evaporated to yield the 1-(4-piperidyl)-2-imidazolidinone, melting point 155°-157°C (recrystallized from methylene chloride-petroleum ether).

The producing of (cis)-(S)-1-[1-[2-(1,4-benzodioxan-2-yl)ethyl]-4-piperidyl]-2-imidazolidinone fumarate:

The mixture of 4.9 g of 2-(2-tosyloxyethyl)-1,4-benzodioxan, 2.54 g of 1-(4-piperidyl)-2-imidazolidinone, 5.0 g of anhydrous sodium carbonate and 100 ml of 4-methyl-2-pentanone is stirred and refluxed for 3 days. It is filtered, evaporated, to yield the 1-[1-[2-(1,4-benzodioxan-2-yl)-ethyl]-4-piperidyl]-2-imidazolidinone, melting point 125°C, (recrystallized from isopropanol).

To the solution of 2.0 g of 1-[1-[2-(1,4-benzodioxan-2-yl)-ethyl]-4-piperidyl]-2-imidazolidinone in the mini-mum amount of ethanol, the saturated solution of 0.78 g of furmaric acid in boiling ethanol is added. The mixture is cooled to 0°C and the precipitate collected, to yield the 1-[1-[2-(1,4-benzodioxan-2-yl)-ethyl]-4-piperidyl]-2-imidazolidinone fumarate, melting point 190°C.

The (cis)-(S)-form may be produced by chromatographic division of isomers of 1-[1-[2-(1,4-benzodioxan-2-yl)ethyl]-4-piperidyl]-2-imidazolidinone fumarate.

References

Huebner Ch. F.; US Patent No. 4,329,348; May 11, 1982; Assigned: Ciba-Geigy Corporation, Ardsley, N.Y.

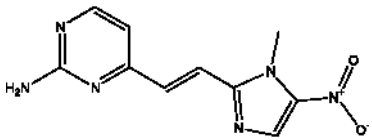
AZANIDAZOLE

Therapeutic Function: Antiprotozoal, Antibacterial

Chemical Name: 2-Amino-4-[2-(1-methyl-5-nitroimidazol-2-yl)vinyl] pyrimidine

Common Name: Nitromidine

Structural Formula:



Chemical Abstracts Registry No.: 62973-76-6

Trade Name	Manufacturer	Country	Year Introduced
Triclose	Ist. Chemioter.	Italy	1977
Triclose	I.C.I.	Italy	-

Raw Materials

2-Amino-4-methylpyrimidine
2-Formyl-1-methyl-5-nitroimidazole
Sulfuric acid

Manufacturing Process

Into a mixture of 1.6 g of 2-amino-4-methylpyrimidine with 10 ml of glacial acetic acid is slowly added 2.13 g of concentrated sulfuric acid. A mixture of 2.4 g of 2-formyl-1-methyl-5-nitroimidazole in 20 ml of glacial acetic acid is slowly added to the mixture of the pyrimidine under stirring. The reaction

mixture is maintained at a temperature of about 55°C for 4 hours. The resultant mixture is then diluted with 200 ml of distilled water and neutralized with a saturated aqueous solution of sodium bicarbonate. A brownish-yellow precipitate (MP 232° to 235°C) is formed and recovered. The product is analyzed by infrared spectroscopy and is found to conform to 2-amino-4-[2-(1-methyl-5-nitro-2-imidazolyl)vinyl]pyrimidine.

References

Merck Index 902
DOT 14 (6) 234 (1978)
I.N. p. 109
Garzia, A.; US Patent 3,882,105; May 6, 1975; Assigned to Istituto Chemioterapico Italiano SpA
Garzia, A.; US Patent 3,969,520; July 13, 1976; Assigned to Istituto Chemioterapico Italiano SpA

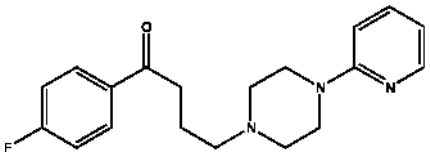
AZAPERONE

Therapeutic Function: Neuroleptic, Hypnotic

Chemical Name: 1-Butanone, 1-(4-fluorophenyl)-4-(4-(2-pyridinyl)-1-piperazinyl)-

Common Name: Azaperone; Sedaperone

Structural Formula:



Chemical Abstracts Registry No.: 1649-18-9

Trade Name	Manufacturer	Country	Year Introduced
Azaperone	Dayang Chemicals Co. Ltd.	-	-
Azaperolo	C.E.R. Laboratoire D'Hormonologie	-	-
Azaperone	C.E.R. Laboratoire D'Hormonologie	-	-

Raw Materials

γ-Chloro-4-fluorobutyrophenone
1-(2'-Pyridyl)piperazine

Manufacturing Process

A mixture of γ-chloro-4'-fluorobutyrophenone and 1-(2'-pyridyl)piperazine is heated on an oil bath. The mixture is then boiled in diisopropyl ether and the precipitates is collected and boiled with water and benzene. The benzene layer is treated with activated charcoal, added to the ethereal filtrate, and evaporated to give a residue which is taken up in diisopropyl ether. After cooling an oil is precipitated, which after decantation and drying yields 1-[γ-(4'-fluorobenzoyl)propyl]-4-(2'-pyridyl)piperazine.

References

Janssen P.A.J.; US Patent No. 2,958,694; Nov. 1, 1960

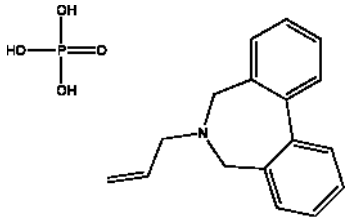
AZAPETINE PHOSPHATE

Therapeutic Function: Adrenergic blocker

Chemical Name: 6,7-Dihydro-6-(2-propenyl)-5H-dibenz[c,e]azepine phosphate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 130-83-6; 146-36-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Ilidar	Roche	US	1954
Ilidar	Roche	W. Germany	-

Raw Materials

Diphenic acid
Lithium aluminum hydride
Allyl bromide
Ammonia
Acetic anhydride
Phosphoric acid

Manufacturing Process

29 grams of diphenic acid were stirred in 900 cc of acetic anhydride at 120°C for one hour, The cooled mixture was filtered and washed with acetic acid to give diphenic anhydride, colorless crystals, MP about 222-226°C.

24.11 grams of diphenic anhydride were mixed with 50 cc of concentrated ammonia. The mixture warmed up and cooling was applied, after which the mixture was stirred until a clear solution formed and for 1½ hours afterward. The mixture was acidified and allowed to stand overnight. Water was added, initiating precipitation. The mixture was chilled and filtered to yield diphenamic acid, a colorless solid, MP about 191-193°C.

23.5 grams of diphenamic acid were heated at 200°C in an oil bath, first for about 20 hours at atmospheric pressure and then for about 10 hours at about 20 mm.

Melting points were taken at intervals in order to gain an idea of the extent of reaction. The final residue was boiled with alcohol but since the solid exhibited insufficient solubility in the hot solvent, the mixture was filtered. The residue consisted of tan crystals, MP about 220-221°C, and the filtrate on cooling gave an additional crop of tan crystals, MP about 219-221°C. The two materials were identical and consisted of diphenimide.

5.58 g of diphenimide were placed in a Soxhlet thimble and extracted for about 3 days with a boiling mixture of 9.0 g of lithium aluminum hydride in 600 cc of sodium-dried ether. Excess lithium aluminum hydride was then decomposed cautiously with water and the mixture was filtered through a filter aid by suction. The filtrate consisted of two layers. The ether layer was separated and dried with anhydrous potassium carbonate and acidified with alcoholic hydrochloric acid to give 6,7-dihydro-5H-dibenz[c,e]azephine hydrochloride, MP about 287-289°C.

One gram of 6,7-dihydro-5H-dibenz[c,e]azepine hydrochloride was dissolved in water, made alkaline with concentrated ammonia, and the resultant base extracted twice with benzene, The benzene layers were combined, dried with anhydrous potassium carbonate, and mixed with 0.261 g of allyl bromide at 25-30°C. The reaction solution became turbid within a few minutes and showed a considerable crystalline deposit after standing 3½ days. The mixture was warmed 1 3/4 hours on the steam bath in a loosely-stoppered flask, then cooled and filtered. The filtrate was washed twice with water and the benzene layer evaporated at diminished pressure. The liquid residue was dissolved in alcohol, shaken with charcoal and filtered. Addition to the filtrate of 0.3 gram of 85% phosphoric acid in alcohol gave a clear solution which, when seeded and rubbed, yielded 6-allyl-6,7-dihydro-5H-dibenz[c,e]azepine phosphate, MP about 211-215°C with decomposition.

References

Merck Index 904
Kleeman and Engel p. 65
I.N. p. 109
Schmidt, R.A. and Wenner, W.; US Patent 2,693,465; November 2, 1954; Assigned to Hoffmann-La Roche, Inc.

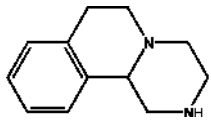
AZAQUINZOLE

Therapeutic Function: CNS depressant

Chemical Name: 1,3,4,6,7,11b-Hexahydro-2H-pyrazino[2,1-a]isoquinoline

Common Name: Azaquinzole

Structural Formula:



Chemical Abstracts Registry No.: 5234-86-6

Trade Name	Manufacturer	Country	Year Introduced
Azaquinzole	Onbio Inc.	-	-

Raw Materials

Diethyl ester of oxalic acid
Lithium aluminum hydride
1-Aminomethyl-1,2,3,4-tetrahydroisoquinoline
Ethylene dibromide
Potassium carbonate
Sodium hydroxide

Manufacturing Process

2 Methods of producing of 1,2,3,6,7,11b-hexahydro-4H-pyrazino-[2,1-a]isoquinoline:

1). 214.0 g diethyl ester of oxalic acid are mixed with a solution of 238.0 g 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline in 200 ml alcohol are boiled for 7 h. After cooling, the obtained crystals of 1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline-3,4-dione are vacuum-filtered and washed with acetone and dried, melting point 220°C. Yield: 240.0 g.

55.0 g lithium aluminum hydride are dissolved in 650 ml absolute tetrahydrofuran and mixed dropwise with a suspension of 120.0 g 1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline-3,4-dione in 300 ml absolute tetrahydrofuran. After 7 h of boiling, the residual hydride is decomposed by the addition of water, and the reaction solution is worked up. The obtained 1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline is distilled in vacuum, boiling point 98°-100°C/0.01 mm. Yield: 86.0 g.

2). 16.2 g 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline and 18.7 g ethylene dibromide are boiled for 4 h in n-butanol, with the addition of 13.8 g potassium carbonate. After the solvent is evaporated, the residue is treated

with water, mixed with sodium hydroxide solution, and shaken out with chloroform. The chloroform solution is dried, concentrated by evaporation, and the resulting 1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline is distilled at 98°-100°C/0.01 mm. The yield amounts to 7.5 g.

References

Thesing J. et al.; US Patent No. 3,393,195; July 16, 1968; Assigned: E. Merch Aktiengeselischaft, Darmstadt, Germany

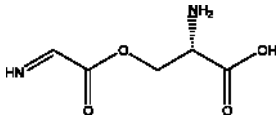
AZASERINE

Therapeutic Function: Antineoplastic, Antifungal

Chemical Name: L-Serine diazoacetate (ester)

Common Name: Azaserine

Structural Formula:



Chemical Abstracts Registry No.: 115-02-6

Trade Name	Manufacturer	Country	Year Introduced
Azaserine	TG International Chemical Co.	-	-
Azaserine	Sigma	-	-
Azaserine	Calbiochem-Novabiochem Corp.	-	-
Azaserine	ICN Biomedicals Inc.	-	-

Raw Materials

Streptomyces fragilis
Soybean expeller oil meal
Yeast
Sodium hydroxide
Ammonium nitrate
Mineral oils
Glucose
Acid hydrolyzed casein
Sodium chloride
Calcium carbonate
Castile soap

Manufacturing Process

The azaserine is produced by microbiological synthesis using culture of Streptoniyces fragili:

10 gallons of a nutrient medium having the following composition (%):glucose 1.0; soybean expeller oil meal 1.0; acid hydrolyzed casein 0.5; debittered yeast 0.5; sodium chloride 0.5; water sufficient to make 100.0% is placed in a 30 gallon stainless steel fermenter, the pH adjusted to 7.5 with 6 N sodium hydroxide solution and 0.1% calcium carbonate added. The medium is sterilized by heating at 121°C for 30 min after which the pH of the medium is 6.85. The medium is cooled and inoculated with the spares from two fourteen day old Moyer's sporulation agar slant cultures of Streptoniyces fragilis suspended in 20 ml of sterile 0.01% castile soap solution. The culture mixture is incubated at 27°C for 24 h during which time aeration is supplied through a sparger at the rate of one volume of air per volume of medium per minute.

The incubated culture thus obtained is used to inoculate the main culture as described below. 150 gallons of a medium having the following composition (%): glucose 1.0; soybean expeller oil meal 1.0; acid hydrolyzed casein 0.5; debittered yeast 0.5; sodium chloride 0.5; ammonium nitrate 0.25; water sufficient to make 100.0 percent. 6 N sodium hydroxide solution-sufficient to bring the pH to 7.5;calcium carbonate - (added after pH adjustment) is placed in a 200-gallon stainless steel fermenter and sterilized by heating at 121°C for 30 min. The medium is cooled, inoculated with the 10-gallon culture of Streptomyces fragilis prepared as described above, and incubated at 26°C for 44 h. During the incubation period air is supplied through a sparger at the rate of 1.5-volumes of air per volume of medium per min and the mixture stirred at the rate of 150 r.p.m. for the first 12 h and at 300 r.p.m. for the final 32 h, 1.5 gallons of a sterilized mixture of crude lard and mineral oils containing mono- and diglycerides being added as needed to control foaming.

The solid material present in the incubated fermentation mixture is removed by filtration and the filter cake washed with water. The washings are combined with the main filtrate and 110 gallons of this solution stirred with 2079.0 g of activated carbon for about 1 h. The carbon is removed by filtration and the filter cake washed with deionized water. The combined filtrate and washes (136 gallons) are concentrated in vacuum to a volume of about 20 gallons. Three volumes of acetone are added to the concentrate with stirring, and the precipitate which forms removed by filtration and the filter cake washed with 75% aqueous acetone. The combined aqueous acetone filtrate and washings is concentrated in vacuum to a volume of about 19.5 gallons, the concentrate so obtained frozen and dried from the frozen state under high vacuum. 1.0 kg of dry powder is extracted with one 10-liter portion of 90% (by volume) ethanol followed by extraction with one 2-liter portion of the same solvent. The combined extracts (about 12 L) are diluted with sufficient water to reduce the ethanol concentration to 75% by volume, and this alcoholic solution passed through an adsorption column prepared as described below.

3.0 kg of alumina are stirred with dilute hydrochloric acid so that the pH remains constant at 7.7. The alumina is removed, washed with water and activated by heating at 200°C for 4 h. The alumina is stirred with 75% aqueous ethanol and packed into an adsorption column having a diameter of 4 inches. The total packed volume is approximately 3500 ml.

The alcoholic solution prepared above is added to the adsorption column at the rate of 6 L/h and the percolate discorded. The column is washed with 35 L of 75% ethanol (by volume), the washing discarded and the column finally washed with 21 L of 50% ethanol. Some O-diazoacetyl-L-serine may be

detected in the last wash solution. After the washing has been completed the adsorbed O-diazoacetyl-L-serine is eluted from the adsorption column by passing 17.5 L of distilled water through the column. The aqueous eluate is concentrated and frozen and the concentrate dried from the frozen state under high vacuum. The powder thus obtained, a O-diazoacetyl-L-serine content of 5.8%.

500.0 g of the material assaying 5.8% O-diazoacetyl-L-serine is dissolved in 1,320 ml of water. A column of activated charcoal is prepared. A mixture of 2.0 kg of activated charcoal (Darco (1-60) and 2.0 kg of diatomaceous earth is packed as a thick slurry in a 6 inch column. The pH of the water is 5.2-5.5. With this bed, a head of 4 feet of solvent is necessary to achieve a suitable flow rate. After packing, the column is washed with water for several hours to settle and remove solubles. The solution is applied to the column with positive pressure equivalent to a head of four foot of water. One retention volume of 9 L of water is then applied to the column. This is followed by a 5% acetone solution. The total solvent flow is 36 L. The colorless eluate is discarded. The elution front which is easily detected is a light yellowish-green solution. This solution is retained. The solution is concentrated by vacuum distillation until a concentration of 20-25 mg/ml is reached. This solution is applied to a column prepared in an identical manner as described herein and treated by the same procedure as the primary adsorption. The percolate is concentrated by vacuum distillation until a concentration of 60-75 mg/ml is reached. The quantity of solution is now approximately 300 ml. Absolute alcohol (450 ml) is added. The solution is gently warmed to complete solution and then stored at 5°C for several hours. The O-diazoacetyl-L-serine which separates in crystalline form is collected and purified by recrystallization from 60-70% ethanol; is an aqueous buffer of pH 7.

References

Ehrlich J. et al.; US Patent No. 2,996,435; Aug. 15, 1961; Assigned: Parke, Davis and Company, Detroit, Moch., a corporation of Michigan

AZASETRON HYDROCHLORIDE

Therapeutic Function: Antiemetic

Chemical Name: (+/-)-N-1-Azabicyclo[2.2.2]oct-3-yl-6-chloro-3,4-dihydro-4-methyl-3-oxo-2H-1,4-benzoxazine-8-carboxamide monohydrochloride

Common Name: Azasetron hydrochloride; Nazasetron hydrochloride

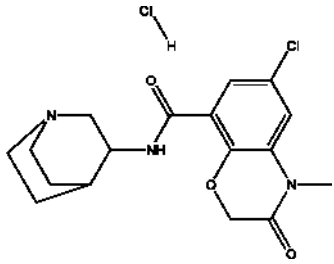
Chemical Abstracts Registry No.: 123040-69-7 (Base); 141922-90-9

Raw Materials

2-(2-Carboxy-4-chlorophenoxy)acetic acid
Nitric acid
Ferric sulfate heptahydrate
Potassium t-butoxide
Sulfuric acid
Ammonia
Hydrochloric acid
Methyl iodide

3-Amino-8-azabicyclo[3.2.1]octane
Ethyl chlorocarbonate
Sodium hydrogen carbonate
Triethylamine
Potassium hydroxide

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Azasetron hydrochloride	Pharm Chemical	-	-
Azasetron hydrochloride	HangZhou Ohua Pharmaceutical Technology Co., Ltd.	-	-
Serotone	Yoshimoti	-	-

Manufacturing Process

To a solution of 2-(2-carboxy-4-chlorophenoxy)acetic acid in concentrated sulfuric acid is added dropwise a mixed liquid of fuming nitric acid and concentrated sulfuric acid under stirring with keeping at a temperature below 10°C. After the addition, the reaction mixture is stirred and poured into 10 L of ice-cold water. The precipitated crystals are collected by filtration, washed with 2 L of water four times and them dried to give 2-(2-carboxy-4-chloro-6-nitrophenoxy)acetic acid.

To a solution of ferrous sulfate heptahydrate in of hot water is added a solution of 2-(2-carboxy-4-chloro-6-nitrophenoxy)acetic acid and aqueous concentrated ammonia solution in water under stirring. After stirring, to the reaction mixture is twice added aqueous concentrated ammonia solution. While the reaction mixture becomes exothermic, stirring is continued. The resultant mixture is filtered through a celite layer under reduced pressure and washed with hot water twice. The filtrate is cooled and made acid with concentrated hydrochloric acid. The precipitated crystals are washed with water and dried to give 6-chloro-3,4-dihydro-3-oxo-2H-1,4-benzoxazine-8-carboxylic acid.

A mixture of 6-chloro-3,4-dihydro-3-oxo-2H-1,4-benzoxazine-8-carboxylic acid, methanol and concentrated sulfuric acid is refluxed under heating with stirring, and then cooled. The precipitated crystals are collected by filtration, washed with methanol and dried to give methyl 6-chloro-3,4-dihydro-3-oxo-2H-1,4-benzoxazine-8-carboxylate, melting point 239°-241°C.

To a solution of methyl 6-chloro-3,4-dihydro-3-oxo-2H-1,4-benzoxazine-8-

carboxylate in dimethylformamide is added potassium t-butoxide and solution stirred at room temperature. To the resultant solution is added dropwise a solution of methyl iodide in dimethylformainide under stirring. After the reaction solution is stirred, water is added thereto. The insoluble substance is collected by filtration, washed with water and dried to give methyl 6-chloro-3,4-dihydro-4-methyl-3-oxo-2H-1,4-benzoxazine-8-carboxylate.

A mixture of methyl 6-chloro-3,4-dihydro-4-methyl-3-oxo-2H-1,4-benzoxazine-8-carboxylate, ethanol and 4% aqueous potassium hydroxide solution is refluxed with heating. The resultant solution is cooled and water is added thereto followed by filtration. The filtrate is made acid with concentrated hydrochloric acid. The precipitated crystals are collected by filtration, washed with water and dried, and then recrystallized from ethanol to give 6-chloro-3,4-dihydro-4-methyl-3-oxo-2H-1,4-benzoxazine-8-carboxylic acid, melting point 241°-243°C.

A solution of 6-chloro-3,4-dihydro-4-methyl-3-oxo-2H-1,4-benzoxazine-8-carboxylic acid in tetrahydrofuran and dimethylformamide is cooled to below 0°C and triethylamine is added under stirring thereto. Further, ethyl chlorocarbonate is added and the mixture is stirred at room temperature. To the resultant mixture is added 3-amino-8-azabicyclo[3.2.1]octane and the mixture stirred. After completion of the reaction, aqueous sodium hydrogen carbonate and ethyl acetate are added. The organic layer is separated, washed with water and dried over magnesium sulfate. The solvent is distilled off to give 6-chloro-3,4-dihydro-4-methyl-N-(8-azabicyclo[3.2.1]oct-3-yl)-3-oxo-2H-1,4-benzoxazine-8-carboxamide.

In practice it is usually used as hydrochloride.

References

Tahara T. et al.; US Patent No. 4,892,872; Jan. 9, 1990; Assigned: Yoshitomi Pharmaceutical Industries, Ltd., Osaka, Japan

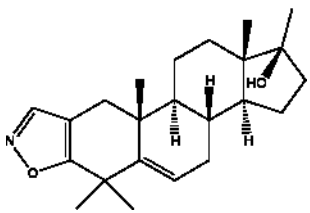
AZASTENE

Therapeutic Function: Contraceptive

Chemical Name: Androsta-2,5-dieno[2,3-d]isoxazol-17-ol, 4,4,17-trimethyl-, (17β)-

Common Name: Azastene

Structural Formula:



Chemical Abstracts Registry No.: 13074-00-5

Trade Name	Manufacturer	Country	Year Introduced
Azastene	ZYF Pharm Chemical	-	-

Raw Materials

4,4,17α-Trimethyl-2,5-androstdien-17β-ol-3-one
Sodium
Methanol
Ethyl formate
Hydrochloric acid
Sodium acetate
Hydroxylamine hydrochloride
Acetic acid

Manufacturing Process

A solution of 4,4,17α-trimethyl-androsta-2,5-dien-17β-ol-3-one in benzene was added to sodium methoxide (from sodium and of absolute methanol, concentrating the solution and drying the residue for 1 h at 150°-160°C and 15 mm). Ethyl formate was then added with stirring in a nitrogen atmosphere. The reaction mixture was stirred for 4 h at room temperature, allowed to stand for about 15 h, stirred for 2 h and then poured into water. The reaction mixture was extracted with benzene, the aqueous layer warmed until clear, filtered and cooled below room temperature. Concentrated hydrochloric acid and ice were added to the filtrate until the mixture was acid to Congo red, and the product was extracted with chloroform. The chloroform extracts were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated vacuum, whereupon there separated 2-hydroxymethylene-4,4,17α-trimethyl-androsta-2,5-dien-17β-ol-3-one.

To a solution of sodium acetate in acetic acid was added hydroxylamine hydrochloride, and methanol was added until solution resulted. This solution was added to a solution of 2-hydroxymethylene-4,4,17α-trimethyl-androsta-2,5-dien-17β-ol-3-one in absolute methanol, and the combined solution was refluxed for 40 min on a steam bath. The reaction mixture was concentrated, the residue extracted with ethyl acetate, and the ethyl acetate extracts were washed with ethyl acetate, and the ethyl acetate extracts were washed with 5% hydrochloric acid, dried over anhydrous sodium sulfate and concentrated whereupon there separated solid material.

The mother liquors were concentrated to dryness and the residue recrystallized from ether to give solid product. The latter was chromatographed on a column of silica gel in benzene solution, recrystallized from ethyl acetate and dried at 75°C for 20 h to give 17β-hydroxy-4,4,17α-trimethyl-androsta-2,5-dien[2,3-d]isoxazole.

The crude product was chromatographed on silica gel in benzene solution, eluted with benzene containing 5% of ether and recrystallized from ethanol to give 17β-hydroxy-4,4,17α-trimethyl-androsta-2,5-dien[2,3-d]isoxazole.

References

Clinton R.O., Manson A.J.; US Patent No. 3,135,743; June 2, 1964; Assigned: Sterling Drug Inc., New York, N.Y., a corporation of Delaware

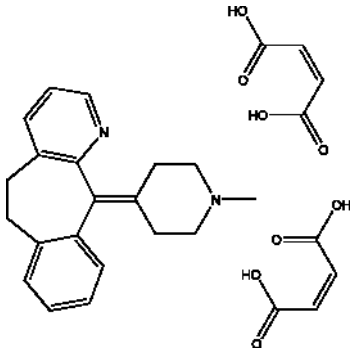
AZATADINE MALEATE

Therapeutic Function: Antihistaminic

Chemical Name: 6,11-Dihydro-11-(1-methyl-4-piperidinylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine maleate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 3978-86-7

Trade Name	Manufacturer	Country	Year Introduced
Idulian	Unilabo	France	1968
Optimine	Schering	US	1977
Optimine	Warrick	UK	1978
Optimine	Warrick	Italy	1983
Optimine	Byk-Essex	W. Germany	1983
Trinalin	Schering	US	-
Verben	Schering	-	-
Zadine	Schering	-	-

Raw Materials

N-Methyl-4-chloropiperidine
Polyphosphoric acid
4-Aza-10,11-dihydro-5-H-dibenzo-[a,d]cycloheptene-5-one
Ethyl bromide

Magnesium
Maleic acid

Manufacturing Process

Preparation of 4-aza-5-(N-methyl-4-piperidyl)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-ol: Add 17.4 g of N-methyl-4-chloropiperidine to a stirred mixture containing 3.2 g of magnesium, 20 ml of anhydrous tetrahydrofuran, 1 ml of ethyl bromide and a crystal of iodine. Reflux for two hours, cool to 30-35°C and add a solution of 13 g of 4-aza-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-one in 25 ml of tetrahydrofuran. Stir for five hours, remove the solvent by distillation in vacuum and add 250 ml of ether. Add 100 ml of 10% ammonium chloride solution and extract the mixture with chloroform. Concentrate the chloroform solution to a residue and recrystallize from isopropyl ether obtaining 20 g of the carbinol, MP 173-174°C.

Preparation of 4-aza-5-(N-methyl-4-piperidylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene: Heat 5.4 g of the carbinol and 270 g of polyphosphoric acid for 12 hours at 140-170°C. Pour into ice water and make alkaline with sodium hydroxide. Extract with ether. Dry ether solution and concentrate to a residue. Crystallize from isopropyl ether, MP 124-126°C.

Preparation of 4-aza-5-(N-methyl-4-piperidylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene dimaleate: To a solution containing 4.3 g of 4-aza-(N-methyl-4-piperidylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene in 55 ml of ethyl acetate, add a solution of 3.45 g of maleic acid dissolved in ethyl acetate. Filter the resulting precipitate and recrystallize the desired product from an ethyl acetate-methanol mixture to yield 4-aza-5-(N-methyl-4-piperidylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene dimaleate, MP 152-154°C.

References

Merck Index 906
PDR pp. 1643, 1657
OCDS Vol. 2 p. 424
DOT 5 (2) 47 (1969)
I.N. p. 110
REM p. 1131
Villani, F.J.; US Patents 3,326,924; January 20, 1967; 3,357,986; December 12, 1967; and 3,419,565; December 31, 1968; all Assigned to Schering Corp.

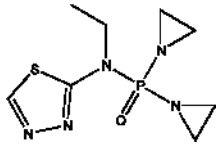
AZATEPA

Therapeutic Function: Antineoplastic

Chemical Name: Phosphinic amide, P,P-bis(1-aziridinyl)-N-ethyl-N-1,3,4-thiadiazol-2-yl-

Common Name: Azatepa; Azetepa; Thiatriamide

Structural Formula:



Chemical Abstracts Registry No.: 125-45-1

Trade Name	Manufacturer	Country	Year Introduced
Azatepa	ZYF Pharm Chemical	-	-

Raw Materials

2-Ethylamino-1,3,4-thiadiazole hydrochloride
Phosphorus oxychloride
Ethylenimine
Triethylamine

Manufacturing Process

N-Ethyl-N-(1,3,4-thiadiazol-2-yl)amidophosphoryl chloride is prepared by refluxing 16.4 parts of 2-ethylamino-1,3,4-thiadiazole hydrochloride with 84 parts of phosphorus oxychloride for 6 h and then removing the excess phosphorus oxychloride by distillation under reduced pressure. The residual oil is washed with cold petroleum ether, dried and dissolved in 310 parts of dry benzene.

The solution of N-ethyl-N-(1,3,4-thiadiazol-2-yl)amidophosphoryl chloride is added slowly at 10°C to a mixture of 9.5 parts of ethylenimine, 30.3 parts of triethylamine, and 44 parts of warm dry benzene. Agitation is continued for 2 h without cooling after which the triethylamine hydrochloride is filtered off. The benzene is distilled from the filtrate under reduced pressure, and the N,N'-diethylene-N''-ethyl-(N'-(1,3,4-thiadiazo-2-yl)phosphoramide is recrystallized from hexane, melting point 95°-96°C.

References

GB Patent No. 885,370; Dec. 28, 1961; Assigned: American Cyanamid Company, State of Maine, USA

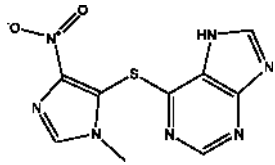
AZATHIOPRINE

Therapeutic Function: Immunosuppressive

Chemical Name: 6-[(1-Methyl-4-nitroimidazol-5-yl)thio]purine

Common Name: Azothioprine

Structural Formula:



Chemical Abstracts Registry No.: 446-86-6

Trade Name	Manufacturer	Country	Year Introduced
Imuran	Wellcome	UK	1964
Imurel	Wellcome	France	1967
Imurek	Wellcome	W. Germany	1967
Imuran	Wellcome	US	1968
Imuran	Wellcome	Italy	1968
Imuran	Tanabe	Japan	1969
Azamun	Medica	Finland	-
Azanin	Tanabe	Japan	-
Azapress	Lennon	S. Africa	-

Raw Materials

N,N'-Dimethyloxaldiamide
Nitric acid
Phosphorus pentachloride
6-Mercaptopurine

Manufacturing Process

N,N'-Dimethyloxaldiamide is reacted with PCl5, to give 4-chloro-1-methyl imidazole. This is nitrated with HNO3 to give 5-nitro-1-methyl-4-chloroimidazole. Then, a mixture of 4.6 grams of anhydrous 6-mercaptopurine, 5 grams of 1-methyl-4-chloro-5-nitroimidazole and 2.5 grams of anhydrous sodium acetate in 100 ml of dry dimethyl sulfoxide was heated at 100°C for 7 hours.

After standing overnight at room temperature, the mixture was poured into 200 ml of cold water and the yellow precipitate of 6-(1'-methyl-4'-nitro-5'-imidazolyl)mercaptopurine (7.0 grams) collected. After recrystallization from 50% aqueous acetone, the product melted at 243-244°C, dec., and had an UV spectrum with λ maximum = 280 nm at pH 1 and λ max. = 285 nm at pH 11.

References

Merck Index 907
Kleeman and Engel p. 67
PDR p. 744
OCDS Vol. 2 p. 464
DOT 16 (10) 360 (1980)
I.N.p. 110

REM p. 1143
Hitchings, G.H. and Elion, G.B.; US Patent 3,056,785; October 2, 1962: Assigned to Burroughs Wellcome and Co.

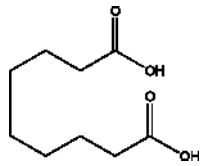
AZELAIC ACID

Therapeutic Function: Antiacne, Depigmentor

Chemical Name: 1,7-Heptanedicarboxylic acid

Common Name: Acide azelaique; Acidum azelaicum; Anchoic acid; Azelaic acid; Azelainsaure; Lepargylic acid

Structural Formula:



Chemical Abstracts Registry No.: 123-99-9

Trade Name	Manufacturer	Country	Year Introduced
Azelaic acid	Schering Health Care	-	-
Azelan	Schering-Plough	-	-
Azelex	Schering-Plough	-	-
Aziderm	Micro Labs	India	-
Skinoran	Schering	-	-
Skinoren	Schering	-	-

Raw Materials

Oleic acid
Hydrogen peroxide
Nitric acid
Linoleic acid
Formic acid
Sodium metavanadate

Manufacturing Process

Two step oxidation of tall oil fatty acid using peroxyformic acid and nitric acid/sodium metavanadate were used to produce azelaic acid.

Step 1 (derivatization of the double bond):

A hydroxy acyloxy derivative of tall oil fatty acid (TOFA) was prepared by mixing 200 g of TOFA (63% oleic acid, 31% linoleic acid) with 500 mL of

formic acid. The resulting mixture was vigorously stirred by magnetic action. Hydrogen peroxide solution, 180 mL of 35% by weight, was added in aliquots to the mixture throughout the course of the reaction. A third of the total amount of peroxide solution was added at once to initiate the reaction. The peroxyformic acid in this case was prepared in situ.

The start of the reaction was signalled by heat evolution and a dramatic color change, from pale yellow to deep rust red. The exothermicity of the reaction required external cooling to control the temperature. The reaction was maintained at 40°C to minimize oxygen loss through the decomposition of the peroxide. As required, the temperature of the reaction was maintained with an external heating source. A total reaction time of 5 to 6 hours was necessary for complete reaction. The end of the reaction was indicated by a color change; the reaction mixture changed from rust red back to yellow. One last aliquot of peroxide solution was added at the end of the reaction period to provide a peroxide atmosphere during the reaction work-up. TOFA as a substrate produced a mixture of mono- and dihydroxy formoxystearic acid from the oleic and linoleic acid components, respectively. The final product was obtained in essentially 100% yield by removing the unreacted formic acid and hydrogen peroxide as well as water. It was obtained as a viscous, syrupy yellow oil that upon gas chromatographic analysis of the methyl esters of the reaction mixture gave no evidence of unreacted substrate.

Step 2 (oxidation of derivative obtained from step 1):

A 2 L three neck flask fitted with an air condenser attached to a gas scrubbing apparatus was filled with 500 mL of concentrated nitric acid (70% by weight). The acid was stirred by magnetic action and 1 g of sodium metavanadate was added to it. The resulting mixture was heated slowly to 40°-50°C. At this point a small amount of product as obtained from Step 1 was added to the acid-catalyst mixture. Heating was continued until a sharp temperature increase accompanied by evolution of NO_x gases was observed. The reaction temperature was self-sustained with the addition of aliquots of the hydroxy formoxy ester mixture obtained from Step 1. (External cooling may be required throughout the substrate addition period to keep the temperature within 65°-70°C). At the end of the addition period the reaction temperature was maintained for an additional 1.5 to 2 hours, for a total reaction time of 3 hours.

The final products were obtained by quenching the reaction by adding excess water and extracting the organic layer with purified diethyl ether. The ether extract was dried over anhydrous sodium sulfate overnight before its removal with a roto-vap apparatus. Addition of petroleum ether (boiling range 35°-60°C) to the product mixture caused precipitation of the diacid component. Vacuum filtration was used to remove the solid diacids from the liquid monoacid mixture. The latter was obtained by removing the excess petroleum ether from the resulting filtrate. Quantitative analysis by gas chromatography of the methyl esters showed that the products to be 96% yield of diacid (66% azelaic, 30% suberic).

References

Malek A. et al.; US Patent No. 5,380,928; Jan. 10, 1995; Assigned: Synergistic Industries, Inc., Canada

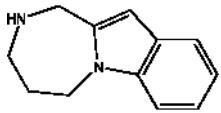
AZEPINDOLE

Therapeutic Function: Antidepressant

Chemical Name: 1H-[1,4]Diazepino[1,2-a]indole, 2,3,4,5-tetrahydro-

Common Name: Azependole

Structural Formula:



Chemical Abstracts Registry No.: 26304-61-0

Trade Name	Manufacturer	Country	Year Introduced
Azependole	ZYF Pharm Chemical	-	-
McN-2453	McNeil Laboratories, Inc.	-	-

Raw Materials

Ethyl indole-2-carboxylate
Acetic acid
Acetic anhydride
Hydrogen
Lithium aluminum hydride
Acrylonitrile
Tenzyltrimethylammonium hydroxide
Nickel Raney
Sodium hydride

Manufacturing Process

Ethyl indole-2-carboxylate (9.84 g, 0.052 mole) is dissolved in 150 ml dioxane. Acrylonitrile (3.11 g, 0.0588 mole) and benzyltrimethylammonium hydroxide (Triton B) (2 ml) are added and the mixture is warmed, with stirring, at 50°-55°C for 45 min. The solution is cooled to room temperature and stirred overnight. The reaction mixture is added to 500 ml water containing 3 ml glacial acetic acid. The mixture is extracted with methylene chloride, the organic layer washed with 2x25 ml water and dried over magnesium sulfate. The solvent is removed under reduced pressure. The remaining oil is dissolved in ether and filtered through alumina with ether as eluant. Evaporation of the ether gives a solid. The product obtained is ethyl N-(β-cyanoethyl)indole-2-carboxylate, melting point 84°-86°C.

A 2.42 g (0.01 mole) of ethyl N-(β-cyanoethyl)indole-2-carboxylate is suspended in acetic anhydride (20 ml). The suspended compound is hydrogenated on a Parr shaker in the presence of Raney nickel. The uptake of hydrogen is complete after 1.5 h. The product recovered is recrystallized from benzene-hexane. The product obtained is ethyl 1-(3-acetamidopropyl)indole-2-carboxylate, melting point 83.5°-84.5°C.

Ethyl 1-(3-acetamidopropyl)indole-2-carboxylate (1.44 g, 0.005 mole) is cyclized in the presence of sodium hydride (0.30 g, 0.00625 molar in hydride) in xylene under reflux. A few drops of absolute ethanol are added after 1 h reflux. Total reflux time is 2 h. The product recovered is crystallized from benzenehexane. The product obtained is 2,3,4,5-tetrahydro-1H-1,4-diazepino[1,2-a]indol-1-one, melting point 181°-183°C.

2,3,4,5-Tetrahydro-1H-1,4-diazepino[1,2-a]indol-1-one (6.0 g, 0.03 mole) in 200 ml of monoglyme is added dropwise to a stirred suspension of lithium aluminum hydride (2.8 g, 0.08 mole) in 200 ml of monoglyme, and the mixture heated under reflux overnight. Water is added to the cooled mixture, and the mixture filtered. The filtrate is dried with anhydrous magnesium sulfate and concentrated in vacuum, giving an oil which solidifies on standing to give about 85% theoretical yield of the free amine, 2,3,4,5-tetrahydro-1H-1,4-diazepino[1,2a]indol, melting point 75°-77°C.

References

Reynolds B.E., Carson J.R.; US Patent No. 3,867,374; February 18, 1975; Assigned: McNeil Laboratories, Incorporated, Ft. Washington, Pa.

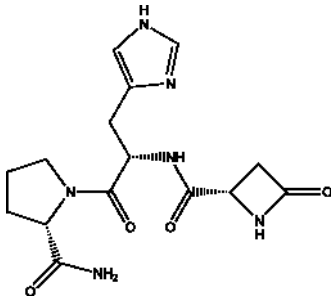
AZETIRELIN

Therapeutic Function: TRH analogue

Chemical Name: L-Prolinamide, N-((4-oxo-2-azetidinyl)carbonyl)-L-histidyl-, (S)-

Common Name: Azetirelin

Structural Formula:



Chemical Abstracts Registry No.: 95729-65-0

Trade Name	Manufacturer	Country	Year Introduced
Azetirelin	ZYF Pharm Chemical	-	-
Azetirelin	Yamanouchi	-	-

Raw Materials

L-Histidyl-L-prolinamide 2-hydrobromide
Triethylamine
(S)-2-Azetidinone-4-carboxylic acid
Hydroxybenzotriazole
Dicyclohexylcarbodiimide

Manufacturing Process

In 13 ml of DMF was dissolved 826.0 mg of L-histidyl-L-prolinamide 2-hydrobromide and then 2 ml of a DMF solution of 405.0 mg of triethylamine was added to the solution under ice-cooling. After maintaining 30 min under ice-cooling, the precipitates thus formed were filtered off to provide L-histidyl-L-prolinamide.

In 10 ml of DMF was dissolved 230.0 mg of (S)-2-azetidinone-4-carboxylic acid and then 351.0 mg of N-hydroxy-1,2,3-benzotriazole and 453.0 mg of dicyclohexylcarbodiimide were added to the solution under ice-cooling. Then, after stirring the mixture for 15 min, the reaction was maintained for 15 min at room temperature. The reaction mixture was ice-cooled again and 15 ml of a DMF solution of foregoing L-histidyl-L-prolinamide was added to the reaction mixture followed by reaction overnight at 0°C. The precipitates thus formed were filtered off, the filtrate was concentrated to dryness, the residue was dissolved in 10 ml of chloroform-methanol (4:1) and subjected to silica gel column chromatography. The eluates by chloroform-methanol (7:3) were collected and concentrated to dryness to provide 509.0 mg of crude product. When the product was subjected to silica gel column chromatography again and eluted by a mixture of chloroform, methanol, and aqueous ammonia (40:10:1) to provide 394.0 mg of pure $N^{epsilon}$-[(S)-2-azetidinone-4-carbonyl]-L-histidyl-L-prolinamide, melting point 183°-185°C (crystallization from a small amount of methanol).

References

Tamura T. et al.; US Patent No. 4,636,567; January 13,1987; Assigned: Yamanouchi Pharmaceutical Co., Ltd., Tokyo, Japan

AZIDAMFENICOL

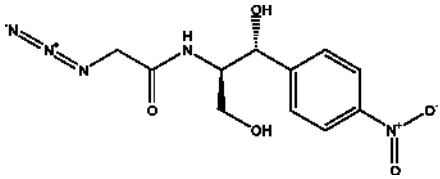
Therapeutic Function: Antibiotic

Chemical Name: Acetamide, 2-azido-N-((1R,2R)-2-hydroxy-1-(hydroxymethyl)-2-(4-nitrophenyl)ethyl)-

Common Name: Azidamfenicol; Azidoamphenicol

Chemical Abstracts Registry No.: 13838-08-9

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Berlicetin-Augentropfen	Chauvin	-	-
Berlicetin	Chauvin Ankerpharm	-	-
Leucomycin-N	Bayer	-	-
Posifenicol	Ursapharm	-	-
Thilocanfol	Alcon	-	-

Raw Materials

D-(-)-Threo-1-p-nitrophenyl-2-aminopropane-1,3-diol
Azidoacetonitrile
Hydrochloric acid

Manufacturing Process

21.2 g of D-(-)-threo-1-p-nitrophenyl-2-aminopropane-1,3-diol are stirred with 10 g of azidoacetonitrile (B.P. 68°C/25 mm) in a mixture of 125 ml of methanol and 125 ml of water at 30-40°C for a few days. The mixture is filtered off from a little undissolved base and the solvent is distilled in vacuo. The residue is treated with a little normal hydrochloric acid until acid to Congo red and extracted with ethylacetate. By evaporating the solvent and recrystallizing the residue from ethylene chloride is obtained D-(-)-threo-1-p-nitrophenyl-2-azidoacetylamino-propane-1,3-diol; M.P. 107°C.

References

Merck Index, Monograph number: 941, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Meisser W. et al.; US Patent No. 2,882,275; Apr. 14, 1959; Assigned to Farbenfabriken Bayer Aktiengesellschaft, Germany

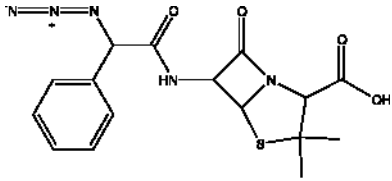
AZIDOCILLIN

Therapeutic Function: Antibacterial

Chemical Name: 6-(D-2-Azido-2-phenylacetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid

Common Name: α-Azidobenzylpenicillin

Structural Formula:



Chemical Abstracts Registry No.: 17243-38-8

Trade Name	Manufacturer	Country	Year Introduced
Nalpen	Beecham	W. Germany	1972
Longatren	Bayer	Italy	1981
Longatren	Bayer	Japan	-
Astracilina	Astra	Sweden	-
Finacillin	Sedequil	Portugal	-
Syncillin	Tropon	W. Germany	-

Raw Materials

α-Azidophenylacetic acid
6-Aminopenicillanic acid
Thionyl chloride
Ethyl chloroformate
Triethylamine

Manufacturing Process

Example 1: α-Azidobenzylpenicillin via the Mixed Anhydride - A solution of α-azidophenylacetic acid (8.9 grams, 0.05 mol) of triethylamine (5.1 grams, 0.05 mol) in 50 ml of dry dimethylformamide was stirred and chilled below -5°C. At this temperature ethyl chloroformate (4.7 ml) was added in portions so that the temperature was never above -5°C. After the mixture had been stirred for 20 minutes, dry acetone (100 ml), chilled to -5°C, was added in one portion, immediately followed by an ice-cold solution of 6-aminopenicillanic acid (10.8 grams, 0.05 mol) and triethylamine (5.1 grams, 0.05 mol) in 100 ml of water, and the stirring was continued for 1½ hours at 0°C.

The pH of the mixture was adjusted to 7.5 by adding a saturated sodium bicarbonate solution. After being washed twice with diethyl ether, the reaction solution was acidified to pH 2 with dilute hydrochloric acid and extracted with ether. The ether solution containing the free penicillin was washed twice with water and then extracted with 50 ml of N potassium bicarbonate solution. After freeze drying of the obtained neutral solution, the potassium salt of α-azidobenzylpenicillin was obtained as a slightly colored powder (11.2 grams, 54% yield) with a purity of 55% as determined by the hydroxylamine method (the potassium salt of penicillin G being used as a standard).

The infrared spectrum of this substance showed the presence of an azido group and a beta-lactam system. The substance inhibited the growth of *Staph. aureus Oxford* at a concentration of 0.25 mcg/ml.

Example 2: α-Azidobenzylpenicillin via the Acid Chloride - 6-aminopenicillanic acid (18.5 grams, 0.085 mol) and sodium bicarbonate (21 grams, 0.025 mol) were dissolved in 200 ml of water and 100 ml of acetone. To this solution, chilled in ice, was added α-azidophenylacetyl chloride (16.6 grams, 0.085 mol), diluted with 10 ml of dry acetone. The temperature is held at 0° to 5°C and the reaction mixture was stirred for 2½ hours.

The resulting solution was treated as described in Example 1 to give the potassium salt of α-azidobenzylpenicillin as a white powder (29.4 grams, 84% yield) with a purity of 83% as determined by the hydroxylamine method (the potassium salt of penicillin G being used as a standard).

The product showed the same properties as the product obtained in Example 1;. it inhibits the growth of Staph. aureus Oxford at a concentration of 0.13 mcg/ml.

The α-azidophenylacetyl chloride was prepared by treating α-azidophenylacetic acid with thionylchloride in portions at room temperature and then heating the solution under reflux for one hour. The α-azidophenylacetyl chloride distils at 115°C under a pressure of 10 mm Hg.

References

Merck Index 913
Kleeman and Engel p. 68
DOT 7 (5) 186 (1971) and 8 (7) 248 (1972)
I.N.p. 111
Sjoberg, B.O.H. and Ekstrom, B.A.; US Patent 3,293,242; December 20, 1966; Assigned to Beecham Group Limited, England

AZIMILIDE HYDROCHLORIDE

Therapeutic Function: Antiarrhythmic

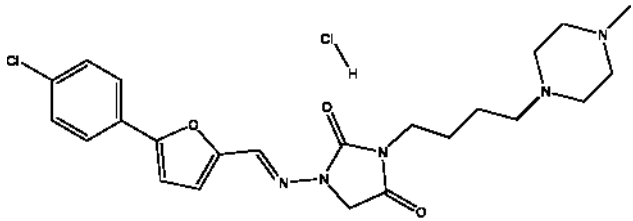
Chemical Name: 1-{[5-(4-Chlorophenyl)furan-2-ylmethylene]amino}-3-[4-(4-methylpiperazin-1-yl)butyl]imidazolidine-2,4-dione dihydrochloride

Common Name: Azimilide hydrochloride; Stedicor

Chemical Abstracts Registry No.: 149908-53-2 (Base); 149888-94-8

Trade Name	Manufacturer	Country	Year Introduced
Stedicor	Procter and Gamble	-	-

Structural Formula:



Raw Materials

1-Bromo-4-chlorobutane	1-(Benzylideneamino)hydantoin
Sodium hydride	Sodium iodide
1-Methylpiperazine	Sodium bicarbonate
Hydrogen chloride	Palladium on carbon
Hydrogen	5-(4-Chlorophenyl)-2-furancarboxaldehyde
Sodium iodide	

Manufacturing Process

1-Phenylmethylenamino-3-(4-chlorobutyl)-2,4-imidazolidinedione dihydrochloride is prepared by adding 60% sodium hydride in mineral oil (7.8 g, 0.1944 mole) over 1 h to a stirred solution o f 1-(benzy1ideneamino)hydantoin [prepared as described by J. Gut, A Novacet, and P. Fiedler, Coll. Czech. Chern. Comrnun., Vol. 33, pp. 2087-2096; No. 71, 1968] (39.5 g , 0.1944 mole) in dimethyl formamide (1000 ml). After complete addition, the solution is heated at steam bath temperature (approximately 100°C) for 1.5 h. The resulting mixture is allowed to cool to room temperature (30°C).

While stirring at room temperature, 1-bromo-4-chlorobutane (100 g ,0.5832 mole, 3 eq.) is added in one portion. The mixture becomes exothermic reaching around 35°C in approximately 30 min. The near-solution is heated a t approximately 80°C by steam bath for 4 h, cooled and stirred for approximately 8 h at room temperature (30°C). The cloudy mixture is filtered, removing a small amount of insoluble solid. The filtrate is concentrated under reduced pressure to a semi-solid residue. This residue is triturated with H_2O (400 ml), collected, recrystallized from acetonitrile, and then air-dried to give 43.1 g (0.1467 mole) of 1-phenylmethyleneamino-3-(4-chlorobutyl)-2,4-imidazolidinedione.

A mixture of 1-phenylmethyleneamino-3-(4-chlorobutyl)-2,4-imidazolidinedione (43.1 g, 0.1467 mole), acetone (1200 ml) and sodium iodide (48.4 9, 0.3227 mole) is heated to reflux. Reflux is maintained for 5 h. The mixture is filtered, collecting the insoluble. The filtrate is recharged with sodium iodide (10.0 g) and reflux is resumed and is maintained for 15 h. After cooling to room temperature, the mixture is filtered, removing the insoluble NaCl (total recovery, 9.5 g, 110%). The filtrate is poured into H_2O (2000 ml) while stirring. After stirring for 30 min, the solid is collected and air-dried to yield 51.5 g (0.1337 mole) of 1-phenylmethyleneamino-3-(4-iodobutyl)-2,4-imidazolidinedione.

A solution of 1-phenylmethyleneamino-3-(4-iodobutyl)-2,4-imidazolidinedione (10.0 g, 0.0260 mole), dimethylformamide (150.0 mg) and 1-methylpiperazine (11.5 ml, 10.4 9, 0.1040 mole) is heated to reflux. Reflux is maintained for 3 h. After cooling to approximately 40°C, the solution is concentrated under reduced pressure by rotary evaporator to an oily-solid residue. This residue is dissolved in H_2O (200 ml) then made basic with saturated $NaHCO_3$ (200 ml). The resulting mixture is stirred for 2 h. The solid is collected and air-dried, and is next dissolved in absolute ethanol (150 ml), next filtered, then made acidic to wet litmus with EtOH/HCl. After cooling several hours, the solid is collected and air-dried to give 8.04 g (0.0187 mole) of 1-phenylmethyleneamino-3-[4-(4-methyl-1-piperazinyl)butyl]-2,4-imidazolidinedione dihydrochloride.

A mixture of 1-phenylmethyleneamino-3-[4-(4-methyl-1-piperazinyl)butyl]-2,4-imidazolidinedione dihydrochloride (8.04 g, 0.0187 mole), 2 N HCl (125 ml) and 5% Pd/C: 50% H_2O (1.5 g) is subjected to hydrogen on a Parr apparatus at 40 psi at room temperature. After 2 h, the catalyst is removed by filtration. The filtrate is divided into two equal portions. Each is concentrated under reduced pressure on a rotary 10 evaporator to an oily residue of 1-amino-3-[4-(4-methyl-1-piperazinyl)butyl]-2,4-imidazolidinedione hydrochloride.

A solution of 1-amino-3-[4-(4-methyl-1-piperazinyl)butyl]-2,4-imidazolidinedione hydrochloride (0.0094 mole), dimethylformamide (75 ml) and 5-(4-chlorophenyl)-2-furancarboxaldehyde [prepared as described in U.S. Patent No. 20 4,882,354, to Huang et al., assigned to Norwich Eaton Pharmaceuticals, Inc., issued November 21, 1984; see Cols. 7 and 8] (1.94 g , 0.0094 mole) is stirred at room temperature for 72 h. The mixture is filtered, collecting the solid. Recrystallization from absolute ethanol/H_2O and air-drying gives 2.63 g (0.0050 mole) of 1-[[[5-(4-chlorophenyl)-2-furanyl]methylene]amino]3-[4-(4-methyl-1-piperazinyl)butyl]-2,4-imidazolidinedion hydrochloride.

1-[[[5-(4-Chlorophenyl)-2-furanyl]methylene]amino]-3-[4-(4-methyl-1-piperazinyl)butyl]-2,4-imidazolidinedione hydrochloride, (6.56 g, 0.0124 mole) is dissolved in H_2O (300 ml) and washed with (1x100 ml). The aqueous phase is made basic with saturated NaHCO3 solution. The resulting mixture is extracted with CH_2Cl_2 (4x100 ml). The extract is washed with saturated NaCl (2x50 ml), dried over $MgSO_4$ (activated charcoal), filtered and concentrated under reduced pressure to a solid residue. This solid is triturated in anhydrous ether, collected and air-dried. Recrystallization once from absolute EtOH and then from toluene (activated charcoal), next washing with anhydrous ether and air drying gives 2.05 g (0.0045 mole) of 1-[[[5-(4-chlorophenyl)-2-furanyl]methylene]amino]-3-[4-(4-methyl-1-piperazinyl)butyl]-2,4-imidazolidinedione.

References

Pelosi S.S., Calcagno M.A.; WO Patent No. 93/04061; March 4, 1993; Assigned: Procter and Gamble Pharmaceuticals [US/US]; NY (US)

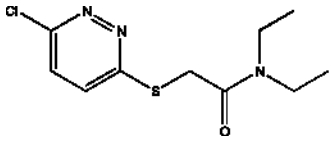
AZINTAMIDE

Therapeutic Function: Choleretic

Chemical Name: (6-Chlorpyridazin-3-ylthio)diethylacetamide

Common Name: Azintamide; Azinthiamide

Structural Formula:



Chemical Abstracts Registry No.: 1830-32-6

Trade Name	Manufacturer	Country	Year Introduced
Azintamide	Bristhar Laboratorios	-	-
Azintamide	Nycomed Austria GmbH	-	-
Azintamide	Pharm Chemical Shanghai Lansheng Corporation	-	-
Biluen	Byk Argentina	-	-
Colerin	Laboratorios LAB, LDA	-	-
Ora-Gallin purum	Nycomed	-	-
Oragallin	Austerreichcshe Shtkttofwerke	-	-
Soragallin	Misr Co.	-	-
Soragallin	Linz Co.	-	-

Raw Materials

3-Chloro-6-mercaptopyridazine
Chloroacetic acid diethyl amide
Caustic soda

Manufacturing Process

7.3 parts of 3-chloro-6-mercaptopyridazine are neutralised with 20 parts of 10% caustic soda solution, diluted with 60 parts of 50% ethanol, and heated to 60°C. 7.5 parts of chloroacetic acid diethyl amide dissolved in 20 parts of ethanol are added to this solution over a period of 10 min and the resulting mixture is heated to 60°C for 30 min. The reaction solution is then cooled, the

resulting crystallisate is removed by suction, and the filtrate is extracted with ethyl acetate. The solvent is removed by evaporation and the concentration residue is combined with the crystallisate. After two recrystallisations from benzene, 11 parts of 3-chloro-pyridazine-6-mercaptoacetic acid diethyl amide, having a melting point of from 139° to 140°C are yielded.

References

Merck Index, Monograph number: 945, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Stormann, Arzneim.-Forsch., 1964, 14, 266

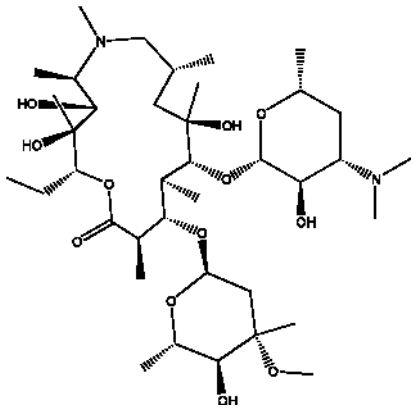
AZITHROMYCIN

Therapeutic Function: Antibiotic

Chemical Name: Azithromycin

Common Name: Azithromycin

Structural Formula:



Chemical Abstracts Registry No.: 83905-01-5

Trade Name	Manufacturer	Country	Year Introduced
ATM	Indoco Remedies Ltd.	India	-
AZ-1	Kopran Limited	India	-
Azee Rediuse	Protech Biosystems	-	-
Azicare	Olcare Laboratories	India	-
Azifast	Innova (IPCA)	India	-
Azilide	Micro Nova Pharmaceuticals Ltd.	India	-

Trade Name	Manufacturer	Country	Year Introduced
Azithral	Alembic Ltd.	India	-
Azithro-250	Ind-Swift Ltd.	India	-
Azithromycin	Alembi	India	-
Azitop	Talent Laboratories	India	-
Aziwok	Wockhardt Ltd.	India	-
Hemomycin	Hemofarm	Serbia and Montenegro	-
Licathrom	Replica Remedies	India	-
Sumamed	Pliva	Croatia	-
Vicon	Pfizer	-	-
Zady	Mankind Pharma Pvt. Ltd.	India	-
Zathrin	FDC Ltd.	India	-
Zithromax	Teuto/Neo Quimica	-	-
Zithromax	Pfizer	-	-
Zycin	IRM Pharma	India	-

Raw Materials

11-Aza-10-deoxo-10-dihydroerythromycin A
Formic acid
Formaldehyde

Manufacturing Process

To a solution of 0.54 g (0.000722 mole) of 11 aza-10-deoxo-10-dihydroerythromycin A in 20 ml $CHCl_3$ were added 0.0589 ml (0.000741 mole) of formaldehyde (approx. 35% w./w.) and 0.00283 g (0.000735 mole) of formic acid (approx. 98 to 100% w./w.). The reaction mixture was stirred for 8 hours while heating under reflux, then cooled to ambient temperature, whereupon were added 15 ml of water (pH 5.8). The pH of the reaction mixture was adjusted to 5.0 by means of 2 N HCl, whereupon the $CHCl_3$ layer was separated. To the aqueous part was added 15 ml of $CHCl_3$, the pH of the reaction suspension was adjusted to 7.5 by means of 20% NaOH, the layers were separated and subsequently the aqueous layer was extracted three times with 15 ml of $CHCl_3$. The combined chloroform extracts having pH 7.5 were dried over $K2CO_3$ and evaporated under reduced pressure, yielding 0.45 g (82.4%) of N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A (azithromycin), m.p. 113°-115°C. $[\alpha]_D^{20}$= - 37.0 (1% in $CHCl_3$).

References

Murphu H.W. et al.; US Patent No. 3,417,077; Dec. 17, 1968
Kobrehel G. et al.; US Patent No. 4,328,334; May 4, 1982; Assigned: PLIVA Pharmaceutical and Chemical Works (Zagreb, YU)
Bright G.M.; US Patent No. 4,474,768; Oct. 2, 1984; Assigned: Pfizer Inc. (New York, NY)

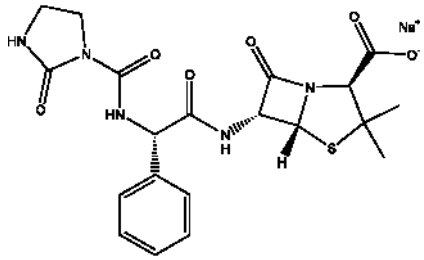
AZLOCILLIN

Therapeutic Function: Antibacterial

Chemical Name: D-α-(Imidazolidin-2-on-1-yl-carbonylamino)benzylpenicillin, sodium salt

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 37091-66-0; 37091-65-9 (Sodium Salt)

Trade Name	Manufacturer	Country	Year Introduced
Securopen	Bayer	W. Germany	1977
Securopen	Bayer	Switz.	1980
Securopen	Bayer	UK	1980
Azlin	Miles	US	1982
Securopen	Bayer	France	1983

Raw Materials

D-(-)-α-[(Imidazolidin-2-on-1-yl)carbonylamino]phenyl acetic acid
6-Aminopenicillanic acid

Manufacturing Process

3.8 parts by weight of D-(-)-α-[(imidazolidin-2-on-1-yl)carbonylamino]phenyl-acetic acid were dissolved in 65 parts by volume of dichloromethane. 2.7 parts by weight of 1-methyl-2-chloro-δ1-pyrrolinium chloride were added, and after cooling to -10°C 2.0 parts by volume of triethylamine were added gradually. This reaction mixture was then stirred for one hour at -5°C (mixture A). 4.0 parts by weight of 6-aminopenicillanic acid in 80 parts by volume of dichloromethane were treated with 4.4 parts by volume of triethylamine and 4.0 parts by weight of anhydrous sodium sulfate and then stirred for two hours at room temperature. After filtration, the solution was cooled to -20°C and combined with the mixture A. The reaction mixture was left to reach 0°C of its own accord, and was then stirred for a further hour at 0°C. The solvent was removed in a rotary evaporator, the residue was dissolved in water, and the solution was covered with a layer of ethyl acetate

and acidified with dilute hydrochloric acid at 0° to 5°C, while stirring, until pH 1.5 was reached. The organic phase was then separated off, washed with water, dried over magnesium sulfate while cooling, and filtered, and after dilution with an equal amount of ether the sodium salt of the penicillin was precipitated from the filtrate by adding a solution of sodium 2-ethylcaproate dissolved in ether containing methanol. Yield: 1.3 parts by weight.

References

Merck Index 916
Kleeman and Engel p. 69
PDR p. 1247
OCDS Vol. 3 p. 206 (1984)
DOT 13 (10) 409 (1977)
I.N.p. 111
REM p. 1200
Konig, H.B., Schrock, W., Disselknotter, H. and Metzger, K.G.; US Patents 3,933,795; January 20, 1976; 3,936,442; February 3, 1976; 3,939,149; February 17, 1976; 3,974,140; August 10, 1976; 3,978,223; August 31, 1976 and 3,980,792; September 14, 1976; all

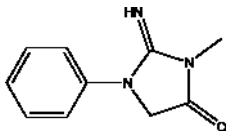
AZOLIMINE

Therapeutic Function: Diuretic

Chemical Name: 4-Imidazolidinone, 2-imino-3-methyl-1-phenyl-

Common Name: Azolimine

Structural Formula:



Chemical Abstracts Registry No.: 40828-45-3

Trade Name	Manufacturer	Country	Year Introduced
Azolimine	ZYF Pharm Chemical	-	-

Raw Materials

Sodium hydroxide
Phenylcyanamide
N-Methylchloroacetamide
Sodium methoxide
Phenylcyanamide hemihydrate

Manufacturing Process

2 methods of producing of 1-phenyl-2-imino-3-methyl-4-oxoimidazolidine:

1). In 29 ml of water containing 1.0 g of sodium hydroxide was dissolved 3.55 g of phenylcyanamide. To the clear solution was added 2.7 g of N-methylchloroacetamide. The reaction mixture was left to stir for 120 h at room temperature. The solvent was therefore stripped off on a rotary evaporator under vacuum. The solid residue was slurried in dilute alkali and filtered to yield 1.0 g (21%) of 1-phenyl-2-imino-3-methyl-4-oxoimidazolidine, melting point 163°-165°C.

2). 133.0 g of phenylcyanamide hemihydrate was dissolved in 1500 ml of absolute alcohol. To this solution was added 55.0 g of sodium methoxide. This mixture was stirred for 30 min and 113.0 g of N-methylchloroacetamide then added. This mixture was heated to reflux for 4 h and allowed to stand overnight. The white precipitate was filtered and washed with ethanol. This ethanol filtrate was concentrated on the rotating evaporator and cooled giving additional product. Both crops of product were combined, washed with water and dried to give 87.0 g (47%) of 1-phenyl-2-imino-3-methyl-4-oxoimidazolidine, melting point 169°-170°C.

References

Hanifin J.W. et al.; US Patent No. 4,044,021; August 23, 1977; Assigned: American Cyanamid Company, Stamford, Conn.

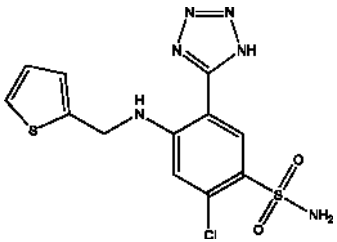
AZOSEMIDE

Therapeutic Function: Diuretic

Chemical Name: 5-(4'-Chloro-2'-thenylamino-5'-sulfamoylphenyl)tetrazole

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 27589-33-9

Trade Name	Manufacturer	Country	Year Introduced
Diurapid	Boehringer Mannheim	W. Germany	1981

Raw Materials

4-Chloro-2-fluoro-5-sulfamoyl benzonitrile
Thenylamine
Sodium azide

Manufacturing Process

The 4-chloro-5-sulfamoyl-2-thenylaminobenzonitrile used as starting material is obtained by the reaction of 4-chloro-2-fluoro-5-sutfamoyl-benzonitrile with thenylamine in anhydrous tetrahydrofuran.

Then the 5-(4'-chloro-5'-sulfamoyl-2'-thenylamino)phenyltetrazole (MP 218° to 221°C; yield 37% of theory) is obtained by the reaction of 4-chloro-5-sulfamoyl-2-thenylaminobenzonitrite (MP 170° to 174°C) with sodium azide and ammonium chloride,

References

Merck Index 922
DFU 4 (6)393 (1979)
OCDS Vol. 3 p. 27 (1984)
Popelek, A., Lerch, A., Stach, K., Roesch, E. and Hardebeck, K.; US Patent 3,665,002; May 23, 1972; Assigned to Boehringer Mannheim GmbH

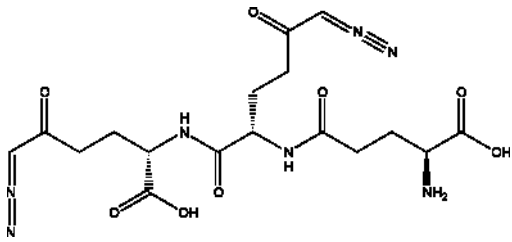
AZOTOMYCIN

Therapeutic Function: Antineoplastic

Chemical Name: L-Norleucine, 6-diazo-N-(6-diazo-N-L-γ-glutamyl-5-oxo-L-norleucyl)-5-oxo-

Common Name: Azotomycin; Duazomycin B

Structural Formula:



Chemical Abstracts Registry No.: 7644-67-9

Trade Name	Manufacturer	Country	Year Introduced
Azotomycin	ZYF Pharm Chemical	-	-

Raw Materials

γ-OBzl-N-Boc-L-Glu
Trifluoroacetic acid
N-Methylmorpholine
Oxalyl chloride
Sephadex LH-20
Diazomethane
Isobutyl chloroformate
Palladium on carbon
Triethylamine

Manufacturing Process

Azotomycin is anticancer antibiotic produced by Streptomyces ambofaciens. Total sythesis of it from γ-benzyl-N-tert-butyloxycarbonyl-L-glutamic acid (γ-OBzl-N-Boc-L-Glu) has been accomplished in nine steps. The mixed carbonic anhydride method was chosen for peptide bond formation. Commerically available γ-OBzl-N-Boc-L-Glu was esterified with ethereal diazomethane, deprotected with trifluoroacetic acid-methylene chloride (1:1), and converted to hydrochloride γ-benzyl-L-glutamic acid α-methyl ester (γ-OBzl-L-Glu-α-OMe HCl) by treatment with dry hydrogen chloride in ethyl ether, MP: 129°-135°C (dec.); $[\alpha]_D^{25}$= + 13.3° ($CHCl_3$).

Reaction of γ-OBzl-N-Boc-L-Glu with isobutyl chloroformate and N-methylmorpholine followed by addition of γ-OBzl-L-Glu-α-OMe HCl afforded dipeptide γ-OBzl-N-Boc-L-Glu-γ-OBzl-L-Glu-α-OMe; yield 93%, MP: 58.5°-60°C; $[\alpha]_D^{25}$= + 7.10° ($CHCl_3$). After cleaving (trifluoroacetic acid-methylene chloride) the Boc group of above dipeptide, N-Tfa-L-Glu-OMe (Tfa-trifluoroacetyl) was condensed with the product to afford tripeptide N-(γ-N-Tfa-L-Glu-α-OMe)-v-OBzl-N-Boc-L-Glu-γ-OBzl-L-Glu-α-OMe as colorless crystals, MP: 120°-122°C, $[\alpha]_D^{25}$= + 7.7° ($CHCl_3$). Following hydrogenolysis of benzyl esters using palladium-on-carbon (10%), diacid N-(γ-N-Tfa-L-Glu-α-OMe)-L-Glu-L-GluOMe was obtained in yield 94% as colorless crystals, MP: 181°-184°C; $[\alpha]_D^{25}$= - 37.6° (CH_3OH).

Selectively protected above diacid was converted to (γ-N-Tfa-L-Glu-α-OMe)-L-Glu-L-Glu-tetra-OMe next way. To a solution of N-(γ-N-Tfa-L-Glu-α-OMe)-L-Glu-L-Glu-α-OMe (0.18 g) in dry acetone (20 ml cooled to 0°C was added with magnetic stirring ethereal diazomethane (0.8 mole) until yellow color persisted. After evaporation of solvent, the colorless solid was recrystallized from methylene chloride-hexanes to afford 0.17 g (92%) of colorless crystals of (γ-N-Tfa-L-Glu-α-OMe)-L-Glu-L-Glu-tetra-OMe; MP: 150°-152°C; $[\alpha]_D^{25}$= - 8.5° ($CHCl_3$).

A 1.00 g (1.9 mmoles) of (γ-N-Tfa-L-Glu-α-OMe)-L-Glu-L-Glu-tetra-OMe was dissolved under argon in dry dimethoxyethane (30 ml) with warming and magnetic stirring, and triethylamine (0.55 ml, 3.97 mmoles) was added. The reaction mixture was cooled to -30°C (dry ice isopropyl alcohol), and oxalyl chloride (0.35 ml, 3.97 mmoles) was added followed by dimethylformamide (2

drops). The reaction mixture was warmed to 0°C by addition of hot isopropyl alcohol to the dry ice bath, stirred for 40 min, and then cooled to -78°C.

The cold acid chloride solution was slowly (30 min) added through the sintered-glass filter into ethereal solution of diazomethane (0.5 moles, 30 ml) cooled to -23°C (dry ice-carbon tetrachloride). After the mixture was stirred 30 min at -23°C and 30 min at 0°C, solvent was evaporated by steam argon, and the residue was chromatographed in 19:1 ethyl acetate-methanol on column of silica gel (70 g). The fraction (24:1 ethyl acetate-methanol) with TLC Rf 0.16 were collected and solvent evaporated to 0.30 g (38 %) of light yellow crystals of N-Tfa(-)-azotomycin-di-OMe, which upon recrystallization from chloroform-ethyl ether, melted at 134°-136°C; $[\alpha]_D^{25}$= - 22.9°.

To a mixture of N-Tfa(-)-azotomycin-di-OMe (106 mg, 0.18 mmoles) and methanol (0.12 ml) was added 1.0 N sodium hydroxide (0.83 ml, 8.3 mmoles) at room temperature and stirred for 30 min. Then the solution was acidified to pH 6.9 with 0.1 N hydrochloric acid and extracted with chloroform (2x25 ml). The aqueous phase was dissolved in methanol and passed through a column of Sephadex LH-20 (250 g), and fractions containing the magor product (TLC R_f 0.31, methanol, tailing) were collected. Solvent was evaporated and the residue was freeze-dried to yield 54.3 mg (65%) of (-)-azotomycin as a light yellow solid, which slowly decomposed at ambient temperature; $[\alpha]_D^{25}$= - 4.3°; IR, UV, ^{1}H NMR, ^{13}C NMR spectrum confirmed the structures of all described compounds.

References

Pettit G.R., Nelson P.S.; J Org.Chem.; v.51, No 8, pp 1282-1286; 1986

AZTREONAM

Therapeutic Function: Antibiotic

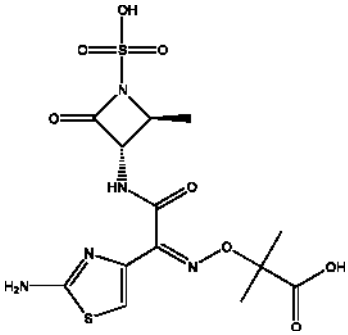
Chemical Name: Propanoic acid, 2-(((Z)-(1-(2-amino-4-thiazolyl)-2-(((2S,3S)-2-methyl-4-oxo-1-sulfo-3-azetidinyl)amino)-2-oxoethylidene) amino)oxy)-2-methyl-

Common Name: Azthreonam; Aztreonam

Chemical Abstracts Registry No.: 78110-38-0

Trade Name	Manufacturer	Country	Year Introduced
Azactam	Bristol-Myers Squibb	USA	-
Azenam	Aristo Pharmaceutical Ltd.	India	-
Aztreonam	Bristol-Myers Squibb	-	-

Structural Formula:



Raw Materials

Arrobacterium radiobacter A.T.C.C. No. 31700
Carbohydrates
Dimethybenzylammonium chloride
Sodium tiocyanate
Glucose

Manufacturing Process

The solutions for fermentation having the following composition was preparated:

Yeast extract	2%
Glucose	10%
Oatmeal	2%
Tomato paste	2%

This mixture was sterilized for 15 minutes at 121°C at 15 lbs/inch^2 steam pressure prior to use. The fermentation flasks were incubated at 25°C for 40 to 45 hours on a of rotary shaker. A 250 liter batch of Agrobacterium radiobacter A.T.C.C. No. 31700 is fermented in a 100 gallon steel vessel with a media and operating conditions described below. Culture of Agrobacterium radiobacter grown out on agar slants, pH 7.3 consisted of yeast extract (1 g), beef extract (1 g), NZ amine A (2 g), glucose (10 g), agar (15 g) in 1000 ml distilled water. Loopful of surface growth from agar slant was used as the source of incolumn. Medium of oatmeal (20 g), tomato paste (20 g) tapped water to 1000 ml, pH 7, was sterilized for 15 min at 121°C at 15 lbs/inch2 steam pressure prior to use. 100 ml of the medium, containing incolumn is incubated at 25°C for about 24 hours on a rotary shaker. It was added to a mixture of yeast extract (5 g), glucose (10 g) in 1 L distilled water and incubated for about 42 hours at 25°C in 100 gallon stainless steel fermentation vessel.

During incubation, the broth is agitated at 155 r.p.m. and aerated at rate of 10.0 cubic feet per minute. An antifoam agent (Ucon LB625, Union Carbide) was added as needed. The fermentation beer was adjusted to pH 4 with aqueous HCl and calls separated by centrifugation. The supernatante (200 L)

was extracted with 40 L of 0.05 m cetyldimethylbenzyl ammonium chloride in dichloromethane and extract concentrated in vacuo to 5.5 L. The concentrate was then extracted with solution of 177 g of sodium thiocyanate in 2 L of water, adjusting the mixture of pH 4.35 with phosphoric acid. The aqueous extract was concentrated in vacuo to 465 ml and added to 1840 ml of methanol. Solids are filtrated yielded 194 g of crude solid product. It was dissolved and chromatographed on a 5x106.5 cm column of Sephadex G-10 three times and after concentrating in vacuo gave 3.5 g of crude antibiotic M53 (azetreonam) which was chromatographed at first on QAE Sephadex A-25 (liner gradient, prepared from 2.5 L of water and 2.5 L of 0.25 M sodium nitrate). Then the residue (fractions 26-75) gave M53 (natrium salt) after evaporation. It was triturated with methanol and the souble fraction, 0.40 g was chromatographed on a 2.5x20 cm column of Diaion HP20AG, eluting at 2 ml per minute with water and collecting 20 ml fractions. Fractions 26-75 gave 51.9 mg of antibiotic M53 (sodium salt).

In practice it is usually used as free base.

References

Sykes R.B. et al.; US Patent No. 4,321,326; Mar. 23, 1982; Assigned: E. R. Squibb and Sons, Inc. (Princeton, NJ)

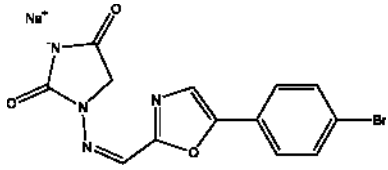
AZUMOLENE SODIUM

Therapeutic Function: Muscle relaxant

Chemical Name: 2,4-Imidazolidinedione, 1-(((5-(4-bromophenyl)-2-oxazolyl) methylene)amino)-, sodium salt

Common Name: Azumolene sodium

Structural Formula:



Chemical Abstracts Registry No.: 64748-79-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Azumolene sodium	ZYF Pharm Chemical	-	-
Azumolene sodium	Procter and Gamble	-	-

Raw Materials

2-Bromo-4'-bromoacetophenone
Hexamethylenetetramine
[[(2,4-Dioxo-1-imidazolidinyl)imino]methyl]formyl chloride
Hydrogen chloride
Amine hydrochloride
Phosphorus oxychloride

Manufacturing Process

To a stirred solution of 2-bromo-4'-bromoacetophenone (100.0 g, 0.36 mole) in chloroform (500 ml) was added hexamethylenetetramine (50.0 g, 0.36 mole). The mixture was stirred for 2.5 h and 143.0 g of the product was collected by filtration (100%).

The product above was combined with a solution of methanol (300 ml) and conc. HCl (410 ml), and the mixture was stirred for 52 h. The solid was collected by filtration and was washed with isopropanol. The product was recrystallized from methanol (Darco) to give 55.0 g (61%, in three crops), melting point 284°-287°C.

To a stirred mixture of the above amine hydrochloride (55.0 g, 0.22 mole) and [[(2,4-dioxo-1-imidazolidinyl)imino]methyl]formyl chloride (42.0 g, 0.22 mole) was added a solution of 440 ml of dimethylformamide and 44 ml of pyridine. The mixture was stirred for 20 h and poured into 2 L of water. The solid was collected by filtration and washed with ethanol and ether to give 36.0 g (28%) of N-[2-(4-bromophenyl)-2-oxoethyl]-[[(2,4-dioxo-1-imidazolidinyl)-imino]methyl]formamide, melting point 267°-269°C (recrystallization from 2200 ml acetic acid).

The of N-[2-(4-bromophenyl)-2-oxoethyl]-[[(2,4-dioxo-1-imidazolidinyl) imino]methyl]formamide (22.0 g, 0.061 mole) was combined with phosphorus oxychloride (310 ml) and the mixture was stirred and refluxed for 7 h. The solid was filtered off and stirred into an ice and water mixture (1 L). The 15.0 g (70%) of 1-[[[5-(4-bromophenyl)-2-oxazolyl]methylene]amino]-2,4-imidazolidinedione was collected by filtration, melting point 290°-292°C (recrystallization from 700 ml acetic acid).

In practice it is usually used as sodium salt.

References

White R.L.; US Patent No. 4,049,650; September 20, 1977; Assigned: Morton-Norwich Products, Inc., Norwich, N. Y.