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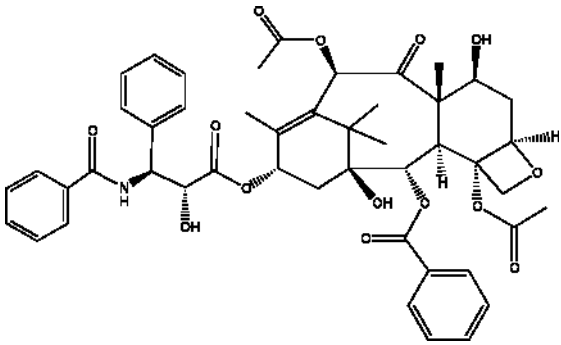
PACLITAXEL

Therapeutic Function: Antineoplastic

Chemical Name: 5β,20-Epoxy-1,2α,4,7,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-(α-phenylhippurate)

Common Name: 7-epi-Taxol; Paclitaxel; Plaxicel

Structural Formula:



Chemical Abstracts Registry No.: 33069-62-4

Trade Name	Manufacturer	Country	Year Introduced
Altaxel	Cytomed (A div. of Alembic)	India	-
Betaxel	Biological E. Limited	India	-
Biotax	Bio Therap.	-	-
Genexol	Samyang	-	-
Intaxel	Dabur Pharmaceuticals Ltd.	India	-
Onxol	IVAX Pharmaceuticals, Inc.	USA	-
Paclitax	Cipla Limited	India	-
Paclitaxel	Dabur Pharmaceuticals Ltd.	India	-
Paclitaxel	Taihua Natural Plant Pharmaceutical Company	China	-

Trade Name	Manufacturer	Country	Year Introduced
Paclitaxel	Shanghai Jinhe Bio-TechnologyCo., Ltd.	China	-
Paclitaxel	Bristol - Myers Squibb Co.	USA	-
Paclitaxel-Ebewe	Ebewe	Austria	-
Paxen	Ivax-CR a.s.	Czech Republic	-
Taxol	Polysciences Inc.	USA	-
Taxol (A)	Bristol-Myers Squibb	Italy	-
Taxol (A)	Bristol-Myers Squibb	USA	-

Raw Materials

t-Butyl isocyanate
Triethylamine
Trimethylsilyl chloride
Hydrogen fluoride
Thiophenol
Potassium butoxide
7-SDMS Baccatin III
p-Nitrophenylsulfonyl chloride
(2R,3S)-β-Phenyl-isoserine methyl ester
Benzaldehyde dimethylacetal
4-Toluenesulfonic acid
Sodium bicarbonate
Benzoyl chloride
Triethylamine trihydrofluoride

Manufacturing Process

(2R,3S)-β-Phenyl-isoserine methyl ester (4.35 g, 22 mM) is dissolved in dry THF (100 ml) and the flask cooled to 0°C. To the mixture is added t-butyl isocyanate (2.8 ml, 25 mM). TLC after 15 min shows some starting material left so additional isocyanate (0.5 ml) is added. TLC after 1 h shows no starting material so the solvent is concentrated under reduced pressure to give the N-(t-butylaminocarbonyl)-β-phenyl isoserine methyl ester.

Triethylamine (4.8 ml, 34.4 mmol) is added to a stirred solution of methyl (2R,3S)-phenylisoserinate (7.26 g, 31.3 mmol) in methylene chloride (80 ml) at 0°C. To this slurry of is added trimethylsilyl chloride (4.4 ml, 34.7 mmol). Additional methylene chloride (45 ml) is added. The mixture is cooled to -65°C and triethylamine (9.8 ml, 70.3 mmol) is added. p-Nitrophenylsulfonyl chloride (6.93 g, 31.3 mmol) is added. The reaction rate is too slow at -65°C so the temperature is gradually raised to 0°C. Hydrogen fluoride (10% aqueous, 5 equivalents) is added. The aqueous phase is separated from the organic (methylene chloride) phase and methanol is added to the organic phase. The methylene chloride is removed under reduced pressure and the methyl (2R,3S)-3-(4-nitrobenzenesulfonamido)-3-phenyl-2-hydroxypropionate is obtained, melting point 187-189°C.

Benzaldehyde dimethylacetal (200 µl, 1.33 mmol) and a catalytic amount of p-toluenesulfonic acid (37 mg) are added to methyl (2R,3S)-3-(4-nitrobenzenesulfonamido)-3-phenyl-2-hydroxypropionate (315 mg, 0.83 mmol) in toluene 5 ml. The mixture is heated at 100°C under reduced pressure (15 mm mercury) with no condenser. After 1 h the crude reaction mixture is diluted with ethyl acetate and washed with water (2 times). After drying the organic layer over magnesium sulfate the crude material is purified by column chormatography (silica gel; eluting with ethyl acetate/cyclohexane, 35/65) to give the (2S,4S,5R)-2,4-diphenyl-3-(4-nitrobenzenesulfonamido)-5-methoxycarbonyl-1,3-oxazolidine, melting point 118°-120°C.

Water (8 ml), methanol (8 ml) and THF (8 ml) are added to (2S,4S,5R)-2,4-diphenyl-3-(4-nitrobenzenesulfonamido)-5-methoxycarbonyl-1,3-oxazolidine (1.50 g, 3.19 mmol). Potassium carbonate (1.018 g, 7.71 mmol) is then added. The resulting mixture is stirred at 20°-25°C until complete by TLC. After 5 h the reaction is complete and the reaction mixture is extracted with basic methylene chloride (2 times). The aqueous phase is then acidified with hydrochloric acid and extracted with ethyl acetate. The ethyl acetate phase is then washed with water, saline and dried over magnesiuim sulfate. Concentration of the organic phase (ethyl acetate) gives the (2S,4S,5R)-2,4-diphenyl-3-(4-nitrobenzenesulfonamido)-5-carboxy-1,3-oxazolidine, melting point 61°-65°C.

Then the (2S,4S,5R)-2,4-diphenyl-3-(4-nitrobenzenesulfonamido)-5-carboxy-1,3-oxazolidine react with the 7-SDMS Baccatin III, that is 7-(3-methylbut-2-yl)dimethylsilyl baccatin III (Baccatin III: 7,11-methano-1H-cyclodeca(3,4) benz(1,2-b)oxet-5-one,6,12b-bis(acetyloxy)-12(benzoyloxy)-1,2a,3,4,4a,6, 9,10,11,12,12a,12b-dodecahydro-4,9,11-trihydroxy-4a,8,13,13-tetramethyl-, (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS), isolated from Taxus baccata).

(2S,4S,5R)-2,4-Diphenyl-3-(4-nitrobenzenesulfonamido)-5-carboxy-1,3-oxazolidine(323 mg, 0.711 mmol) is mixed with toluene (2.5 ml) at 20°-25°C. Dicyclohexylcarbodiimide (160 mg, 0.775 mmol) is then added to the reaction mixture. 7-SDMS Baccatin III (156 mg, 0.218 mmol) is added followed by 4-(dimethylamino)pyridine (35 mg, 0.286 mmol) and the reaction mixture is stirred at 20°-25°C until complete (1 h) by TLC. Sodium bicarbonate (50% aqueous, 10 ml) and more toluene (5 ml) is added to the reaction mixture and then stirred at 20°-25°C for 2 h. The reaction mixture is filtered through a medium frit to remove the urea byproduct. After filtering the phases are separated and the aqueous phase is extracted with ethyl acetate. The combined organic phases are washed with aqueous sodium bicarbonate (50%), water and saline. The organic phases are dried over magnesium sulfate, filtered and then concentrated. The concentrate is purified by column chromatograpy (silica gel; eluting with ethyl acetate/cyclohexane, 20/80) to give the 7-SDMS baccatin III 13-(2R,4S,5R)- and (2S,4S,5R)-2,4-diphenyl-3-(4-nitrobenzenesulfonamido)-1,3-oxazolidine-5-carboxylic acid ester.

THF (13.5 ml) and DMF (1.5 ml) are cooled to -35°C and degased by alternating reduced pressure and nitrogen three times. Thiophenol (0.22 ml, 2.14 mmol) is added followed by potassium butoxide/THF (1.978 M, 0.7 ml, 1.38 mmol). After 5 min, 7-SDMS baccatin III 13-(2R,4S,5R)- and (2S,4S,5R)-2,4-diphenyl-3-(4-nitrobenzenesulfonamido)-1,3-oxazolidine-5-carboxylic acid ester (877 mg, 0.762 mmol) is added. After the solids are added, the reaction mixture is slowly warmed to -10°C. The mixture is stirred at -10°C until the red color fades to yellow. After 3 h the bath is dropped allowing the mixture to warm to 20-25°C. At 20°-25°C the reaction is stirred for 1 h before assaying by TLC and HPLC. Sodium bisulfite (241 mg, 2.31 mmol) is added in water (5 ml). The mixture is stirred at 20°-25°C and after approximately 115 h the reaction is complete (by TLC) giving the free amine 7-SDMS baccatin III 13-(2R,3S)-3-amino-3-phenyl-2-hydroxypropionate.

Sodium bicarbonate (485 mg, 5.77 mmol) and water (10 ml) are added to 7-SDMS baccatin III 13-(2R,3S)-3-amino-3-phenyl-2-hydroxypropionate. The mixture is cooled to 0°C and then benzoyl chloride (150 ml, 1.3 mmol) is added. After 1 hr the reaction is complete and the reaction mixture is diluted

with water and extracted with ethyl acetate. The organic phases are combined and washed with water, saline and dried over magnesium sulfate. Chromatography of the crude product (silica gel column; 20% to 100% ethyl acetate gives the 7-SDMS baccatin III 13-(2R,3S)-3-benzamido-3-phenyl-2-hydroxypropionate.

7-SDMS Baccatin III 13-(2R,3S)-3-benzamido-3-phenyl-2-hydroxypropionate (126 mg, 0.128 mmol) is dissolved in acetonitrile (2.5 ml). Triethylamine trihydrofluoride (123 mg, 0.763 mmol) is added under nitrogen and the resulting mixture is stirred at 5°C until complete by HPLC. When complete, the mixture is extracted with methyl t-butylether and washed with sodium bicarbonate solution. The aquesous washes are back extracted and combined with the organic phase. The combined organic phases are washed with water and saline, dried over magnesium sulfate, filtered and concentrated to give the Taxol (Paclitaxel), as needle from methanol with melting point 213-216°C.

References

Wuts P.G.M., Kelly R.C.; US Patent No. 6,057,452; May 2, 2000; Assigned to Pharmacia and Upjohn Company

Haugwitz R.D. et al.; US Patent No. 4,942,184; July 17, 1990; Assigned: USA as represented by the Department of Health and Human Services, Washington, D.C.

Stella V.J., Mathew A.E.; US Patent No. 4,960,790; Octouber 2, 1990; Assigned: University of Kansas, Lawrence, Kans

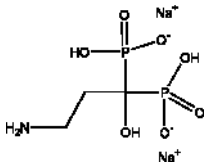
PAMIDRONATE SODIUM

Therapeutic Function: Bone resorption suppressant

Chemical Name: 3-Amino-1-hydroxypropane-1,1-diphosphonate, disodium salt

Common Name: Dinatrium pamidronat; Disodium pamidronate: Pamidronate sodium

Structural Formula:



Chemical Abstracts Registry No.: 57248-88-1; 40391-99-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Aredia	Novartis	India	-
Aredia	American Pharmaceutical Partners, Inc.	-	-
Aredia	Chiron Inc.	-	-
Aredia	Ciba-Geigy	-	-
Pamidronate Disodium	Novartis Pharmaceuticals	-	-
Pamidronate Disodium	Haorui Pharma-Chem Inc.	-	-
Pamidronate Disodium	Bedford Laboratories	-	-
Pamisol	David Bull Laboratories	-	-

Raw Materials

Mannitol
Pamidronic acid
Sodium hydroxide

Manufacturing Process

For a batch size of 5 L, 587.5 g (3.2 moles) of mannitol is dissolved in 3.5 L of water. Pamidronic acid (31.6 g, 0.133 moles) is mixed with a 1.0 L aliquot of the mannitol solution to form a slurry. The slurry is then transferred into the remainder of the mannitol solution, and stirred for at least 15 min. Aqueous 1 N sodium hydroxide (270 ml) is then added and the mixture is stirred until a clear, colorless solution results. The pH is then adjusted to 6.50.1 using either 1 M aqueous phosphoric acid or 1 N aqueous sodium hydroxide, as needed. The solution is then filtered through a 0.22 micron filter, and filled at 20°C into vials at 4.0 ml (4.172 g)/vial, under sterile conditions. The aqueous solution is frozen at -37°C and lyophilized (20 mbar, 20°-40°C) to yield 1,250 vials, each containing 30 mg of amorphous disodium pamidronate. The vials are sealed under positive nitrogen pressure. The disodium pamidronate is amorphous (noncrystalline) by X-ray diffraction and contains 0.7 wt-% water.

References

Shinal E.C.; US Patent No. 6,160,165; Dec. 12, 2000; Assigned: Aesgen, Inc., Princeton

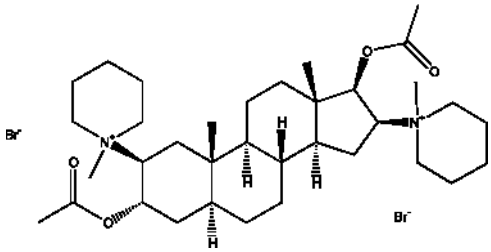
PANCURONIUM BROMIDE

Therapeutic Function: Muscle relaxant

Chemical Name: 1,1'-[3α,17β-Bis(acetyloxy)-5α-androstane-2β,16β-diyl]bis[1-methylpiperidinium] dibromide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 15500-66-0

Trade Name	Manufacturer	Country	Year Introduced
Pavulon	Organon-Teknika	UK	1968
Pancuronium	Organon	W. Germany	1969
Pavulon	Organon-Teknika	France	1971
Pavulon	Organon	US	1972
Myoblock	Organon-Sankyo	Japan	1973
Pavalon	Ravasini	Italy	1973

Raw Materials

Piperidine
m-Chloroperbenzoic acid
Acetic anhydride
3,17-Diacetoxy-5α-androstane-2,16-diene
Sodium borohydride
Methyl bromide

Manufacturing Process

A solution of 2α,3α,16α,17α-diepoxy-17β-acetoxy-5α-androstane (25 grams), prepared from 3,17-diacetoxy-5α-androstane-2,16-diene (Chem. Abs. 1960, 54, 8908) by treatment with m-chlor-perbenzoic acid, in piperidine (120 ml) and water (40 ml) was boiled under reflux for 5 days, the solution was concentrated and the product precipitated by the addition of water. The solid was collected, dissolved in dilute hydrochloric acid, filtered to give a clear solution and precipitated by the addition of sodium hydroxide solution. Crystallization from acetone gave 2β,16β-bis-piperidino-5α-androstan-3α-ol-17-one (18.9 grams), MP 179-185°C.

A solution of sodium borohydride (8 grams) in water (16 ml) was added to a stirred solution of 2β,16β-bis-piperidino-5α-androstan-3α-ol-17-one (17 grams) in tetrahydrofuran (70 ml) and methanol (30 ml) and the solution stirred at room temperature for 16 hours. The product was precipitated by the addition of water, filtered off, dried, and crystallized from acetone to give the diol (14.9 grams).

A solution of the piperidino-diol (9 grams) in acetic anhydride (18 ml) was heated at 90°C for 1 hour, the solution cooled, excess acetic anhydride

destroyed by the careful addition of water, and the resulting solution carefully made alkaline with 2 N caustic soda solution to precipitate a solid product. The solid was dried, extracted with n-hexane and the solution filtered free of insoluble material before percolation down a column (4 x 1'' diameter) of alumina. Elution with n-hexane gave a fraction (4.2 grams) which was crystallized twice from ether to give the diacetate, MP 176°-180°C.

Methyl bromide (17 grams) was added to a solution of the bis-piperidinodiacetate (4 grams) in methylene chloride (10 ml) and the resulting solution allowed to stand at room temperature for 4 days. The solution was evaporated to dryness, the residue triturated with ether, and filtered to give the bis-methobromide (5.2 grams), MP 206°C. Recrystallization from acetone-methylene chloride gave material MP 214°-217°C.

References

Merck Index 6870
Kleeman and Engel p. 681
PDR p. 1288
OCDS Vol. 2 p. 163 (1980)
DOT 5 (3) 104 (1969)
I.N.p. 726
REM p. 924
Hewett, C.L. and Savage, D.S.; US Patent 3,553,212; January 5, 1971; assigned to Organon Inc.

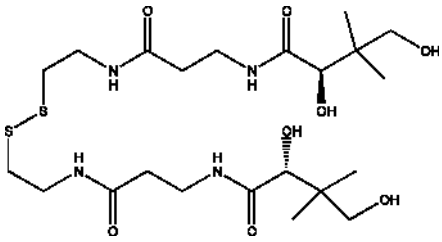
PANTETHINE

Therapeutic Function: Growth factor, Antihyperlipidemic

Chemical Name: Butyramide, N,N'-(dithiobis (ethyleneiminocarbonylethylene))bis(2,4-dihydroxy-3,3-dimethyl-, D-(+)-

Common Name: LBF disulfide form; Pantethine; Pantetina

Structural Formula:



Chemical Abstracts Registry No.: 16816-67-4

Trade Name	Manufacturer	Country	Year Introduced
Atarone	Vinas	-	-
Lipodel	Shanghai Lansheng Corporation	-	-
Obliterol	Faes	-	-
Pantogen	Maruko	-	-

Raw Materials

Hydrazine hydrate
Methyl D-pantothenate
Super-filtrol
Bis(β-aminoethyl)disulfide dihydrochloride
Carbon

Manufacturing Process

To 11 g of hydrazine hydrate (85%) cooled in an ice bath are added 11.5 g of methyl d-pantothenate and the cold mixture is stirred vigorously. After the reaction takes place and the mixture is warmed to 30°C, it is allowed to stand at room temperature for two days, and then evaporated to dryness in vacuo at 50°C. The residue (14.7 g) of pantothenyl hydrazide is a clear glassy oil.

To 7.3 g of crude d-pantothenyl hydrazide dissolved in 21 ml of water and stirred in a beaker cooled on an ice bath is added sufficient. 6 N hydrochloric acid to shift the pH to 4. Then a solution of 1.7 g of sodium nitrite in 5 ml of water is added dropwise over a period of one hour, keeping the pH at 4 by additions of 6 N hydrochloric acid. After stirring for one-half hour, 2.8 g of bis(β-aminoethyl)disulfide dihydrochloride are added. The pH is then adjusted to 8.5 with 50% aqueous sodium hydroxide solution and the solution allowed to stir for one and one-half hours. It is then acidified to pH 7.5 and concentrated in vacuo to clear colorless viscous oil. The pure product can be isolated from this oil by the next method. The crude bis(N-pantothenylamidoethyl)disulfide so obtained is purified by dissolving the crude reaction product in 45 ml of anhydrous n-butanol and pouring the resulting solution through a chromatograph column containing 272 g of activated carbon. The column is washed with n-butanol and fractions are collected from time to time and the fractions containing solids assaying about 25 to 40% pure bis(N-pantothenylamidoethyl)disulfide against Lactobacillus: helveticus 80 poured onto a chromatograph column containing 136 g of an alkaline earth aluminum silicate known commercially as Super -filtrol. The column is washed thoroughly with anhydrous n-butanol and the washings and main solution discarded. N-Butanol saturated with water is poured through the column to elute the bis(N-pantothenylamidoethyl)disulfide and the resulting solution evaporated to dryness in vacuum at low temperature to obtain the desired product in pure form.

Instead of pouring the anhydrous n-butanol solution onto the alkaline earth aluminum silicate chromatograph column, one can simply repeat the treatment with a carbon chromatograph column to obtain the pure product. In some instances, the first carbon treatment produces fractions containing pure bis(N-pantothenylamidoethyl)disulfide and in those cases it is, of course, not necessary to treat the fraction with alkaline earth aluminum silicate nor again with activated carbon.

References

Snell E.E., More J.A.; US Patent No. 2,625,565; Assigned to Parke, Davis and Company, Detroit, Mich., a corporation of Michigan

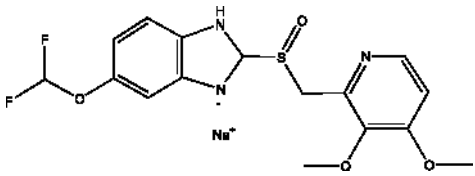
PANTOPRAZOLE SODIUM

Therapeutic Function: Antiulcer

Chemical Name: 1H-Benzimidazole, 5-(difluoromethoxy)-2-(((3,4-dimethoxy-2- pyridinyl)methyl)sulfinyl)-, sodium salt

Common Name: Pantoprazole sodium

Structural Formula:



Chemical Abstracts Registry No.: 138786-67-1; 102625-70-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Controloc	Byk Gulden	Germany	-
Pangest	Beta	-	-
Pantoloc	Solvay Pharma	-	-
Pepmark	Unimarck Pharma (India) Ltd.	India	-
Protium	Lupin Laboratories Ltd.	-	-
Protonix	Wyeth Pharmaceuticals	USA	-
Somac	Pharmacia and Upjohn	-	-

Raw Materials

Sodium hydroxide 5-Difluoromethoxy-1H-benzimidazole-2-thiol
Sodium thiosulfate Sodium hypochlorite
2-Chloromethyl-4,5-dimethoxy-3-methylpyridinium chloride

Manufacturing Process

2-Chloromethyl-4,5-dimethoxy-3-methylpyridinium chloride (about 1.5 g) are added to a solution of 5-difluoromethoxy-1H-benzimidazole-2-thiol in 10 ml of ethanol and 10 ml of 1 N sodium hydroxide solution. The yellow reaction mixture is stirred at 20°C for 1 hour, a further 10 ml of water are added,

whereupon a colorless solid precipitates out, the mixture is stirred for a further 5 hours and filtered and the residue is rinsed with 1 N sodium hydroxide solution and water and dried to constant weight. The 5-difluoromethoxy-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazole is obtained as an oil.

5-Difluoromethoxy-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazole (about 1 g) are dissolved in 10 ml of dioxane and 2 ml of 1 N sodium hydroxide solution. An equimolar amount of a titrated aqueous sodium hypochlorite solution, to which 1 mole per liter of sodium hydroxide solution has been added, is first added dropwise, while cooling with ice. After one hour a further equivalent and after 3 hours half the equimolar amount of sodium hypochlorite are added, to achieve complete reaction. After a reaction time of 4 hours, 5 ml of 5% strength sodium thiosulfate solution and another 25 ml of dioxane are added and the upper dioxane phase is separated off, washed once with 5 ml of sodium thiosulfate solution and concentrated on a rotary evaporator. The oily residue is dissolved in 20 ml of water and 10 ml of ethyl acetate and the solution is brought to pH 7 with about 100 ml of a buffer solution of pH 6.8. The solid which has precipitated out is filtered off with suction over a suction filter, washed with water, extracted by stirring at 0C with acetone and dried. 5-Difluoromethoxy-2-[(4,5-dimethoxy-2-pyridyl)methanesulfinyl]-1H-benzimidazole is prepared; yield about 85%.

In practice it is usually used as sodium salt.

References

Kohl B. et al, US Patent No. 4,758,579; July 19, 1988; Assigned to BYK Gulden Lomberg Chemische Fabrik GmbH (Konstanz, DE)

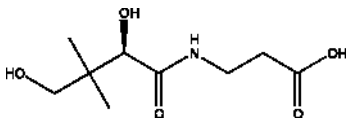
PANTOTHENIC ACID

Therapeutic Function: Vitamin

Chemical Name: β-Alanine, N-(2,4-dihydroxy-3,3-dimethyl-1-oxobutyl)-, (R)-

Common Name: Achromothrichiefaktor; Acidum pantothenicum; Chick antidermatitis factor; Filtrat-Faktor; Kueken-Antidermatitis-Faktor; Pantothenic acid; Pantothensaeure

Structural Formula:



Chemical Abstracts Registry No.: 79-83-4

Trade Name	Manufacturer	Country	Year Introduced
Panto-250	Bio-Tech Pharmacal	-	-

Raw Materials

Isobutylaldehyde
Potassium chromate
Hydrochloric acid
β-Alanine
Formaldehyde
Sodium cyanide
α-Phenylethylamine

Manufacturing Process

Isobutylaldehyde reacted with formaldehyde in the presence potassium chromate as a result 2,2-dimethyl-3-hydroxy-propanal was obtained.

The 2,2-dimethyl-3-hydroxy-propanal was treated by sodium cyanide so 2,4-dihydroxy-3,3-dimethyl-butironitrile was prepared.

The 2,4-dihydroxy-3,3-dimethyl-butironitrile was treated hydrochloric acid and D,L-3-hydroxy-4,4-dimethyl-dihydro-furan-2-one (D,L-pantolacton) was obtained. The racemic mixture of D- and L-pantolactons was a division of D- and L- isomers by the adding of α-phenylethylamine. So D-pantolacton was isolated.

Acrylic acid contacted with $NH_3$and β-alanine was obtained.

D-Pantalacton reacted with β-alanine as a result 3-(2,4-dihydroxy-3,3-dimethyl-butyrylamino)-propanoic acid was produced.

References

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

PAPAIN

Therapeutic Function: Enzyme, Wound adhesion inhibitor

Chemical Name: Enzyme; used to prevent wound adhesions

Common Name: -

Structural Formula: Has folded polypeptide chain of 212 residues with a molecular weight of about 23,400

Chemical Abstracts Registry No.: 9001-73-4

Trade Name	Manufacturer	Country	Year Introduced
Papain	Green Cross	Japan	1969
Panafil	Rystan	US	-
Prevenzyme	Legere	US	-

Raw Materials

Papaya fruit
Methanol

Manufacturing Process

Crude papain, obtained as the dried exudate of the fruit and leaves of Carica papaya L., Caricaceae, is usually found to have been contaminated during collection, drying, or storage by insects, rodent hair and excreta, botanical plant parts, sand, etc. and may thereby become further contaminated by harmful bacteria and enteric organisms.

Heretofore papain has been purified by dispersing the crude enzymes in water, filtering and spray-drying. In this procedure, however, the soluble contaminants are retained in the dried product. It has also been known to purify papain by dispersing it in water and adding acetone to reprecipitate the enzymes leaving many of the acetone-soluble and water-soluble impurities in the supernatant liquid. The material thus purified possesses a very disagreeable sulfidelike taste probably due to the reaction between the acetone and reactive sulfhydryl groups present in the papaya latex.

It has now been found that an enzyme mixture of high purity which contains none of the objectionable sulfidelike taste can be obtained by dispersing the crude enzymes in water, adding a quantity of a water-miscible lower-alkanol to the incipient precipitation point of the proteolytic enzymes thereby retaining the maximum proteolytic activity (i.e., the maximum amount of the proteolytic enzymes) in the solvent phase while precipitating the major portion of the lower-alkanol insoluble contaminants, removing the lower-alkanol insoluble contaminants and precipitated inert materials, for example, by filtration or centrifugation, and then adding an additional quantity of the water-miscible lower-alkanol sufficient to precipitate the proteolytic enzymes.

The following is a specific example of the conduct of the present process. 100 g of crude papain were stirred with 120 ml of 0.01 M cysteine hydrochloride for one hour during which time the papain was completely dispersed. To the dispersion was added slowly and with vigorous stirring 147 ml of methanol. The mixture, which contained 55% methanol by volume, was stirred for about thirty minutes and centrifuged and the clear supernatant liquid was removed and saved. The precipitate was washed with 50 ml of 55% aqueous methanol, and the mixture was centrifuged again. The precipitate containing the undesirable, insoluble contaminants was discarded, and the clear wash liquid was combined with the main supernatant. To the combined clear supernatant liquid was added slowly and with vigorous stirring 265 ml of methanol to give a mixture containing 75.5% methanol by volume. The enzymes were precipitated as a taffylike gum which was isolated by decantation of the supernatant liquid containing the undesirable, soluble contaminants and tray-drying. Alternatively, the precipitated enzymes can be redissolved in pure

water and spray-dried.

References

Merck Index 6878
PDR pp. 1033, 1576
REM p. 1038
Losuk, A.; US Patent 3,011,952; December 5, 1961; assigned to Sterling Drug, Inc.

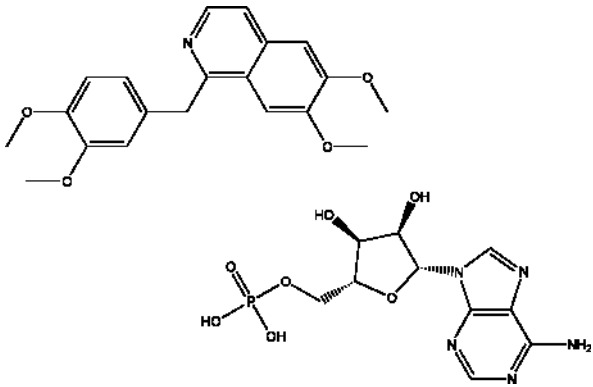
PAPAVERINE MONOPHOSADENINE

Therapeutic Function: Vasodilator, Platelet aggregation inhibitor

Chemical Name: Papaverine adenosine 5-monophosphate

Common Name: Papaverine adenylate

Structural Formula:



Chemical Abstracts Registry No.: 58-74-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Lempav Ty-Med	Lemmon	US	1975
Artegodan	Artesan	W. Germany	-
Cepaverin	Eurand	Italy	-
Cerespan	U.S.V.	US	-
Dylate	Elder	US	-
Omnopon	Roche	UK	-
Pameion	Simes	Italy	-
Panergon	Mack	W. Germany	-
Papaverlumin	Pidefe	Spain	-
Papaversan	Abello	Spain	-

Trade Name	Manufacturer	Country	Year Introduced
Pavabid	Marion	US	-
Pavacron	Cenci	US	-
Pavagrant	Amfre-Grant	US	-
Pavakey	Key	US	-
Pavatym	Everett	US	-
Paver	Mulda	Turkey	-
Spastretten	Tropon	W. Germany	-
Sustaverine	I.C.N.	US	-
Udip	Marion	US	-

Raw Materials

Papaverine base
Adenosine-5'-monophosphoric acid

Manufacturing Process

To 3.65 g (0.01 mol) of monohydrated adenosine-5'-monophosphoric acid, brought into suspension in a mixture of 45 ml of water and 5 ml of ethanol, are added 339 g (0.01 mol) of papaverine base (melting point, 147°C). The mixture is gently heated until a final temperature of 40°C is reached. The solution obtained is then filtered and the filtrate is concentrated under vacuum. The remaining product quickly crystallizes. After drying to 50°C to constant weight, there are obtained 6.68 g of desired product, in the monohydrated state, as a white crystalline powder, which melts at 140°C and is very soluble in water.

References

Merck Index 6880
Kleeman and Engel p. 683
PDR pp. 830, 875, 993, 1079, 1569, 1606, 1810
OCDS Vol. 1 p. 347 (1977)
DOT 11 (8) 315 (1975)
I.N. p. 728
REM p. 852
Mauvernay, R.Y.; US Patent 3,823,234; July 9, 1974; assigned to Centre Europeen de Recherches Mauvernay C.E.R.M.

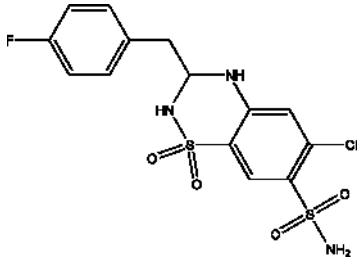
PARAFLUTIZIDE

Therapeutic Function: Diuretic

Chemical Name: 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3,4-dihydro-6-chloro-3-((4-fluorophenyl)methyl)-, 1,1-dioxide

Common Name: Paraflutizide

Structural Formula:



Chemical Abstracts Registry No.: 1580-83-2

Trade Name	Manufacturer	Country	Year Introduced
Paraflutizide	Shanghai Lansheng Corporation	-	-

Raw Materials

Potassium bichromate
ρ-Fluorophenylethyl alcohol
Hydrochloric acid
5-Chloro-2,4-disulphamylaniline

Manufacturing Process

A mixture of 5.0 g (0.0357 g/mol) of ρ-fluorophenylethyl alcohol, 2.0 g (0.007 g/mol) of 5-chloro-2,4-disulphamylaniline, 2.0 g (0.0068 g/mol) of potassium bichromate and 15 ml of concentrated hydrochloric acid (0.176 g/mol) and 25 ml of water is heated under reflux for 1 h. The mixture is allowed to cool, and 15 ml of ether are added to separate the excess of ρ-fluorophenylethyl alcohol. The aqueous layer is decanted and frozen for 2 h and the precipitate is separated, washed with water and dried in vacuum over phosphoric anhydride. There are collected 1.35 g (yield 47.5%) of the 1,1-dioxide of 3-ρ-fluorophenyl-methyl-7-sulphamyl-6-chloro-3,4-dihydrobenzo-1,2,4-thiadiazine, which when recrystallised from 30 ml of 50% alcohol on "Norit" active carbon takes the form of a white crystalline substance, melting point is 239°C.

References

GB Patent No. 961,641; July 31, 1962; Assigned: Les Laboboratoires Dausse, a French Body Corporate,of 58-60, Rue de la Glaciere, Paris, France

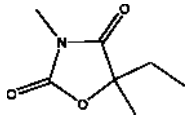
PARAMETHADIONE

Therapeutic Function: Anticonvulsant

Chemical Name: 5-Ethyl-3,5-dimethyl-2,4-oxazolidinedione

Common Name: Isoethadione

Structural Formula:



Chemical Abstracts Registry No.: 115-67-3

Trade Name	Manufacturer	Country	Year Introduced
Paradione	Abbott	US	1949

Raw Materials

Methyl ethyl ketone
Urea
Methanol
Sodium cyanide
Sodium
Dimethyl sulfate

Manufacturing Process

About 143.1 grams (one mol) of 5-methyl-5-ethyloxazolidine-2,4-dione is dissolved in 300 cc of methanol containing 23 grams of sodium. To the above mixture is added 126 grams of dimethyl sulfate in 10 cc portions while the temperature is maintained at about 50°C by external cooling. The mixture is then heated briefly to boiling, cooled, diluted with about 500 cc of water and extracted with two 250 cc portions of benzene. The benzene extract is separated, washed once with sodium bicarbonate solution and once with water. The benzene is removed by evaporation on a steam bath and the residue is fractionally distilled. The material boiling at 112° to 116°C at 25 mm pressure is taken; n_D^{25}=1.4495. Upon further fractionation, a very pure specimen boils at 101°-102°C at 11 mm.

The 5-methyl-5-ethyloxazolidine-2,4-dionemay be prepared by reacting methyl ethyl ketone with sodium cyanide and with ammonium thiocyanate followed by desulfurization. This intermediate may also be prepared by condensing α-hydroxy-α-methylbutyramide with ethyl chlorocarbonate or by condensing ethyl α-hydroxy-α-methylbutyrate with urea. Another method described (Traube and Aschar, Ber., 46, 2077-1913) consists in the condensation of ethyl α-hydroxy-α-methylbutyrate with guanidine followed by hydrolysis.

References

Merck Index 6890
Kleeman and Engel p. 685
PDR p. 545
OCDS Vol. 1 p. 232 (1977)
I.N. p. 730
REM p. 1080

Spielman, M.A.; US Patent 2,575,693; November 20, 1951; assigned to Abbott Laboratories

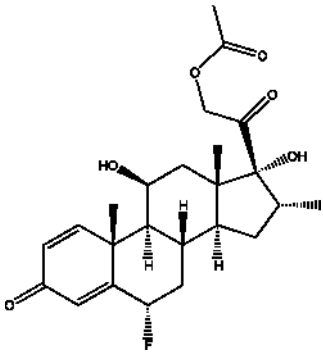
PARAMETHASONE ACETATE

Therapeutic Function: Glucocorticoid

Chemical Name: 6α-Fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 1597-82-6; 53-33-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Haldrone	Lilly	US	1961
Dilar	Cassenne	France	1962
Paramezone	Recordati	Italy	1962
Monocortin	Gruenenthal	W. Germany	1963
Stemex	Syntex	US	1970
Cortidene	I.F.L.	Spain	-
Metilar	Syntex	UK	-
Paramesone	Tanabe	Japan	-
Sintecort	Medicamenta	Portugal	-
Triniol	I.F.L.	Spain	-

Raw Materials

Hydrogen chloride
5α,11β,17α,21-Tetrahydroxy-6β-fluoro-16α-methylallopregnane-3,20-dione-21-acetate 3-ethylene glycol ketal

Manufacturing Process

A solution of 0.144 g of the 3-ethylene glycol ketal of 5α,11β,17α,21 - tetrahydroxy-6β-fluoro-16α-methylallopregnane-3,20-dione-21 acetate in 12 ml of chloroform and 0.1 ml of absolute alcohol was cooled to -10°C in an ice-salt bath and a stream of anhydrous hydrochloric acid was gently bubbled through the solution for 2.5 hours while the temperature was maintained between -5°C and -15°C. The solution was then diluted with 25 ml of chloroform, washed with dilute sodium bicarbonate and water, dried over anhydrous sodium sulfate, and evaporated to dryness under reduced pressure at 60°C or less to give 6α-fluoro-11β,17α,21-trihydroxy-16α-methyl-4-pregnene-3,20-dione 21-acetate.

References

Merck Index 6891
Kleeman and Engel p. 686
OCDS Vol. 1 p. 200 (1977)
I.N. p. 730
REM p. 969
Lincoln, F.H., Schneider, W.P. and Spero, G.B.; US Patent 3,557,158; January 19, 1971; assigned to The Upjohn Co.

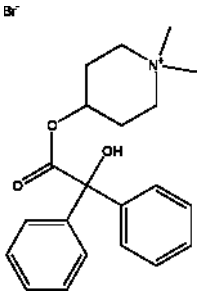
PARAPENZOLATE BROMIDE

Therapeutic Function: Antiulcer

Chemical Name: N-Methyl-4-piperidylbenzilate methobromide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 5634-41-3

Trade Name	Manufacturer	Country	Year Introduced
Spacine	Unilabo	France	1968
Vagopax	Essex	Italy	1976
Vagopax	Centrane	France	-

Raw Materials

Methyl iodide
Diphenylchloroacetyl chloride
Silver bromide
N-Methyl-4-piperidinol HCl

Manufacturing Process

N-methyl-4-piperidyl benzilate and the methiodide: An intimate mixture of 0.1 mol of N-methyl-4-piperidinol hydrochloride and 0.1 mol diphenylchloroacetyl chloride is heated at 160°C to 180°C until the evolution of hydrogen chloride ceases (usually about 4 to 5 hours). The melt is then dissolved in 500 ml of water and the resultant mixture heated on a steam bath for about ½ hour, after which time complete solution is effected. The acid solution is cooled and rendered alkaline with ammonium hydroxide solution whereupon the ester is precipitated. The ester is purified either by removal by filtration and recrystallization from benzene petroleum ether or by extracting the mixture with benzene and precipitating the ester by the addition of petroleum ether. After recrystallization there is obtained about 0.06 mol of N-methyl-4-piperidyl benzilate, melting point 162°C to 163°C.

To a solution of 0.05 mol of the above obtained ester in about 100 ml of anhydrous benzene there are added 15 ml of methyl iodide. The ensuing mixture is refluxed for several hours whereupon the quaternary salt is deposited and removed by filtration. Recrystallization from ethanol or ethanol-ether yields the quaternary salt, melting point 199°C to 200°C.

N-methyl-4piperidyl benzilate methobromide: To a suspension of 0.15 mol of freshly prepared silver bromide in 300 ml of anhydrous methanol is added a solution of 0.1 mol of quaternary iodide obtained as above. The mixture is stirred and refluxed for several hours after which time transhalogenation is complete. The mixture is cooled, the insoluble silver salt removed by filtration and the methanolic solution of the quaternaty bromide is concentrated in vacuo. The residue is recrystallized from methanol or methanol-ether yielding the quaternary bromide in quantitative amounts, melting point 237°C to 238°C.

References

OCDS Vol. 2 p. 75 (1980)
DOT6 (3) 92 (1970)
I.N. p. 731
Papa, D.; British Patent 788,126; December 23, 1957; assigned to Schering Corp.

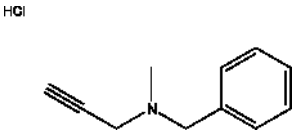
PARGYLINE HYDROCHLORIDE

Therapeutic Function: Antihypertensive

Chemical Name: N-Methyl-N-2-propynylbenzenemethanamine hydrochloride

Common Name: N-Methyl-N-propargylbenzylamine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 306-07-0; 555-57-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Eutonyl	Abbott	US	1963

Raw Materials

N-Methylbenzylamine
Sodium carbonate
Propargyl bromide
Hydrogen chloride

Manufacturing Process

A mixture of 23.8 grams (0.2 mol) of propargyl bromide, 24.2 grams (0.2 mol) of N-methylbenzylamine and 400 ml of anhydrous ethanol in the presence of 42.4 grams (0.4 mol) of anhydrous sodium carbonate was heated at the boiling temperature and under reflux for a period of 17 hours.

The sodium carbonate was then removed by filtration and the alcohol was removed by distillation under reduced pressure. The residue was treated with 300 ml of dry ether and the resulting solution was filtered to remove sodium bromide.

The filtrate was dried and fractionally distilled under reduced pressure to obtain the desired N-methyl-N-propargylbenzylamine which boiled at 96°-97°C at 11 mm pressure.

Analysis calculated for $C_{11}H_{13}N$: C = 82.97%; H = 8.23%; N = 8.80%. Found: C = 82.71%; H = 8.51%; N = 8.93%.

The hydrochloride salt of this amine was prepared by dissolving the amine in ether and adding ethereal hydrogen chloride to the ether solution. The solid hydrochloride salt which precipitated was recrystallized from an ethanol-ether mixture and was found to melt at 154° - 155°C.

References

Merck Index 6902
Kleeman and Engel p. 688
PDR p. 523
OCDS Vol. 1 p. 54 (1977) and 2, 27 (1980)
DOT9 (6) 217 (1973)
I.N. p. 732
REM p. 850 Martin, W.B. US Patent 3,155,584; November 3, 1964; assigned to Abbott Laboratories

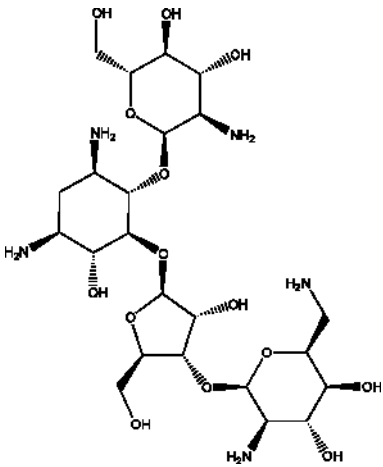
PAROMOMYCIN

Therapeutic Function: Amebicidal

Chemical Name: O-2,6-Diamino-2,6-dideoxy-β-L-idopyranosyl-(1-->3)-O-β-D-ribofuranosyl-(1-->5)-O-[2-amino-2-deoxy-α-D-glucopyranosyl-(1-->4)]-2-deoxystreptamine

Common Name: Catenulin; Aminosidine; Crestomycin; Hydroxymycin; Neomycin E; Paucimycin

Structural Formula:



Chemical Abstracts Registry No.: 7542-37-2

Trade Name	Manufacturer	Country	Year Introduced
Humatin	Parke Davis	US	1960
Humatin	Parke Davis	W. Germany	1961
Humatin	Parke Davis	Italy	1961
Humagel	Parke Davis	France	1963

Trade Name	Manufacturer	Country	Year Introduced
Aminosidine	Kyowa	Japan	-
Aminoxidin	Farmalabor	Italy	-
Gabbromycin	Montedison	Italy	-
Gabbroral	Farmalabor	Italy	-
Paramicina	Ragionieri	Italy	-

Raw Materials

Glucose
Soybean meal
Bacterium Streptomyces rimosus forma paromomycinus

Manufacturing Process

As described in US Patent 2,916,485: 12 liters of a nutrient medium having the following composition is placed in a 30 liter fermenter equipped with stainless steel fittings including sparger, impeller, baffles and sampling lines and the medium is sterilized by heating at 121°C for two hours.

	Percent
Glucose monohydrate	0.5
Glycerol	0.5
Casein, acid hydrolyzed	0.3
Peptone	0.25
Brewer's yeast	0.1
Corn steep solids	0.25
Soybean oil meal	0.25
Acetone-butanol fermentation residue	0.25
Sodium chloride	0.5
Calcium carbonate	0.1
Water sufficient to make	100%

The medium is cooled and inoculated with 20 ml of a suspension of the spores from two Mover's sporulation agar slant cultures of Streptomyces rimosus forma paromomycinus in sterile 0.1% sodium heptadecyl sulfate solution. The inoculated culture mixture is incubated at 26°C for sixty hours during which time the mixture is stirred at 200 rpm and sterile air is passed into the medium through the sparger at the rate of 12 liters per minute. A portion of the resulting incubated culture mixture is employed for inoculation of 16 liters of a nutrient medium having the following composition:

	Percent
Glucose monohydrate	1.0
Soybean oil meal	1.0
Sodium chloride	0.5
Calcium carbonate	0.1
Ammonium chloride	0.167
Hog stomach residue, saline extracted	0.5
Water sufficient to make	100%

The pH of the latter nutrient medium is adjusted to 7.5 with 10 N sodium hydroxide solution and is placed in a 30 liter glass fermenter equipped with

sparger, impeller, baffles and sampling line, The medium is sterilized by heating at 121°C for two hours, is allowed to cool and is then inoculated with 800 ml of the culture mixture obtained as described above.

The resulting culture mixture is incubated at 26°C for 94 hours during which time the mixture is stirred at 200 rpm and sterile air is passed into the medium through the sparger at the rate of 16 liters per minute. During the incubation, foaming is avoided by the addition, as needed, of crude lard and mineral oils containing mono-and diglycerides.

At the end of the incubation period the fermentation culture mixture is adjusted to pH 2 with concentrated hydrochloric acid, the solid material present is removed by filtration, and the filter cake is washed with water. The washings are combined with the main filtrate, adjusted to pH 7.0; and 15.5 liters of the filtered culture liquid is introduced into a columnar exchanger (1.5'' i.d.) packed with 380 ml of carboxylic acid resin which has been preliminarily washed in succession with two liters of an aqueous solution of 37.5 grams of sodium hydroxide and with two liters of water. The column containing paromomycin is washed with two hold-up volumes of water and is eluted with 0.5 N hydrochloric acid.

The first 19.4 liters of percolate contains little or no paromomycin and varies in pH from 6 to 7.3. When the pH of the eluate begins to fall below 6.0, two liters of the eluate are collected.

The two liter portion of the eluate, collected as indicated, is neutralized to pH 6 with 10 N sodium hydroxide solution and is filtered. The filtrate is concentrated by evaporation in vacuo to a volume of approximately one liter.

An adsorption column is prepared by pouring a slurried aqueous mixture of 65 grams of acid-washed activated charcoal (Darco G-60) and 50 grams of diatomaceous earth in a 1.5'' column and 300 ml of the concentrated filtrate is added. The column is washed with 400 ml of water and eluted successively with 325 ml of water, 425 mi of 1% aqueous acetone and 400 ml of 10% aqueous acetone. The water and acetone eluates are concentrated and lyophilized to give paromomycin hydrochloride as a powder. The product is purified by taking up the powder in methanol, adding a large excess of acetone to the solution, recovering the precipitate which forms by filtration. The product, paromomycin hydrochloride, has an optical rotation $[\alpha]_D^{25}$ = +56.5° (1% in water). By analysis it contains 35.71% carbon, 6.95% hydrogen, 8.24% nitrogen and 21.5% chlorine.

In order to obtain paromomycin in free base form, the hydrochloride is dissolved in water as a 3% solution, the solution is poured into an adsorption column containing an anion exchange resin (Amberlite IR-45 or preferably IRA-411 or IRA-400) in the hydroxyl form and the column is washed with a small amount of water.

The aqueous percolate is concentrated to dryness by lyophilization, and the solid product obtained is purified by taking up in boiling absolute ethanol, cooling and recovering the solid product paromomycin; $[\alpha]_D^{25}$ = +64° (1% in water). By analysis it contains 45.17% carbon, 7.44% hydrogen and 10.35% nitrogen.

References

Merck Index 6903
Kleeman and Engel p. 688
I.N. p. 733
REM P. 1221
Davisson, J.W. and Finlay, A.C.; US Patent 2,895,876; July 21, 1959; assigned to Chas. Pfizer and Co., Inc.
Frohardt, R.P., Haskell, T.H., Ehrlich, J. and Knudsen, M.P.; US Patent 2,916,485; Dec. 8, 1959; assigned to Parke, Davis and Company

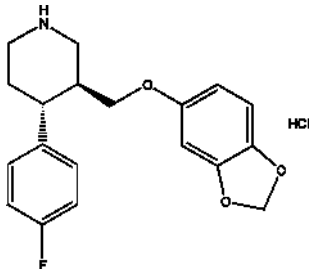
PAROXETINE HYDROCHLORIDE

Therapeutic Function: Antidepressant

Chemical Name: Piperidine, 3-((1,3-benzodioxol-5-yloxy)methyl)-4-(4-fluorophenyl)-, hydrochloride, (3S-trans)-

Common Name: Paroxetine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 78246-49-8; 61869-08-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Paxil	SmithKline Beecham Pharmaceuticals	France	-
Paxyl	SK Beecham	-	-

Raw Materials

- Methyl-4-(4-fluorophenyl)-N-methyl-nipecotinate
- Hydrochloric acid
- Formaldehyde
- Thionyl chloride
- Sulfuric acid
- 4-(4-Fluorophenyl)-1-methyl-1,2,3,6-tetrahydropyridine
- Sodium methoxide
- Tartaric acid, dibenzoate, (-)-
- Palladium on carbon
- 3,4-Methylenedioxyphenol

Manufacturing Process

251 g of methyl-4-(4-fluorophenyl)-N-methyl-nipecotinate, 8 g of sodium methoxide and 500 ml benzene were refluxed for 2 h. The benzene solution was washed with cold water and evaporated to give the pure α-ester which was dissolved in a mixture of 320 ml of water and 450 ml concentrated hydrochloric acid. The solution was slowly distilled to remove methanol and finally evaporated to dryness in vacuo.

400 ml thionyl chloride were added in small portions to the solid. The mixture was allowed to stand for 3 h at room temperature and was then evaporated to dryness in vacuo with tetrachloroethane giving methyl-4-(4-fluorophenyl)-N-methylnipecotic acid chloride. The acid chloride was added in small portions to a solution of 160 g (-)-menthol in 800 ml pyridine at a temperature of 0°-5°C. The mixture was allowed to stand at room temperature to the next day. Ice water and 50% sodium hydroxide were added, and the mixture was extracted with ether. The ether was dried with anhydrous magnesium sulphate, filtered and evaporated. Distillation in vacuo gave the menthol ester in a yield of 75-80%. Boiling point at 0.05 mm Hg was 165°-170°C.

Racemic 4-(4-fluorophenyl)-1-methyl-1,2,3,6-tetrahydropyridine (50 g) was dissolved in a mixture of 21.6 ml of concentrated sulfuric acid and 50 ml of water. To the solution were added 25 ml of concentrated hydrochloric acid and 22.4 ml of 37% formaldehyde solution. The mixture was refluxed for 5 h, cooled, and 125 ml of concentrated ammonia were added. The mixture was extracted with 50 ml of toluene. Drying of the toluene solution and distillation gave 38 g of 4-(4-fluorophenyl)-3-hydroxymethyl-1-methyl-1,2,3,6-tetrahydropyridine with boiling point 110°-120°C at 0.1 mm Hg.

13 g of the racemic compound and 22 g of (-)-dibenzoyltartaric acid were dissolved in 105 ml of hot methanol. On cooling, 9 g of salt of (-)-4-(4-fluorophenyl)-3-hydroxymethyl-1-methyl-1,2,3,6-tetrahydropyridine crystallized. Melting point 167°-168°C.

38 g of (-)-4-(4-fluorophenyl)-3-hydroxymethyl-1-methyl-1,2,3,6-tetrahydropyridine were dissolved in 350 ml of 99% ethanol, 5 g of 5% palladium on carbon were added, and the mixture was treated with hydrogen until 4500 ml were absorbed. The catalyst was filtered off, and the solution was evaporated to yield 37.5 g of (+)-b-4-(4-fluorophenyl)-3-hydroxymethyl-1-methylpiperidine.

To a solution of sodium in methanol (125 ml) were added 3,4-methylenedioxyphenol (29 g) and the (+)-b-4-(4-fluorophenyl)-3-hydroxymethyl-1-methylpiperidine (37,5 g). The mixture was stirred and refluxed. After removal of the solvent in vacuo, the evaporation residue was poured into a mixture of ice (150 g), water (150 ml), and ether (200 ml). The ether layer was separated, and the aqueous layer was extracted with ether. The combined ether solutions were washed with water and dried with anhydrous magnesium sulphate, and the ether was evaporated. The residue was triturated with 200 ml of 99% ethanol and 11.5 ml of concentrated hydrochloric acid, yielding 30 g of (-)-b-4-(4-fluorophenyl-3-(1,3-benzdioxolyl-(3)-oxymethyl)-1-methylpiperidine, hydrochloride were obtained. Melting point 202°C.

References

Christensen J.A., Squires R.F.; US Patent No. 4,007,196; Feb. 8, 1977; Assigned: A/S Ferrosan, Denmark
Lemmens J.M. et al.; US Patent No. 6,686,473 B2; Feb. 3, 2004; Assigned: Synthon BCT Technologies, LLC, Chapel Hill, NC (US)

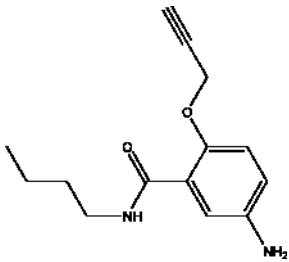
PARSALMIDE

Therapeutic Function: Muscle relaxant, Antiinflammatory, Analgesic

Chemical Name: Benzamide, 5-amino-N-butyl-2-(2-propynyloxy)-

Common Name: Parsalmide; Sinovial

Structural Formula:



Chemical Abstracts Registry No.: 30653-83-9

Trade Name	Manufacturer	Country	Year Introduced
Parsalmide	Shanghai Lansheng Corporation	-	-
Parsal	Midy	-	-

Raw Materials

Thionyl chloride	5-Acetamido-O-salicylic acid
Butylamine	Sodium hydroxide
Sodium	Propargyl bromide
Sulfuric acid	Isopropyl alcohol

Manufacturing Process

5-Acetylamino-2-acetoxybenzoyl chloride was obtained by reaction of 5-acetylamino-2-acetoxy-benzoic acid with thionylchloride.

5-Acetylamino-N-butyl-2-hydroxybenzamide was produced in the result of treatment of 5-acetylamino-2-acetoxybenzoyl chloride with butylamine in the

presence of sodium hydroxide.

5-Acetamino-N-(n-butyl)-2-propargyloxybenzamide was obtained by reaction of 5-acetylamino-N-butyl-2-hydroxybenzamide with propargylbromide in the presence of sodium, isopropyl alcohol and sulfuric acid.

28.8 g (0.1 mole) 5-acetamino-N-(n-butyl)-2-propargyloxybenzamide in 320 ml of 4 N sulfuric acid was heated, under stirring, at 90°-95°C for 2 h. The clear solution was cooled and its pH adjusted to 1 with 1 N NaOH; after filtering, further alkali was subsequently added until a pH of 10 was obtained. At this point the product was separated by filtration and recrystallized from ethanol at 60°C to give 16.6 g (a yield of 68%) of chromatographically pure 5-amino-N-(n-hutyl)-2-propargyloxybenzamide; melting point 85°-87°C.

References

Gradnik B. et al.; US Patent No. 3,739,030; June 12, 1973; Assigned: Societe d'Etudes de Recherches et d'Applications Scientifiques et Medicales E.R.A.S.M.E., Paris, France

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

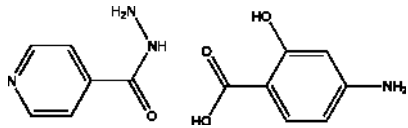
PASINIAZID

Therapeutic Function: Antitubercular

Chemical Name: Isonicotinic acid hydrazide compound with 4-amino-salicylic acid

Common Name: Pasiniazid; Umenazid

Structural Formula:



Chemical Abstracts Registry No.: 2066-89-9

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

Raw Materials

Isonicotinoyl hydrazine

4-Aminosalicylic acid

Manufacturing Process

10 parts by weight of isonicotinoyl hydrazine was dissolved in 200 by volume of methanol by stirring at 60°C. Then 11.2 parts 4-aminosalycylic acid was added at 60°C. On cooling a salt of both compounds crystallized as yellow prisms with MP: 135°-140°C (decomposed).

Isonicotinic acid hydrazide compound with 4-aminosalicylic acid may be prepared from the same components by using 750 parts of water by volume as a solvent.

10 parts 4-aminosalicylic acid was dissolved in 600 volume parts of water containing 39 parts by volume 2 N ammonium hydroxide. 9 parts by weight isonicotinoyl hydrazide was added and the mixture was heated to 30°C. The solution was acidified with 49 parts by volume of 2 N acetic acid. On cooling isonicotinic acid hydrazide compound with 4-amino-salicylic acid crystallized, which decomposed at 135°-140°C.

The yield was almost quantitative.

References

F. Hoffmann-La Roche and Co. Aktiengesellschaft, Basel (Switzerland); S.R. Patent No. 303,085; April 4, 1952

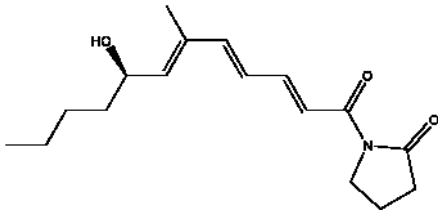
PECILOCIN

Therapeutic Function: Antibiotic

Chemical Name: 2-Pyrrolidinone, 1-(8-hydroxy-6-methyl-2,4,6-dodecatrienoyl)-, (E,E,E)-(R)-

Common Name: Pecilocin; Supral

Structural Formula:



Chemical Abstracts Registry No.: 19504-77-9

Trade Name	Manufacturer	Country	Year Introduced
Variotin	Shanghai Lansheng Corporation	-	-

Raw Materials

Sucrose
Paecilomyces varioti Bainier var. antibioticus ATCC 13435
Sodium nitrate
Ferric sulfate

Manufacturing Process

Paecilomyces varioti Bainier var. antibioticus ATCC 13435 was inoculated into 10 liters of a culture medium having a pH of 6 and containing 3.0% sucrose, 0.3% sodium nitrate, 0.2% potassium dihydrogen phosphate, 0.05% magnesium sulfate, 0.05% potassium chloride and 0.001% ferrous sulfate. The cultivation was carried out in a small-aerated tank at a temperature of 25°C. After cultivation for 60 hours, the production of 30 units of pecilocin (variotin) was accomplished. The fermentation broth was then separated from the mycelium by filtration and the filtrate was extracted twice with 3 litres of ethyl acetate. The combined extracts were concentrated under reduced pressure. The concentrate was dissolved into 100 ml of methanol and, after filtering off the insoluble material which formed on refrigeration of the resulting solution, the methanolic solution was concentrated under reduced pressure. Thus 1.8 g of pecilocin having an activity of 120 u/mg were obtained.

The mycelium separated from the fermentation broth by filtration was treated with 1 liter of methanol and, after thorough grinding and stirring, was centrifugally separated. The methanol was distilled off from the methanol extract under reduced pressure and the residue extracted with ethyl acetate. The extract was concentrated under reduced pressure and the resulting concentrate was dissolved in about 100 ml of methanol. After removing the insoluble materials, which appeared on refrigeration, the methanol solution was concentrated under reduced pressure and 0.8 g of pecilocin having an activity of 90 u/mg were obtained.

100 liters of the same medium as used above were charged into the 200 liters fermentation tank. 50 g of steamed rice which had been inoculated with Paecilomyces varioti Bainier var. antibioticus ATCC 13435 and fully sporulated after cultivation for a week were seeded in the tank and cultivated with aeration and agitation at a temperature of 26°-27°C for 90 hours, said aeration being carried out by sparging of sterilized air at the rate of 90 liters per minute. At the end of 90 hours, the fermentation broth showed a pecilocin content of 16 u/ml. 86 liters of the cultured solution including the mycelium were extracted twice with 30 liters of ethyl acetate and centrifuged in a Sharples centrifugal machine. The combined extracts were concentrated under reduced pressure and about 55 g of brownish colored syrup were obtained. This syrup was dissolved in 250 ml of methanol and then refrigerated. The insoluble materials, which appeared were removed by filtration. The clarified methanol solution was then concentrated under reduced pressure and the resulting syrup was dissolved in ether and the insoluble materials were filtered off. The ether solution was concentrated under reduced pressure to a volume of about 25 ml and the concentrate mixed with ten times its volume of

petroleum ether and refrigerated. Oily material, which precipitated were separated from the solvent by decantation and washed with a small volume of petroleum ether. After drying, the treated oily materials were dissolved in 300 ml of carbon tetrachloride and then refrigerated. Brownish-red colored oily materials, which had formed were removed by decantation and the solution in carbon tetrachloride was concentrated under reduced pressure, thereby 6.6 g of a slightly yellow oily substance having an activity of 145 μ/mg were obtained.

One gram of this oily substance was subjected to a 47 tube counter-current distribution employing a 1:1 mixture of 70% methanol and carbon tetrachloride as the solvent. The results of bio-assay, ultra-violet absorption and weight measurements showed that the biologically active component was distributed mainly in tubes No 12 - 32 and that tube No 21 showed the highest concentration of active component. The samples of tubes No 15 - 26 were combined and again counter-currently distributed, 130 tubes being used. As a result of this counter-current distribution, the pecilocin was distributed in tubes No 47 - 73 of which tube No 61 showed the highest content of pecilocin. Distribution curves were plotted from bio-assay, UV-absorption and weight measurements and these curves agreed well with theoretical curve. It was thus proved that variation is a single substance. The samples of tubes No 58 - 63 were combined and concentrated under reduced pressure whereby 110 mg of colorless oily substance having a pecilocin activity of 166 u/mg were obtained.

References

Yusuke Sumiki et al.; G.B. Patent No. 866,425; April 7, 1959; Assigned to Japan Antibiotics Research Association, an incorporated body organized under laws of Japan, Tokyo, Japan and Nippon Kayaku Kabushiki Kaisha, Japan

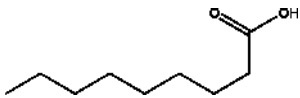
PELARGONIC ACID

Therapeutic Function: Fungicide

Chemical Name: Nonanoic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 112-05-0

Trade Name	Manufacturer	Country	Year Introduced
Pellar	Crookes Barnes	US	1960

Raw Materials

Oleic acid
Oxygen

Manufacturing Process

A body of liquid, 18 inches high, comprising a 35% (by weight) solution of technical (95%) oleic acid in n-propanol, is maintained at a temperature of 86°C in a reactor. The solution also contains dissolved therein 0.042% by weight of cobalt, in the form of cobalt naphthenate. From the bottom of the reactor very fine bubbles of air are passed into and through the solution at the rate of about 0.3 cubic feet per minute, measured at standard conditions, per square foot for 72 hours. The gases leaving the reactor are first passed through an ice water reflux condenser and then vented to the atmosphere. At the end of the 72 hour period the reaction mixture is separated into its components. It is found that 60% of the oleic acid has been consumed in the reaction. For each pound of oleic acid consumed there are obtained 0.30 pound of azelaic acid (representing an efficiency of 46%, calculated on the basis that the technical oleic acid is 100% oleic acid), 0.13 pound of pelargonic acid (representing an efficiency of 23%) and 0.21 pound of 9,10-dihydroxystearic acid (representing an efficiency of 19%).

References

Merck Index 6923
MacKenzie, J.S. and Morgan, C.S. Jr.; US Patent 2,820,046; January 14, 1958; assigned to Celanese Corp. of America

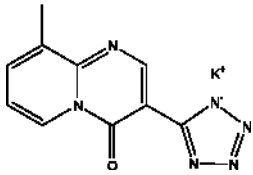
PEMIROLAST POTASSIUM

Therapeutic Function: Antiallergic, Antiulcer

Chemical Name: 4H-Pyrido(1,2-a)pyrimidin-4-one-9-methyl-3-(1H-tetrazol-5-yl), potassium salt

Common Name: Artimast; Pemirolast pottassium

Structural Formula:



Chemical Abstracts Registry No.: 100299-08-9; 69372-19-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Alamast	Santen	-	-

Raw Materials

3-Methylpyridine
N,N-Dimethylaniline
Sodium azide
Potassium hydroxide
Ferric nitrate hexahydrate
Sodium hydroxide
Ethyl ethoxymethylenecyanoacetate

Manufacturing Process

Ferrous nitrate hexahydrate (60 mg) followed by sodium (4.5 g, 0.196 g-atom) were added to liquid ammonia. To this mixture was added a solution of 3-methylpyridine (10.0 g, 0.093 mole) in N,N-dimethylaniline (21 ml) over a period of 5 min. The ammonia was allowed to evaporate and the residue heated under nitrogen by means of an oil bath maintained at 180°C for 18 h. The cooled residue was treated with ice (50 g) followed by 2 N sodium hydroxide (50 ml). The mixture was triturated for 2 h and then filtered. The collected solid was washed with boiling toluene (2 times 100 ml). The toluene layer was separated from the combined filtrate and washings, concentrated to about 50 ml and extracted with 5% aqueous acetic acid (5 times 20 ml). The combined extracts were filtered and reduced to dryness. The residue was recrystallized from methylcyclohexane to give 2-amino-3-methylpyridine acetate (4.9 g, 29%), melting point 85°-95°C. The acetate (2.5 g, 1.37 mmoles) was briefly suspended in 1 N sodium hydroxide (50 ml). The mixture was extracted with methylene chloride. The extract was washed with water, dried, and concentrated to give 2-amino-3-methylpyridine as an oil.

A solution of 2-amino-3-methylpyridine (5.0 g, 0.0462 mole) and ethyl ethoxymethylenecyanoacetate (7.82 g, 0.0462 mole) in toluene (4 ml) was heated for 15 min by means of an oil bath maintained at 100°C. The solution was cooled and the crude product (9.1 g, 85%) collected by filtration. The product was recrystallized from 2-propanol to give an analytical sample of ethyl 2-cyano-3-(3-methyl-2-pyridylamino)acrylate, melting point 144°-146°C.

Aluminum chloride (3.51 g, 0.0263 mole) was added to cold (-30°C) tetrahydrofuran (180 ml). Sodium azide (5.12 g, 0.0788 mole) was added and the mixture heated under reflux for 30 min. The mixture was cooled to 5°C. Ethyl 2-cyano-3-(3-methyl-2-pyridylamino)acrylate (5.0 g, 0.0216 mole) was added and the mixture heated under reflux for 18 h. The tetrahydrofuran was removed under reduced pressure. The residue was treated with ice water (100 ml) and acidified to pH 3 with 6 N hydrochloric acid. The mixture was filtered and the collected solid recrystallized from N,N-dimethylformamide to give the 9-methyl-3-(1H-tetrazol-5-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (2.5 g, 50.7%). Melting point 310°-311°C, dec.

Potassium hydroxide was added dropwise to a stirred mixture of 9-methyl-3-(1H-tetrazol-5-yl)-4H-pyrido[1,2-a]pyrimidin-4-one in water .The mixture was diluted with water to a volume of about 300 ml and was then heated to a temperature of 50°C during 2 min. The mixture was filtered and the water removed from the filtrate by lyophilization. The residue was recrystallized from water:ethanol to give the 9-methyl-3-(1H-tetrazol-5-yl)-4H-pyrido[1,2-

a]pyrimidin-4-one potassium salt.

References

Juby P.F.; US Patent No. 4,122,274; Oct. 24, 1978; Assigned: Bristol-Myers Company, New York, N.Y.

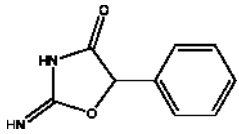
PEMOLINE

Therapeutic Function: Psychostimulant

Chemical Name: 2-Imino-5-phenyl-4-oxazolidinone

Common Name: Phenoxazole; Phenylisohydantoin

Structural Formula:



Chemical Abstracts Registry No.: 2152-34-3

Trade Name	Manufacturer	Country	Year Introduced
Deltamine	Aron	France	1960
Cylert	Abbott	UK	1975
Cylert	Abbott	US	1975
Antimeran	Nichiiko	Japan	-
Betanamin	Sanwa	Japan	-
Dynalert	Restan	S. Africa	-
Hyton	Pharmacia	Sweden	-
Kethamed	Medo	UK	-
Nitan	Teva	Israel	-
Phenoxine	P.C.B.	Belgium	-
Pioxol	Horner	Canada	-
Pondex	Chinoin	Hungary	-
Revibol	Pliva	Yugoslavia	-
Ronyl	Rona	UK	-
Sigmadyn	Spemsa	Italy	-
Sofro	Thilo	W. Germany	-
Stimul	Nadrol	W. Germany	-
Tradon	Beiersdorf	W. Germany	-
Vidil	Waldheim	Austria	-

Raw Materials

Mandelic acid ethyl ester
Guanidine

Manufacturing Process

It is preferably prepared by reacting mandelic acid ethyl ester with guanidine in boiling alcoholic solution whereby it is obtained as difficultly soluble precipitate with a yield of 90%.

This compound is a white, crystalline compound melting at 256°-257°C with decomposition. It is readily soluble in concentrated aqueous alkali hydroxide solutions and in concentrated aqueous mineral acids.

References

Merck Index 6931
Kleeman and Engel p. 690
PDR p. 509
DOT 9 (6) 212 (1973)
I.N. p. 736
REM p. 1137
Schmidt, L. and Scheffler, H.; US Patent 2,892,753; June 30, 1959; assigned to C.H. Boehringer Sohn, Germany

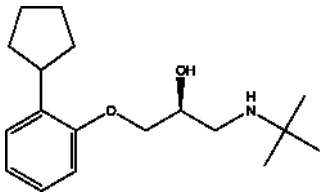
PENBUTOLOL

Therapeutic Function: Beta-adrenergic blocker

Chemical Name: 1-(2-Cyclopentylphenoxy)-3-[(1,1-dimethylethyl)amino]-2-propanol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 38363-40-5

Trade Name	Manufacturer	Country	Year Introduced
Betapressin	Hoechst	W. Germany	1980

Trade Name	Manufacturer	Country	Year Introduced
Betapressin	Hoechst	Switz.	1982
Betapressin	Hoechst	Italy	1983

Raw Materials

2-Cyclopentylphenol
Epichlorohydrin
t-Butylamine

Manufacturing Process

21.8 g (0.1 mol) of 1,2-epoxy-3-(2'-cyclopentylphenoxy)propane, boiling at 113°C to 115°C/0.2 mm Hg (prepared from 2-cyclopentylphenol and epichlorhydrin in the presence of alkali) were dissolved in 250 ml of ethanol; to this solution, there were added dropwise, while stirring.8.9 g (0.15 mol) of t-butylamine. The reaction mixture was stirred for 2 hours at 60°C and then the solvent and the excess t-butylamine were removed by distillation. The residue which had been purified via the aqueous hydrochloride, crystallized, after removal of the ether by evaporation, upon rubbing or inoculation and yielded, after recrystallization from n-heptane, the 1-t-butylamino-2-hydroxy-3-(2'-cyclopentylphenoxy)propane which was found to melt at 69°C to 70°C.

References

Merck Index 6935
DFU 1 (10) 494 (1976)
Kleeman and Engel p. 691
DOT 17 (12) 555 (1981) and 18 (10) 551 (1982)
I.N. p. 737
Ruschig, H., Schmitt, K., Lessenich, H. and Hartfelder, G.; US Patent 3,551,493; Dec. 29, 1970; assigned to Farbwerke Hoechst A.G. (W. Germany)

PENCICLOVIR

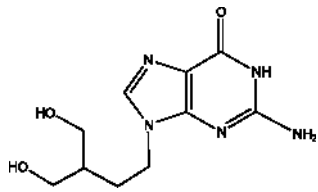
Therapeutic Function: Antiviral

Chemical Name: 6H-Purin-6-one, 1,9-dihydro-2-amino-9-(4-hydroxy-3-(hydroxymethyl)butyl)-

Common Name: Penciclovir

Chemical Abstracts Registry No.: 39809-25-1

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Denavir	Novartis Consumer Health	-	-
Vectavir	SmithKline Beecham Consumer Healthcare	France	-
Vectavir	Beecham	UK	-

Raw Materials

Triphenylphosphine
2,2-Dimethoxypropane
Carbon tetrabromide
Hydrochloric acid
Triethyl 1,1,2-ethanetricarboxylate
4-Toluenesulfonic acid monohydrate
Lithium aluminum hydride
Sodium hydroxide

Manufacturing Process

To a suspension of lithium aluminum hydride (2.87 g, 76 mmol) in tetrahydrofuran (125 ml), a solution of triethyl 1,1,2-ethanetricarboxylate (9.2 ml, 9.85 g, 40 mmol) in tetrahydrofuran (25 ml) was added dropwise with stirring over 2 hours. The inorganic salts were filtered off and washed with ethanol (100 ml). The filtrate and washings were combined and the solvent was evaporated under reduced pressure to afford a colourless oil (4.85 g). To a suspension of this oil in acetone (100 ml) 2,2-dimethoxypropane (25 ml) and p-toluenesulphonic acid monohydrate (2.3 g, 12 mmol) were added. The mixture was stirred for 1 hour. The resulting solution was neutralised with Amberlite IR 45 (methanol washed), filtered and the solvent evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with chloroform-methanol mixtures (40:1 and 25:1) to afford 5-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxan as a colourless liquid (3.01 g, 47%).

To an ice-cooled solution of 5-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxan (1.92 g, 12 mmol) and carbon tetrabromide (7.96 g, 24 mmol) in dimethylformamide (100 ml) triphenylphosphine (6.30 g, 24 mmol) was added and the solution was left at 4°C overnight. To this solution methanol (20 ml) was added and the solvent was then evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with hexane-acetone (12:1) to afford 5-(2-bromoethyl)-2,2-dimethyl-1,3-dioxan as a clear colourless liquid (0.89 g, 40%).

To a solution of 5-(2-bromoethyl)-2,2-dimethyl-1,3-dioxan (0.75 g, 3.7 mmol) in dry dimethylformamide (12 ml) 2-amino-6-chloropurine (0.68 g, 4.0 mmol) and then anhydrous potassium carbonate (0.83, 6.0 mmol) were added. The solution was stirred at room temperature for 5 hours and left at 4°C

overnight. The solution was filtered and the solvent removed. The residue was purified by column chromatography on silica gel, eluting with chloroform-methanol mixtures (80:1 and 60:1) to afford 2-amino-6-chloro-9-[2-(2,2-dimethyl-1,3-dioxan-5-yl)ethyl]purine as a white crystalline solid (0.74 g, 64%), melting point 125°-126°C.

2-Amino-6-chloro-9-[2-(2,2-dimethyl-1,3-dioxan-5-yl)-ethyl]purine (0.59 g, 1.9 mmol) in hydrochloric acid (1.0 M, 4 ml) was stirred at 60°C for 24 hours. The solution was diluted with water and neutralised with Amberlite IR 45. The mixture was filtered, the resin washed with water and the solvent evaporated under reduced pressure. The residue was recrystallised from water to afford 9-(4-hydroxy-3-hydroxymethylbut-1-yl)guanine (238 mg, 49%), melting point 275°-277°C.

References

Javest R.L., Harnden M.R.; US Patent No. 5,075,445; Dec. 24, 1991; Assigned: Beecham Group p.l.c., Middlesex, United Kingdom

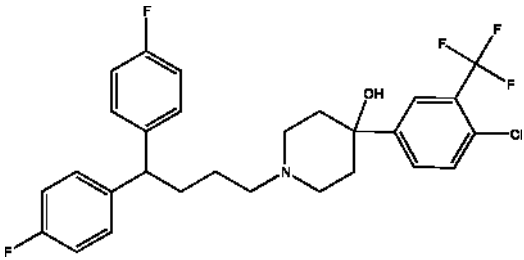
PENFLURIDOL

Therapeutic Function: Antipsychotic

Chemical Name: 1-[4,4-Bis(4-fluorophenyl)butyl]-4-[4-chloro-3-(trifluoromethyl)phenyl]-4-piperidinol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 26864-56-2

Trade Name	Manufacturer	Country	Year Introduced
Semap	Janssen-Le Brun	W. Germany	1975
Semap	Janssen	France	1975
Flupidol	Zambeletti	Italy	1979
Longoran	Isis	Yugoslavia	-
Micefal	Spofa	Czechoslovakia	-
Semap	Abic	Israel	-

Raw Materials

4,4-Bis(p-fluorophenyl)butyl chloride
4-(4-Chloro-α,α,α-trifluoro-m-tolyl)-4-piperidinol

Manufacturing Process

A mixture of 24 parts of 4,4-bis(p-fluorophenyl)butyl chloride, 20.9 parts of 4(4-chloro-α,α,α-trifluoro-m-tolyl)-4-piperidinol, 13.8 parts of sodium carbonate, a few crystals of potassium iodide in 600 parts of 4-methyl-2-pentanone is stirred and refluxed for 60 hours. The reaction mixture is cooled and 150 parts of water is added. The organic layer is separated, dried, filtered and evaporated. The oily residue is crystallized from diisopropylether, yielding 4-(4chloro-α,α,α-trifluoro-m-tolyl)-1-[4,4-bis(p-fiuorophenyl)butyl]-4-piperidinol; melting point 106.5°C.

References

Merck Index 6939
Kleeman and Engel p. 691
OCDS Vol. 2 p. 334 (1980)
DOT 10 (5) 167 (1974)
I.N. p. 737
Hermans, H.K.F. and Niemegeers, C.J.E.J.; US Patent 3,575,990; April 20, 1971; assigned to Janssen Pharmaceutica N.V. (Belgium)

PENGITOXIN

Therapeutic Function: Cardiotonic

Chemical Name: Gitoxin pentaacetate

Common Name: Pengitoxin; Pentaacetylgitoxin

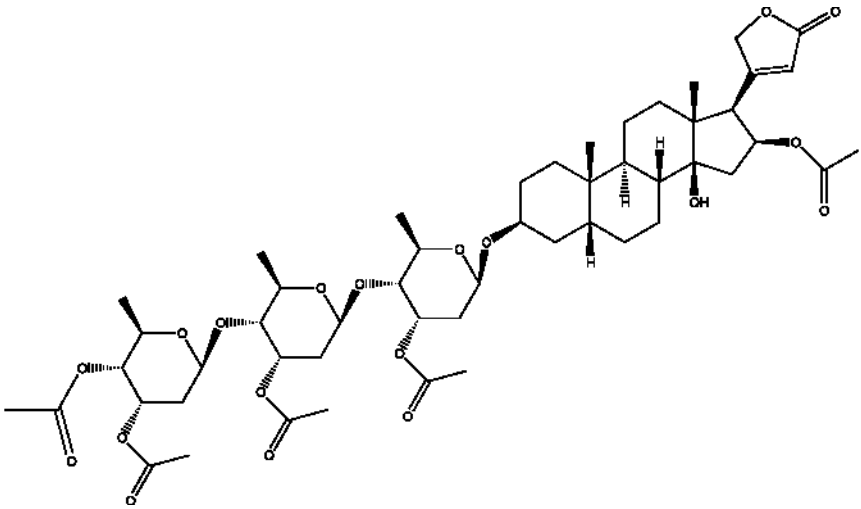
Chemical Abstracts Registry No.: 7242-04-8

Trade Name	Manufacturer	Country	Year Introduced
Pengitoxin	Shanghai Lansheng Corporation	-	-

Raw Materials

Gitoxin
Acetic anhydride
Potassium bicarbonate
Hydrochloric acid

Structural Formula:



Manufacturing Process

Gitoxin is isolated from leaves of Digitalis purpurea L. genus Scrofphulariaceae.

10.0 g pure gitoxin are boiled under reflux with 1 L pure acetic anhydride. Gitoxin thereby goes into solution in the course of 1 h. The boiling is discontinued after 1 h and the acetic anhydride distilled off in a vacuum as completely as possible. After taking up the oily residue with 500 ml chloroform, the solution is successively washed with 200 ml of 2 N potassium bicarbonate solution, 0.1 N hydrochloric acid and water. After drying the chloroform solution with anhydrous sodium sulfate, the chloroform is first distilled off over an open flame and then on a water bath at 40°C in a vacuum, a substantially crystalline residue thereby being obtained. The 12.8 g of crude product obtained are recrystallized from 12 times the amount of a mixture of pyridine, methanol and water (25:10:65) to give rhombic crystals, melting point 151°-155°C.

References

GB Patent No. 1,043,029; Sept. 21, 1966; Assigned: VEB Arzneimittelwerk Dresden, of 35, Wilhelm-Pieck-Strasse, 8122 Radebeul 1, Germany

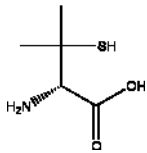
PENICILLAMINE

Therapeutic Function: Antiarthritic

Chemical Name: 3-Mercapto-D-valine

Common Name: Dimethylcysteine

Structural Formula:



Chemical Abstracts Registry No.: 52-67-5; 2219-30-9 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Cuprimine	MSD	US	1963
Trolovol	Bayer	W. Germany	1963
Pendramine	B.D.H.	UK	1973
Pemine	Lilly	Italy	1975
Trolovol	Bayer	France	1979
Depen	Wallace	US	1979
Artamin	Biochemie	Austria	-
Cuprenil	Polfa	Poland	-
Cupripen	Rubio	Spain	-
Depamine	Berk	UK	-
Distamine	Dista	UK	-
Gerodyl	Gea	Denmark	-
Metalcapase	Knoll	W. Germany	-
Reumacillin	Medica	Finland	-
Rhumantin	Gea	Denmark	-
Sufortanon	Lacer	Spain	-

Raw Materials

Sodium hydroxide
Potassium benzyl penicillin
Hydrogen sulfide
Phenylhydrazine
Mercuric chloride

Manufacturing Process

(a) Preparation of mercuric chloride complex of penicillamine: To a solution of 372 g (1 mol) of potassium benzyl-penicillin in 940 ml of distilled water at room temperature is added a solution of 40 g (1 mol) of sodium hydroxide in 180 ml of distilled water over a period of one-half hour. The solution is then stirred for two hours at room temperature. While maintaining room temperature, 67 ml of concentrated hydrochloric acid is added at a slow rate. This solution is then added, over a period of time of one-half hour, to a solution of 271 g (1 mol) of $HgCl_2$ in 3.52 liters of distilled water in the presence of 50 g of Hyflo and 5 ml of octyl alcohol. After one hour of agitation, the resulting mixture is treated with 185 ml of concentrated hydrochloric acid and filtered.

(b) Removal of benzylpenilloaldehyde: To the filtrate obtained in step (a), warmed to 50°C is slowly added 108 g (1 mol) of phenyl hydrazine. The mixture is cooled to room temperature and 84 ml of concentrated hydrochloric acid are added. The mixture is agitated briefly and the precipitated benzylpenilloaldehyde phenyl hydrazone is filtered off.

(c) Preparation of isopropylidene penicillamine hydrochloride: To the filtrate obtained in step (b) is added at 20°C to 25°C a total of 85 g of hydrogen sulfide. The precipitated HgS is filtered off and the filtrate is concentrated under reduced pressure to a volume of 200 to 500 ml. Following a polish filtration, the product-rich concentrate is mixed with 1.5 liters of isobutyl acetate. The mixture is refluxed at about 40°C under reduced pressure in equipment fitted with a water separation device. When no further water separates, the batch is cooled to 30°C and filtered. The reactor is washed with 1 liter of acetone, which is used also to wash the cake. The cake is further washed with 200 ml of acetone. The acetone washes are added to the isobutyl acetate filtrate and the mixture is refluxed for 20 to 30 minutes. After a holding period of one hour at 5°C. the crystals of isopropylidene penicillamine hydrochloride are filtered and washed with 200 ml of acetone. On drying for twelve hours at 25°C this product, containing 1 mol of water, weighs about 178 g (73%).

(d) Preparation of penicillamine hydrochloride: The 178 g of isopropylidene penicillamine hydrochloride obtained in step (c) is dissolved in 350 ml of distilled water. The solution is heated at 90°C to 95°C for one to one and one-half hours, removing acetone by distillation through an efficient column. There is then added 2.6 liters of isobutyl acetate. The mixture is refluxed at a temperature of about 40°C under reduced pressure in equipment fitted with a water separation device. When no further water separates, the pressure is adjusted so that the mixture distills at a vapor temperature of 83°C to 88°C. A total of 650 ml of distillate is collected. The batch is allowed to cool to 50°C and then filtered. The crystals are washed with isobutyl acetate and then dried at 35°C for 24 hours. The virtually anhydrous penicillamine hydrochloride obtained weighs about 128 g (69% from potassium benzyl-penicillin).

References

Merck Index 6940
Kleeman and Engel p. 693
PDR pp. 1153, 1872
DOT 9 (7) 302 (1973)
I.N. p. 738
REM p. 1225
Restivo, A.R., Dondzila, F.A. and Murphy, H. Jr.; US Patent 3,281,461; October 25, 1966; assigned to E.R. Squibb and Sons, Inc.
Sota, K., Ogawa, T. and Sawada, J.; US Patent 4,150,240; April 15, 1979; assigned to Taisho Pharmaceutical Co., Ltd. (Japan)

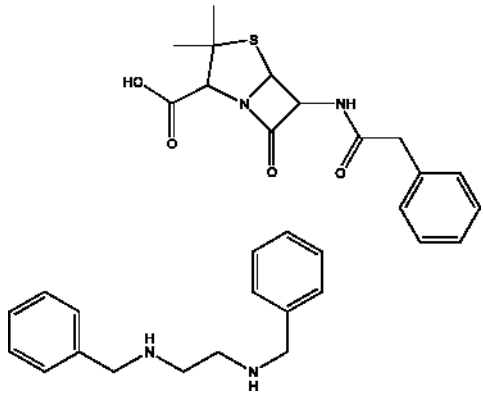
PENICILLIN G BENZATHINE

Therapeutic Function: Antibacterial

Chemical Name: Penicillin G compound with N,N'-dibenzylethylenediamine

Common Name: Benzethacil

Structural Formula:



Chemical Abstracts Registry No.: 1538-09-6

Trade Name	Manufacturer	Country	Year Introduced
Bicillin	Wyeth	US	1951
Permapen	Pfizer	US	1953
Neolin	Lilly	US	1954
Extencilline	Specia	France	-
Benzetacil-Simple	Antibioticos	Spain	-
Brevicilina-Simple	Wassermann	Spain	-
Brunocillin	Mepha	Switz.	-
Cepacilina	Cepa	Spain	-
Depotpen	Dauelsberg	W. Germany	-
Diaminocillina	Farmalabor	Italy	-
Durabiotic	Teva	Israel	-
Longacillin	Besy	Brazil	-
LPG	C.S.L.	Australia	-
Megacillin	Merck-Frosst	Canada	-
Pen-Di-Ben	Bago	Argentina	-
Pendysin	Jenapharm	E. Germany	-
Penidural	Wyeth	UK	-
Peniroger Retard	Roger	Spain	-
Pipercilina	Iskia	Spain	-
Retarpen	Biochemie	Austria	-
Tardocillin	Bayer	W. Germany	-
Tardopenil	Farmabion	Spain	-

Raw Materials

Ethylenediamine
Benzaldehyde
Sodium penicillin G

Manufacturing Process

Ethylenediamine (15 g, 0.25 mol) was added dropwise to 100 ml 98-100% formic acid in a two-necked 500 ml flask, fitted with an addition tube and reflux condenser with drying tube, cooled in an ice-bath. After complete addition of the base, 53 g of benzaldehyde (0.5 mol) was added in one lot. The ice-bath was removed and the flask was heated to the refluxing temperature. The initial rate of carbon dioxide evolution was too rapid to measure. After twenty minutes, the rate was circa 100 ml per minute and decreased rapidly to 8 ml per minute in one hour. Heating at reflux was continued for 35 hours.

Following the refluxing most of the excess formic acid was removed under reduced pressure. Hydrochloric acid (200 ml 6 N) was added to the viscous amber residue and heated under reflux, After 15 minutes, bumping necessitated cooling and filtering to remove crystalline dihydrochloride, which after washing with isopropanol was dried, MP circa 300°C. The mother liquors were refluxed one hour and cooled, obtaining an additional amount of product, MP circa 300°C. The filtrate was concentrated in vacuo to 100 ml, cooled and made alkaline with 40% NaOH. The supernatant oil was extracted with ether, dried, and fractionated from a stillpot packed with glass wool and heated in a sand-bath at 320°C. The first fraction at 106°C at 0.6-0.7 mm was N-benzylethylenediamine (dipicrate, MP 222°C). The N,N'-dibenzylethylenediamine was collected at 177°C to 206°C at 0.6-1.0 mm as a colorless liquid.

To a solution of 60 g of sodium penicillin G in 800 cc of distilled water cooled to 0°C to 4°C in an ice-bath, a solution of 35 g of N,N'-dibenzylethylenediamine diacetate in 200 cc of distilled water is added dropwise with stirring. The thick slurry is filtered with suction, washed twice with 100 cc of cold water, dried by suction and spread out in a thin layer for completion of drying. The product weighed 80 g.

The air-dried powder has a broad melting point, sintering at 100°C, melting above 110°C to a cloudy liquid becoming clear at 135°C.

References

Merck Index 6948
Kleeman and Engel p. 85
PDR pp. 1406, 1941, 1989
I.N. p. 126
REM p. 1197
Szabo, J.L.and Bruce,W.F.; US Patent 2,627,491; February 3, 1953; assigned to Wyeth, Inc.

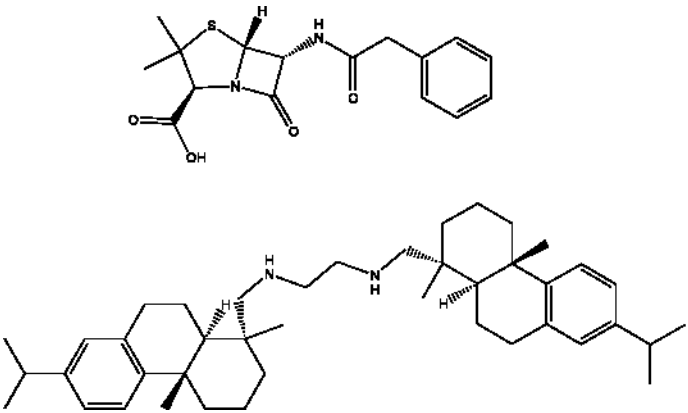
PENICILLIN G HYDRABAMINE

Therapeutic Function: Antibacterial

Chemical Name: N,N'-Bis(dehydroabietyl)ethylenediamine dipenicillin G

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 3344-16-9

Trade Name	Manufacturer	Country	Year Introduced
Compocillin	Abbott	US	1954

Raw Materials

Dehydroabietylamine
Ethylene dibromide
Penicillin G

Manufacturing Process

A mixture of 142.5 g of "Rosin Amine D" containing about 70% dehydroabietylamine and 30% dihydro and tetrahydroabietylamine, 47.0 g of ethylene dibromide, and 60.6 g of triethylamine is dissolved in 350 cc of anhydrous xylene and refluxed for about 16 hours. Thereafter the triethylamine dibromide salt formed is separated from the solution by filtering the cool reaction mixture and washing with ether. The solution is then concentrated under reduced pressure to dryness to remove the ether, xylene and excess triethylamines present. The viscous oil resin is slurried twice with 250 cc portions of methanol to remove any unreacted primary amines. The oil residue after being washed with methanol is dissolved in ethyl alcohol and 75 cc of concentrated hydrochloric acid is added dropwise to the warm alcohol

solution of the base. The dihydrochloride salts of the several hydroabietyl ethylenediamines precipitates immediately from solution. The salt is then separated by filtering and is washed twice with 100 cc portions of cooled ethyl alcohol. The dihydrochloride salts of the dehydroabietyl, dihydroabietyl and tetrahydroabietyl ethylenediamine mixture have a melting point of about 292°C to 295°C. On subjecting the mixture to solubility analyses it is found that the dehydroabietyl ethylenediamine is present in substantially the same proportion as is the dehydroabietylamine in the original "Rosin Amine D."

An amyl acetate-penicillin acid solution (10 liters) having a potency of 100,000 U/ml which is sufficient to supply 565 g (2 mols) of penicillin acid is added with constant agitation to 505 g of crude N,N'-bis-(dehydroabietyl)-ethylenediamine dissolved in 500 ml of amyl acetate. A slight excess of the ethylenediamine bases is added to the mixture until precipitation is completed. The reaction is preferably carried out in a cold room having a temperature of about 5°C. The precipitation salts comprise about 70% N,N'-bis-(dehydroabietyl)-ethylenediamine-dipenicillin salt and approximately 25-30% of the N,N'-bis-(dihydroabietyl)-ethylenediamine-and N,N'-bis-(tetrahydroabietyl)-ethylenediamine-dipenicillin salts are recovered by filtration and are washed with about 1/10 solution volume of amyl acetate. The crude preparation is further washed with 1/10 solution volume of diethyl ether and dried. The melting point of the product is about 153°C when taken on a microblock.

The total yield of the crude precipitation obtained in the above manner comprising about 1 kg is then dissolved in chloroform so as to form a 15% solution of a crude penicillin salt. To the filtered chloroform solution is added ethyl acetate slowly and with agitation until the solution becomes turbid as crystallization begins. Thereafter crystallization is allowed to proceed undisturbed for about 30-60 minutes in a cold room having a temperature of about 5°C. Sufficient ethyl acetate is slowly added to provide a final concentration of about 50% ethyl acetate and the mixture is allowed to stand in the cold room for one hour to complete crystallization. The precipitate is filtered and washed with about 750 ml of ethyl acetate and thereafter washed with the same volume of ether. The crystals are dried in vacuo and a yield of about 900 g of N,N'-bis-(dehydroabietyl)-ethylenediamine-dipenicillin G is obtained. The penicillin product melts with decomposition at a temperature of 170°C to 172°C on a Kofler hot stage. Solubility analysis of the product shows the product to be 95.3% pure.

References

Merck Index 6951
I.N. p. 739
De Rose, A.F.; US Patent 2,812,326; November 5, 1957; assigned to Abbott Laboratories

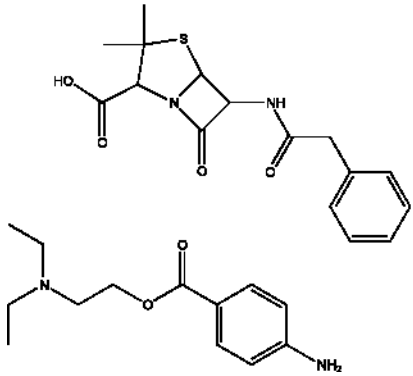
PENICILLIN G PROCAINE

Therapeutic Function: Antibacterial

Chemical Name: Penicillin G compound with 2-(diethylamino)ethyl p-aminobenzoate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 54-35-3

Trade Name	Manufacturer	Country	Year Introduced
Duracillin	Lilly	US	1948
Flo-Cillin	Bristol	US	1949
Ledercillin	Lederle	US	1949
Wycillin	Wyeth	US	1949
Diurnal Penicillin	Upjohn	US	1950
Abbocillin	Abbott	US	1951
Ampin-Penicillin	Badische Arzneim.	W. Germany	-
Aquacaine	C.S.L.	Australia	-
Aquasuspen	SK Kauelsberg	W. Germany	-
Aqucilina	Antibioticos	Spain	-
Cilicaine	Sigma	Australia	-
Distaquaine	Distillers	UK	-
Excolicin	Jenapharm	E. Germany	-
Farmaproina	Cepa	Spain	-
Francacilline	Franca	Canada	-
Hypercillin	Cutter	US	-
Hypropen	Biochemie	Austria	-
Intrasept	Streuli	Switz.	-
Klaricina	Clariana	Spain	-
Novocillin	Solac	France	-
Penifasa	Lifasa	Spain	-
Peniroger Procain	Roger	Spain	-
Premocillin	Premo	US	-
Procapen	Orion	Finland	-
Prokapen	Weifa	Norway	-
Retardillin	EGYT	Hungary	-

Trade Name	Manufacturer	Country	Year Introduced
Sanciline Procaina	Santos	Spain	-
Therapen I.M.	Therapex	Canada	-

Raw Materials

Penicillin G
Procaine

Manufacturing Process

There was added to 250 ml of a concentrated butyl acetate extract containing 74,000 units of the acid form of penicillin per ml, 50 ml of a butyl acetate solution containing 0.238 g per ml of procaine base. The solution was agitated for one hour. The precipitate which formed was very gummy and not in the form of discrete crystals. This precipitate was crystallized by scratching the side of the vessel and agitating further. After this treatment 18.25 g of crystalline procaine penicillin was obtained which assayed 1010 units per mg representing a yield of 99.6% of the activity contained in the concentrated extract.

References

Merck Index 6953
PDR pp. 1408, 1742, 1941, 1989
I.N. p. 739
REM p. 1198
Bardolph, M.P.; US Patent 2,739,962; March 27, 1956; assigned to Commercial Solvents Corp.

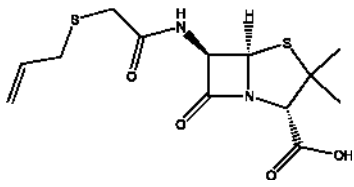
PENICILLIN O

Therapeutic Function: Antibacterial

Chemical Name: 3,3-Dimethyl-7-oxo-6-[[(2-propenylthio)acetyl]amino]-4-thia-1-azabicyclo[3.2.0]-heptane-4-carboxylic acid

Common Name: Allylmercaptomethylpenicillin

Structural Formula:



Chemical Abstracts Registry No.: 87-09-2

Trade Name	Manufacturer	Country	Year Introduced
Cero-O-Cillin	Upjohn	US	1950

Raw Materials

Lactose
Bacterium Penicillium
Corn steep liquor
N-(2-Hydroxyethyl)allylmercaptoacetamide

Manufacturing Process

A culture medium is prepared in the following proportions:

Lactose	125 g
Corn steep solids	150 g
Calcium carbonate	25 g
N-(2-Hydroxyethyl)-allylmercaptoacetamide	0.140 g
Water	5,000 cc

The culture medium is distributed in 200 cc portions in 1 liter Erlenmeyer flasks, sterilized, inoculated with a spore suspension of Penicillium mold strain Q-176, and stoppered with cotton plugs. The flasks are maintained at a temperature of about 23°C to 26°C and shaken constantly for five days. The flask contents are then filtered to remove the mold mycelium, the filtrate cooled to about 0°C, acidified to about pH 2.2 with o-phosphoric acid and shaken with an equal volume of amyl acetate. The amy acetate layer is separated and extracted with three 100 cc portions of cold water to which cold N/10 sodium bicarbonate solution is added during the course of each extraction until a pH of about 7.1 to 7.3 is attained in the aqueous phase. The aqueous extracts are combined, cooled to about 0°C. acidified to about pH 2.2 with o-phosphoric acid and extracted with three 100 cc portions of ether. The ether extracts are combined, and are passed through a chromatographic type silica adsorption column about 30 mm in diameter and 300 mm long, and containing a pH 6.2 phosphate buffer. The silica column is developed by percolation with six 100 cc portions of ether containing successively increasing amounts of methanol in the order of 0.5, 1.5%, 2, 2.5, and 3 percent.

The developed silica column is divided into about 12 equal sections and each section is eluted with three 30 cc portions of M/15 phosphate buffer of pH 7.0. The eluates are assayed bacteriologically to determine their penicillin content. Most of the antibiotic activity originates in a single bank in the silica column and results from the presence of allylmercaptomethylpenicillin. The eluates obtained from this band are combined, cooled to about 0°C, acidified to about pH 2.2and extracted with three 50 cc portions of chloroform. The combined chloroform extracts are then passed through a silica adsorption column containing a pH 6.2 phosphate buffer. This silica gel column is developed by percolation with three 100 cc portions of chloroform containing successively increasing amounts of methanol in the order of 1, 2 and 3 percent. The developed silica column is then divided into 12 equal sections and each section is eluted with three 30 cc portions of M/15 phosphate buffer of pH 7.0.

Again, most of the total antibiotic activity originates in a single band in the silica column. The eluates obtained by extraction of the silica column sections which comprise this band are combined, cooled to about 0°C, acidified to about pH 2.2 and extracted with three 100 cc portions of ether. The ether extracts are combined and extracted with about 75 cc of a cool dilute aqueous solution of sodium hydroxide to which N/10 sodium hydroxide solution is added during the course of the extraction so that a final pH of about 7.0 is obtained in the aqueous phase. From this aqueous solution the sodium salt of allylmercaptomethylpenicillin is separated, for example, by freezing and evaporation in vacuo from the frozen state.

References

Merck Index 6955
I.N. p. 58
Behrens, O.K., Jones, R.G., Soper, Q.F. and Corse, J.W.; US Patent 2,623,876; December 30, 1952; assigned to Eli Lilly and Co.

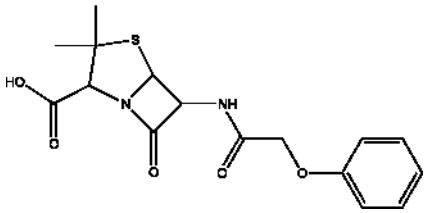
PENICILLIN V

Therapeutic Function: Antibacterial

Chemical Name: 3,3-Dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-4-thia-1-azabicyclo[3.2.0]-heptane-2-carboxylic acid

Common Name: 6-Phenoxyacetamidopenicillanic acid; Phenoxymethylpenicillin

Structural Formula:



Chemical Abstracts Registry No.: 87-08-1

Trade Name	Manufacturer	Country	Year Introduced
Oracilline	Theraplix	France	1954
V-Cillin	Lilly	US	1955
Pen-Vee	Wyeth	US	1955
Calcipen	Farmabion	Spain	-
Fenocin	Dumex	Denmark	-
Fenospen	Farmalabor	Italy	-
Ibaden	Lek	Yugoslavia	-
Intalpen	Inter-Alia Pharm.	UK	-

Trade Name	Manufacturer	Country	Year Introduced
Ospen	Biochemie	Austria	-
Penorline	Allard	France	-
Rivopen V	Rivopharm	Switz.	-
V-Tablopen	Arzneimittelwerk Dresden	E. Germany	-
Weifapenin	Weifa	Norway	-

Raw Materials

Phenoxyacetyl chloride
6-Aminopenicillanic acid

Manufacturing Process

The following description is taken from US Patent 2,941,995. A solution of phenoxyacetyl chloride (360 mg) in dry acetone (5 ml) was added dropwise during 10 minutes to a stirred solution of 6-aminopenicillanic acid (450 mg, approximately 75% pure) in 3% aqueous bicarbonate (18 ml), and acetone (12 ml). When addition was complete the mixture was stirred at room temperature for 30 minutes and then extracted with ether (30 ml in 3 portions), only the aqueous phase being retained. This aqueous solution was covered with butanol (5 ml) and adjusted to pH 2 by the addition of N hydrochloric acid. After separating the layers, the aqueous phase was extracted with two 2.5 ml portions of butanol, adjusting to pH 2 each time. The combined butanol solutions (which at this stage contained the free penicillanic acid) were washed with water (3 x 2 ml) and then shaken with water (10 ml) to which sufficient 3% sodium bicarbonate solution was added to bring the aqueous phase to pH 7. The butanol solution was further extracted with two 5 ml portions of water to each of which was added enough bicarbonate solution to produce an aqueous phase of pH 7. The combined aqueous solutions were washed with ether (20 ml) and then evaporated at low temperature and pressure to leave the crude sodium salt of phenoxymethyl penicillin which, after drying in a vacuum desiccator, was obtained as a slightly hygroscopic powder (591 mg).

References

Merck Index 6957
Kleeman and Engel p. 716
PDR pp. 673, 694, 1071, 1381, 1606, 1723, 1770, 1968
I.N. p. 760
REM p. 1199
Behrens, O.K., Jones, R.G., Soper, Q.F. and Corse, J.W.; US Patent 2,562,410; July 31, 1951; assigned to Eli Lilly and Company
Sheehan, J.C.; US Patent 3,159,617; December 1, 1964; assigned to Arthur D. Little, Inc.
Doyle, F.P., Nayler, J.H.C. and Rolinson, G.N.; US Patent 2,941,995; June 21, 1960; assigned to Beecham Research Laboratories Limited, England

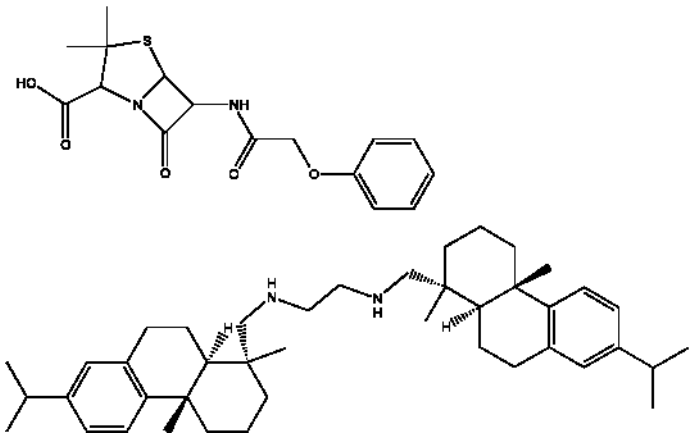
PENICILLIN V HYDRABAMINE

Therapeutic Function: Antibacterial

Chemical Name: N,N'-Bis(dehydroabietyl)ethylendiamine bis(phenoxymethylpenicillin)

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 6591-72-6

Trade Name	Manufacturer	Country	Year Introduced
Compocillin-V	Abbott	US	1954
Flavopen	G.P.	Australia	-

Raw Materials

Penicillin V
Dehydroabietylethylenediamine

Manufacturing Process

The crude dihydrochlorides of dehydroabietylethylenediamine bases (985 g) are extracted with a solution of about 3 liters of chloroform and 3 liters of water which is adjusted to about pH 10 and a second extraction is performed using a solution of about 2 liters of chloroform and the mixture readjusted to about pH 10 with 6 N NaOH if necessary. The chloroform layer containing the mixed free bases is separated from the aqueous layer containing NaCl and is washed with about 1/10 its volume of water to remove any NaCl in the wet chloroform solution. The chloroform solution containing a mixture of the free bases having a volume of about 5 liters is dried with anhydrous Na_2SO_4 and then filtered to obtain a clear solution containing about 0.85 kg of the mixed

free bases.

Approximately 1,000 g of phenoxymethylpenicillin acid (Penicillin V) is dissolved directly in about 5 liters of ethyl acetate to a concentration of 20% w/v. The resulting solution is filtered to remove any insoluble salts. The penicillin V acid (1,000 g) may also be obtained by extracting an aqueous solution of 1,110 g of the potassium salt of phenoxymethylpenicillin at a temperature of about 5°C, this solution being adjusted to pH 2-3 by the addition of 6 N sulfuric acid, twice with a total of 5 liters of ethyl acetate so that the final washed combined volume will have a concentration of about 20% w/v. The abovementioned ethyl acetate solution having a volume of about 5 liters is then dried with anhydrous Na_2SO_4 and filtered to obtain a clear ethyl acetate solution of phenoxymethylpenicillin acid.

In place of the hydrochlorides of the above described bases any other acid salt thereof can be used, including both inorganic and organic salts such as phosphoric, sulfuric, and acetic acids. Also, in place of the mentioned penicillin, any of the other common salts of penicillin can be used as a source of penicillin acid.

The chloroform solution of the free bases prepared in the above manner is then slowly added to the ethyl acetate solution of the penicillin V acid prepared in the above manner. A clear solution forms which rapidly becomes turbid as the bases react with the penicillin acid and crystallization commences. The reaction mixture is allowed to stand overnight in a cool room having a temperature of about 5°C after thoroughly agitating the mixture. Thereafter, the crystalline N,N'-bis-(dehydroabietyl)-ethylenediamine-dipenicillin V is filtered to separate therefrom the cooled mother liquor which contains the unprecipitated N,N'-bis-(dihydroabietyl)-ethylenediamine-dipenicillin salt and N,N'-bis-(tetrahydroabietyl)-ethylenediamine-dipenicillin salt and other impurities. The precipitate is washed thoroughly with about 4 liters of a mixture of chloroform and ethyl acetate (1:1) which is divided into three separate portions. After the final washing, the crystals are substantially colorless. The crystalline penicillin salt is thoroughly dried under vacuum at a temperature of about 50°C. The N,N'-bis-(dehydroabietyl)-ethylenediamine-dipenicillin V salt is obtained having purity as determined by solubility analysis in excess of about 90% and melts with decomposition at 163°C to 165°C on a Kofler hot stage.

References

Merck Index 6959
I.N. p. 494
De Rose, A.F.; US Patent 2,812,326; November 5, 1957; assigned to Abbott Laboratories

PENIMEPICYCLINE

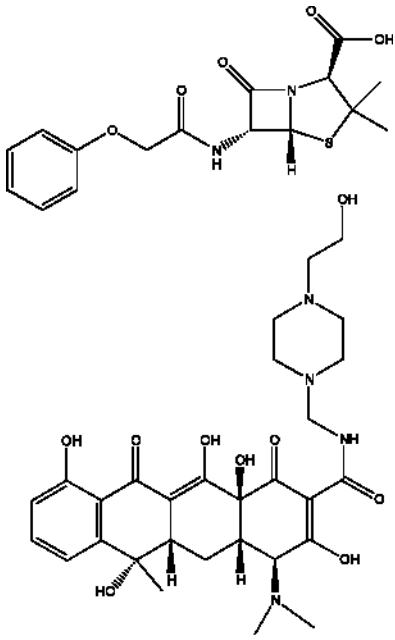
Therapeutic Function: Antibiotic

Chemical Name: 4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-

3,6,10,12,12a-pentahydroxy-N-((4-(2-hydroxyethyl)-1-piperazinyl) methyl)-6-methyl-1,11-dioxo-2-naphthacenecarboxamide salt with phenoxymethylpenicillin

Common Name: Mepenicycline; Penimepiciclina; Penimecycline

Structural Formula:



Chemical Abstracts Registry No.: 4599-60-4

Trade Name	Manufacturer	Country	Year Introduced
Penimepicyclina	Elenco Farmaci	-	-
Duamin	Luso-Farmaco	-	-
Tonsil	Gap	-	-
Ultrabiotic	Latino	-	-

Raw Materials

Tetracycline
Formaldehyde
1-(2-Hydroxyethyl)piperazine
Penicillin V

Manufacturing Process

N-(4^1-β-hydroxyethyl-1^1-piperazinylmethyl)tetracycline was obtained by reaction of tetracycline with 1-(2-hydroxyethyl)piperazine in the presence of formaldehyde.

8.6 g of N-(4^1-β-hydroxyethyl-1^1-piperazinylmethyl)tetracycline and 35.0 g

phenoxymethyl-penicilline, were dissolved in 300 ml methanol, with agitation. The solution was filtered on a Buchner filter, and the filtrate was taken up with 900 ml anhydrous ether with strong agitation, again filtered under pressure, and the filter cake was washed twice with 50 ml anhydrous ether. The product was; dried in vacuum. 84.0 g were obtained of a penimepicycline as yellowish white powder.

References

Gradnik B., Pedrazzoli A.; GB Patent No. 891,004; March 7, 1962; Assigned: Societe D'Etudes de Recherches et D'Applications Scientifiques et Medicales E.R.A.S.M.E., of 67 Avenue de Wagram, Paris 17, France, a French body corporate

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

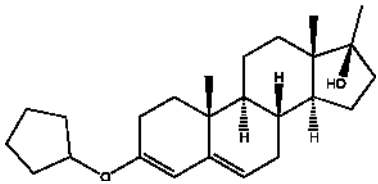
PENMESTEROL

Therapeutic Function: Androgen

Chemical Name: 3-(Cyclopentyloxy)-17-methyl-androsta-3,5-dien-17β-ol

Common Name: Penmesterol; Penmestrol

Structural Formula:



Chemical Abstracts Registry No.: 67-81-2

Trade Name	Manufacturer	Country	Year Introduced
Penmesterol	Shanghai Lansheng Corporation	-	-

Raw Materials

Androsteaedione
4-Toluenesulfonic acid
Methyl magnesium bromide
Orthoformate
Cyclopentanol

Manufacturing Process

A) 14 g of ethyl enolether of androstenedione, melting at 149°-151°C (obtained in a yield of 85% of the theoretical amount by treating androsteaedione with ethyl orthoformate), were added to a boiling solution of

37 ml of cyclopentanol and 0.450 g of p-toluenesulfonic acid in 2.5 L of benzene. The mixture was distilled over an approximately 40 minute period, so that the ethanol, which evolved during the exchange reaction, was evaporated off completely.

Then 0.5 ml of pyridine was added to the remaining solution and the mixture was concentrated under vacuum to dryness. The residue, taken up with a mixture of methanolmethylene chloride containing a few drops of pyridine, gave 13.8 g of cyclopentyl enolether of androstenedione melting at 181°-183°C. Yield about 85%.

B) The cyclopentyl enolether of androstenedione was converted to the corresponding cyclopentyl enolether of 17α-methyl testosterone as follows:

In a 3-necked flask fitted with a dropping funnel, reflux condenser, stirrer and nitrogen inlet tube, there was placed a solution of 25 g of methyl magnesium bromide in 150 ml of ether. With stirring and under an atmosphere of nitrogen, a solution of 4.1 g of androstenedione 3-cyclopentyl enolether in 80 ml of anhydrous benzene was added slowly. The reaction mixture was refluxed for 1 hour and allowed to stand overnight at room temperature. The mixture was then treated with an aqueous solution of 30% ammonium chloride, the organic layer separated off, washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue taken up with dilute methanol to yield 3.2 g of a white product. Crystallization from methanol containing few drops of pyridine give the pure 17α-methyl-testosterone 3-cyclopentyl enolether; MP: 148-152°C; $[\alpha]^D$ =-150° (dioxane).

References

Ercoli A.; US Patent No. 3,019,241; Jan. 30, 1962

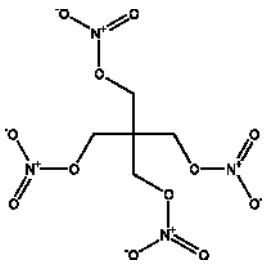
PENTAERYTHRITOL TETRANITRATE

Therapeutic Function: Coronary vasodilator

Chemical Name: 2,2-Bis[(nitroxy)methyl]-1,3-propanediol dinitrate

Common Name: PETN; Pentanitrolum

Structural Formula:



Chemical Abstracts Registry No.: 78-11-5

Trade Name	Manufacturer	Country	Year Introduced
Pentanitrine	Promedica	France	1948
Peritrate	Warner Lambert	US	1952
Pentritol	Armour	US	1955
Pentafin	Tutag	US	1956
Vasodiatol	Rowell	US	1958
Metranil	Meyer	US	1960
Pentryate	Fellows-Testagar	US	1960
Tranite D-Lay	Westerfield	US	1961
Peridex	Robins	US	1962
Antime	Century	US	1962
SK-Petin	SKF	US	1971
Perispan	U.S.V.	US	1971
Pentraspan	Glenwood	US	1980
Pentraspan	Vitarine	US	1983
Cardiacap	Consol. Chem	UK	-
Dilcoran	Godecke	W. Germany	-
Duotrate	Marion	US	-
Hasethrol	Shionogi	Japan	-
Hypothurol	Nissin	Japan	-
Lentrat	Medinova	Switz.	-
Neo-Corodil	Ethica	Canada	-
Neo-Corovas	Amfre-Grant	US	-
Nitrodex	Dexo	France	-
Nitropent	A.C.O.	Sweden	-
Pectolex	Shionogi	Japan	-
Penritol	Langley	Australia	-
Pentalong	Isis-Chemie	E. Germany	-
Peritrine	Norgine	Belgium	-
Perynitrate	Barlow Cote	Canada	-

Raw Materials

Pentaerythritol
Nitric acid

Manufacturing Process

Cooling water was turned on and 420 parts nitric acid of 94% strength was introduced into the nitrator. The amount of acid was such that the ratio of nitric acid to pentaerythritol was 4.29. The agitator was started and the agitator speed adjusted to 120 rpm. 92 parts pentaerythritol, which had been screened previously through a 14-mesh screen was used in each charge. About 45 parts pentaerythritol was added to the nitrator at such a rate that the temperature in the nitrator gradually rose to 110°F. This required about 12 minutes. Time was allowed for the temperature rise to cease before each succeeding increment of material was added.

After reaching 110°F the charge was maintained at about said temperature from 12 to 14 minutes during which time approximately 30 parts pentaerythritol was added to the nitrator. During the following 14 minutes, approximately, the remainder of the 92 parts pentaerythritol was added in like manner to the charge and the temperature gradually reduced. The pentaerythritol was introduced into the acid in finely divided and well-dispersed particles and not in large unitary quantities. The entire 92 parts of pentaerythritol tetranitrate was introduced in 35 to 40 minutes. The pentaerythritol thus obtained was separated from the spent acid by filtering or drowning in water. To recover the spent acid the charge was passed onto a nutsch and filtered. The crude product was washed with water, then with a weak water-soluble alkali solution, such as sodium carbonate for example, and subsequently with water in order to remove the acid.

After the removal of acid, the nitrate was dried by suction on the nutsch for about 15 minutes. The dried material was refined by means of acetone treatment or other suitable refining means. About 210 parts refined pentaerythritol tetranitrate per charge was obtained.

References

Merck Index 6977
DFU 4 (5) 351 (1979)
Kleeman and Engel p. 695
PDR pp. 1382, 1606
I.N. p. 741
REM p. 854
Acken, M.F. and Vyverberg, J.C. Jr.; US Patent 2,370,437; February 27,1945; assigned to E.I. du Pont de Nemours and Co.

PENTAGASTRIN

Therapeutic Function: Gastrosecretory hormone

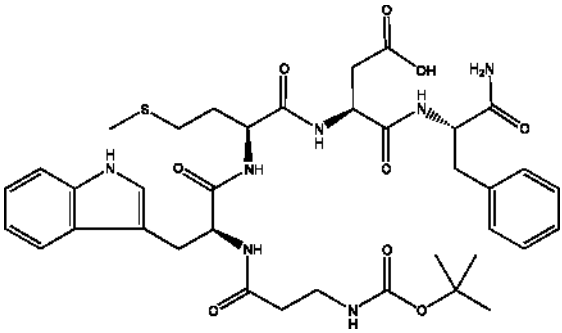
Chemical Name: N-Carboxy-β-alanyl-L-tryptophyl-L-methionyl-L-aspartylphenyl-L-alaninamide N-tert-butylester

Common Name: -

Chemical Abstracts Registry No.: 5534-95-2

Trade Name	Manufacturer	Country	Year Introduced
Peptavlon	I.C.I.	UK	1967
Gastrodiagnost	Merck	W. Germany	1970
Pentagastrin	I.C.I.	Japan	1973
Peptavlon	Ayerst	US	1976
Peptavlon	I.C.I.	France	1981
Acignost	VEB Berlin Chemie	E. Germany	-

Structural Formula:



Raw Materials

L-Tryptophanyl-L-methionyl-L-aspartyl-L-phenylalanine amide trifluoroacetate
N-t-Butyloxycarbonyl-β-alanine 2,4,5-trichlorophenyl ester

Manufacturing Process

A solution of 3.55 parts of L-tryptophanyl-L-methionyl-L-aspartyl-L-phenylalanine amide trifluoroacetate in 30 parts of dimethylformamide is cooled to 0°C, and 1.01 parts of triethylamine are added. The mixture is stirred while 1.84 parts of N-tert-butyloxycarbonyl-β-alanine 2,4,5-trichlorophenyl ester are added at 0°C. The reaction mixture is kept at 0°C for 48 hours and then at 20°-23°C for 24 hours. The mixture is added to a mixture of 100 parts of ice-water, 0.37 part of concentrated hydrochloric acid (SG 1.18), 1.2 parts of acetic acid and 20 parts of ethyl acetate. The mixture is stirred for 15 minutes at 0°-10°C and is then filtered. The solid residue is washed with water and then with ethyl acetate, and is dried at 40°-50°C under reduced pressure. There is thus obtained N-tert-butyloxycarbonyl-β-alanyl-L-tryptophanyl-L-methionyl-L-aspartyl-L-phenylalanine amide, MP 213°C with de composition.

References

Merck Index 6978
PDR p. 2004
DOT 3 (4) 150 (1967)
I.N. p. 742
REM p. 1273
Hardy, P.M., Kenner, G.W., Sheppard, R.C., MacLeod, J.K. and Morley, J.S.; British Patent 1,042,487; assigned to Imperial Chemical Industries Limited, England
Hardy, P.M., Kenner, G.W., Sheppard, R.C., Morley, J.S. and MacLeod, J.K.; US Patent 3,896,103; July 22, 1975; assigned to Imperial Chemical Industries Ltd.

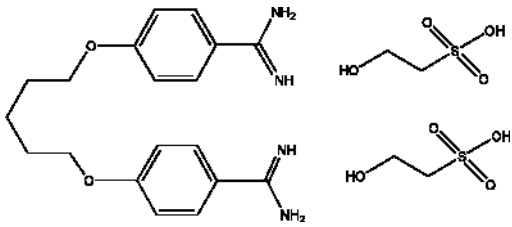
PENTAMIDINE ISETHIONATE

Therapeutic Function: Antiprotozoal

Chemical Name: Ethanesulfonic acid, 2-hydroxy-, compd. with 4,4'-(1,5-pentanediylbis(oxy))bis(benzenecarboximidamide) (2:1)

Common Name: Pentamidine isethionate

Structural Formula:



Chemical Abstracts Registry No.: 140-64-7; 100-33-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Nebupent	Fujisawa Healthcare Inc	USA	-
Nebupent	American Pharmaceutical Partners, Inc.	USA	-
Pentacarinat	Rhone - Poulenc Rorer	USA	-
Pentamidine isethionate	Fujisawa Healthcare Inc	USA	-
Pentam 300	Fujisawa Healthcare Inc	USA	-
Pneumopent	Fisons Corporation	-	-

Raw Materials

p,p'-Dicyano-1:5-diphenoxy-pentane
Ethyl alcoholic ammonia

Manufacturing Process

2.5 g of p,p'-dicyano-1,5-diphenoxy-pentane (obtained by the interaction of p-hydroxybenzonitrile and pentamethylene-dibromide in aqueous alkaline solution, melting point 114°C) are dissolved in 15 cc of nitrobenzene and 2.5 cc of absolute ethyl alcohol added. The solution is saturated with dry hydrochloric acid gas at 0°C and allowed to stand for 48 h. It is then diluted with dry ether and the precipitated 1,5-diphenoxypentane, 4,4'-di(ethoxycarbonimidoyl) dihydrochlorid is filtered and washed with ether.

4 g of 1,5-diphenoxypentane, 4,4'-di(ethoxycarbonimidoyl) dihydrochloride are mixed with 30 cc. of 6 % ethyl alcoholic ammonia and heated in a closed vessel at 50°C for 5 h. The alcohol is removed and the residual 1,5-diphenoxypentane, 4,4'-diamidino dihydrochloride is twice recrystallised from

dilute hydrochloric acid and finally purifled by dissolving in water and precipitating with acetone. Its melts at 236°C, dec.

Pentamidine isetionate salt may be produced by the reaction pentamidine base with isethionic acid.

References

Ewins A.J. et al.; US Patent No. 2,277,861; March 31, 1942; Assigned: May and Baker, Limited, London, England, a company of Great Britain and Northern Ireland

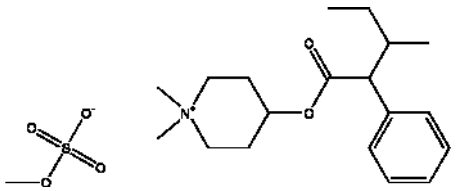
PENTAPIPERIDE METHOSULFATE

Therapeutic Function: Spasmolytic

Chemical Name: α-(1-Methylpropyl)benzeneacetic acid 1-methyl-4-piperidinyl ester methosulfate

Common Name: Pentapiperium methosulfate

Structural Formula:



Chemical Abstracts Registry No.: 7681-80-3; 7009-64-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Quilene	Warner Lambert	US	1969
Crylene	Auclair	France	1971
Crilin	Ayerst	Italy	1973
Perium	Rover	US	-
Togestal	Biosedra	France	-

Raw Materials

Phenylacetonitrile
Thionyl chloride
Sodium amide
1-Methyl-4-piperidinol
Sec-Butyl bromide
Dimethyl sulfate
Sodium hydroxide

Manufacturing Process

Phenylacetonitrile is alkylated with secondary butyl bromide and the resultant nitrile is hydrolyzed to 3-methyl-2-phenylvaleric acid. The acid is converted to the acid chloride with thionyl chloride and the acid chloride is in turn reacted with 1-methyl-4-piperidinol. Finally dimethyl sulfate is reacted with the ester.

References

Merck Index 6988
Kleeman and Engel p. 697
OCDS Vol. 2 p. 76 (1980)
DOT 6 (2) 61 (1970)
I.N. p. 743
Martin, H. and Habicht, E.; US Patent 2,987,517; June 6, 1961; assigned to Cilag Chemie Limited, Switzerland

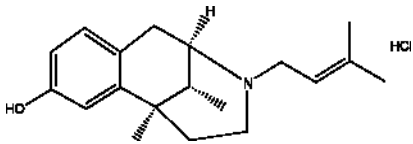
PENTAZOCINE HYDROCHLORIDE

Therapeutic Function: Analgesic

Chemical Name: 2,6-Methano-3-benzazocin-8-ol, 1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-, hydrochloride, (2R,6R,11R)-rel-

Common Name: Pentazocine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 64024-15-3; 68964-90-9; 359-83-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Pentazocine Hydrochloride	Mallinckrodt Inc.	-	-

Raw Materials

Methyliodide
Hydrogen
Hydrobromic acid
Hydrochloric acid
4-Methoxybenylmagnesium chloride
3,4-Dimethylpyridine
Palladium on charcoal

Manufacturing Process

A solution of 3,4-dimethylpyridine was added to a methyliodid. Then to the resulting solution containing 1,3,4-trimethylpyridinium iodide the 4-methoxybenzylmagnesium chloride was added. After reaction process the 1,3,4-trimethyl-2-(4-methoxy-benzyl)-pyridine was obtained.

To the solution of 1,3,4-trimethyl-2-(4-methoxy-benzyl)-pyridine was reduced by hydrogen over 10% palladium-on-charcoal, and when reduction was complete, the catalyst was removed by filtration and the filtrate taken to dryness. The residue was recrystallized to give 2-(4-methoxybenzyl)-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine.

To the 2-(4-methoxybenzyl)-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine the solution of hydrobromic acid was added and heated under reflux.The product obtained was recrystallized and yield N-methyl-1,2,3,4,5,6-hexahydro-6,11-dimethyl-8-hydroxy-2,6-methano-3-benzazocine (2'-hydroxy-2,5,9-trimethylbenzo-6-morphen), which then was demethylated by bromcyan (BrCN). As a result the racemic cis-1,2,3,4,5,6-hexahydro-6,11-dimethyl-8-hydroxy-2,6-methano-3-benzazocine was obtained (that is a. 2'-hydroxy-5,9-dimethyl-6,7-benzomorphen).

A mixture of 8.7 g racemic cis-1,2,3,4,5,6-hexahydro-6,11-dimethyl-8-hydroxy-2,6-methano-3-benzazocine, 6.0 g of 1-bromo-3-methyl-2-butene, 5.0 g of sodium bicarbonate, and 125 ml of N,N-dimethylformamide was stirred and refluxed for approximately 4.5 hours. The reaction mixture was then filtered, and the solid on the filter was washed with ethanol. The filtrate and the wash liquor were combined, concentrated under reduced pressure, and then extracted with chloroform. The chloroform extract was concentrated under reduced pressure to yield a syrup which weighed 15.8 g. This syrup was dissolved in 120 ml of diethyl ether and the resulting solution was filtered to remove approximately 0.5 g of a brown amorphous solid. The filtrate was extracted with a mixture of 5 ml of concentrated hydrochloric acid and 20 ml of water. To the extract there was added 5 ml of concentrated ammonium hydroxide solution and ice. A pale tan syrup separated from solution and after stirring, this syrup solidified. The resulting pale tan solid was collected and dried; it weighed 10.6 g. After two recrystallizations from a mixture of methyl alcohol and water, with charcoaling, the 1,2,3,4,5,6-hexahydro-3-(3-methyl-2-butenyl)-6,11-dimethyl-8-hydroxy-2,6-methano-3-benzazocine weighed 8.2 g and melted at 145°-147°C.

The1,2,3,4,5,6-hexahydro-3-(3-methyl-2-butenyl)-6,11-dimethyl-8-hydroxy-2,6-methano-3-benzazocinewas soluble in a mixture of 0.35 ml of 2 N hydrochloric acid and 0.15 ml of water to the extent of 10%, the pH of the 1% solution being 2.80; and when the pH of the 1% solution was gradually raised by addition of 10 N sodium hydroxide solution, a precipitate formed at pH 5.4. The 1,2,3,4,5,6-hexahydro-3-(3-methyl-2-butenyl)-6,11-dimethyl-8-hydroxy-2,6-methano-3-benzazocine hydrochloride melted at 245°-247°C, dec.

References

Albertson N. F.; US Patent No. 3,936,462; Feb. 3, 1976; Assigned: Sterling Drug Inc., New York, N.Y.

Archer S.; US Patent No. 4,105,659; Aug. 8, 1978; Assigned: Sterling Drug Inc., New York, N.Y.

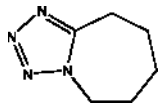
PENTETRAZOL

Therapeutic Function: Analeptic, Central stimulant

Chemical Name: 5H-Tetrazolo[1,5-a]azepine, 6,7,8,9-tetrahydro-

Common Name: Corazol; Leptazol; Pentamethylentetrazol; Pentetrazol; Pentylenetetrazol

Structural Formula:



Chemical Abstracts Registry No.: 54-95-5

Trade Name	Manufacturer	Country	Year Introduced
Pentylenetetrazole	Spectrum Chemicals and Laboratory Products, Inc.	-	-
Angioton	Leo	-	-
Cardiamine	Chropi	-	-
Cardional	Oliveira	-	-
Cardiotonico	C.F.	-	-
Cardiotonicum	Blomberg	-	-
Inocor	Bengen	-	-
Analeptin	Biotica	-	-

Raw Materials

Cyclohexanone
Nitric acid
Sulfuric acid

Manufacturing Process

A solution of 9.8 g cyclohexanone and 8.6 g HNO_3 in about 250 ml benzene were slowly added dropwise to 20 ml concentrate sulfuric acid in 100 ml benzene by ice cooling and stirring. After ending of a generation of N_2 (0.1 moles) to a corresponding quantity of cyclohexane (0.1 moles). Acid layer was diluted with ice, and made neutral with strong alkaline to give a reaction product as oil. Then it was exrtacted with chloroform, all solvents were distilled and the residue was diluted with water. The desired 6,7,8,9-tetrahydro-5H-tetrazoloazepine dropped. Yield was 7.5 g after recrystallization from ester or distillation. M.P: 65°C.

References

Firma Knoll and Co. in Ludwigshafen a. Rh. und Dr. Karl Fridrich Shmidt in Heidelberg; D.R. Patent No. 427,858; July 20, 1923

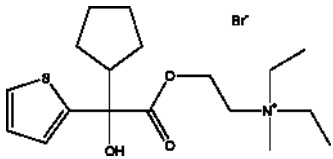
PENTHIENATE BROMIDE

Therapeutic Function: Anticholinergic

Chemical Name: 2-[(Cyclopentylhydroxy-2-thienylacetyl)oxy]-N,N-diethyl-N-methylethanaminium bromide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 60-44-6

Trade Name	Manufacturer	Country	Year Introduced
Monodral	Winthrop	US	1954
Monodral	Kanebo, Ltd.	Japan	1970

Raw Materials

2-Diethylaminoethyl chloride
Cyclopentyl-(α-thienyl)hydroxyacetic acid
Methyl bromide

Manufacturing Process

An aqueous solution of 13.8 g of 2-diethylaminoethyl chloride hydrochloride was neutralized with sodium hydroxide, and the free 2-diethylaminoethyl chloride was extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate, filtered, and the filtrate was added to a solution of 13.6 g of cyclopentyl-(α-thienyl)hydroxyacetic acid in 100 ml of isopropyl alcohol. The mixture was then distilled through a 25-cm Vigreaux-type column until the temperature of the vapors reached 80°C. The residual solution was refluxed overnight and then transferred to a beaker along with 350 ml of isopropyl alcohol. The crystalline hydrochloride had meanwhile separated out, and this was filtered, washed with isopropyl alcohol, ether and then dried, giving 23 g, melting point 172°C to 173.5°C. Recrystallization from 400 ml of isopropyl alcohol gave 20.3 g of 2-diethylaminoethyl

cyclopentyl-(α-thienyl)hydroxyacetate hydrochloride, melting at 174°C to 175°C; deep yellow-orange color with concentrated sulfuric acid.

The hydrochloride may then be converted to the methobromide by reaction with methyl bromide.

References

Merck Index 6996
Kleeman and Engel p. 699
I.N. p. 744
Blicke, F.F.; US Patent 2,541,634; February 13, 1951; assigned to Regents of the University of Michigan

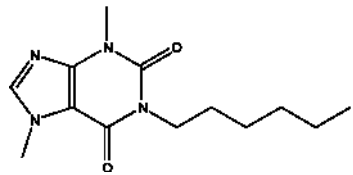
PENTIFYLLINE

Therapeutic Function: Vasodilator, Diuretic

Chemical Name: 1H-Purine-2,6-dione, 3,7-dihydro-1-hexyl-3,7-dimethyl-

Common Name: Hexyltheobromine; Pentifylline

Structural Formula:



Chemical Abstracts Registry No.: 1028-33-7

Trade Name	Manufacturer	Country	Year Introduced
Pentifylline	Shanghai Lansheng Corporation	-	-
Cosaldon retard mono	Aventis	-	-
1-Hexyltheobromine	Fluorochem	-	-
1-Hexyltheobromine	Trans World Chemicals, Inc.	-	-

Raw Materials

Theobromine
Theobromine sodium
n-Hexyl chloride or n-hexyl bromide

Manufacturing Process

The mixture 25 g theobromine, 38 ml 4 N sodium hydroxide, 60 ml isopropanol, and 17 g n-hexyl chloride were heated 24 hours to 100°C in autoclave. The solvent was removed and the residual alkaline solution was extracted with chloroform, water layer was acidified. Yield of 1-hexyl-3,7-dimethylxanthine was 88%; MP: 82°-83°C. The product may be prepared from theobromine sodium. 20.2 g theobromine sodium, 20 n-hexyl bromide and 100 ml toluene were ground 10 hours at 100°C in a ball mill. After above written treatment 22.3 g (84.5%) 1-hexyltheobromine was prepared; MP: 84°C.

References

Eidebenz E., von Schuh H.G.; D.B. Patent No. 860,217; Oct. 28, 1950; Chemishe Werke Albert, Wiesbaden-Biebrich.

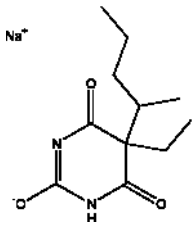
PENTOBARBITAL SODIUM

Therapeutic Function: Hypnotic, Sedative

Chemical Name: 5-Ethyl-5-(1-methylbutyl)-2,4,6-(1H,3H,5H)-pyrimidinetrione monosodium salt

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 57-33-0; 76-74-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Nembutal	Abbott	US	1941
Butylone	Hartz	Canada	-
Hypnol	Stickley	Canada	-
Mintal	Tanabe	Japan	-
Nebralin	Dorsey	US	-
Neodrom	Minden	W. Germany	-
Novopentobarb	Novopharm	Canada	-
Penbon	Adams	Australia	-

Trade Name	Manufacturer	Country	Year Introduced
Pentanca	Anca	Canada	-
Pentogen	Paul Maney	Canada	-
Pentone	Faulding	Australia	-
Prodormol	Teva	Israel	-
Repocal	Desitin	W. Germany	-
Sombutol	Farmos	Finland	-
Somnotol	M.T.C.	Canada	-
Sopental	Continental Ethicals	S. Africa	-

Raw Materials

Sodium
di-n-Butyl ethyl 1-methyl-n-butylmalonate
Butanol
Urea

Manufacturing Process

Sodium (9.6 parts) was dissolved in butanol (192 parts) and di-n-butyl ethyl 1-methyl-n-butylmalonate (62.8 parts) and urea (14.4 parts) were added to the warm solution with agitation. The mixture was then heated to reflux temperature in three quarters of an hour and maintained for 2 hours. The reaction mass was kept, water (150 parts) added, the aqueous portion separated, and the butanol layer extracted with water (3 x 50 parts). The combined aqueous extracts were then given 3 small extractions with benzene, the aqueous liquors separated, charcoaled, filtered and precipitated with concentrated hydrochloric acid (acid to congopaper). The solid was collected, washed with water, dissolved in N-sodium hydroxide and reprecipitated with carbon dioxide. On recrystallization, from aqueous alcohol, the pentobarbitone was obtained.

References

Merck Index 6998
Kleeman and Engel p. 700
PDR pp. 531, 872, 1989
OCDS Vol. 1 p. 268 (1977)
I.N. p. 745
REM p. 1067
The Geigy Co. Ltd.; British Patent 650,354; February 21, 1951

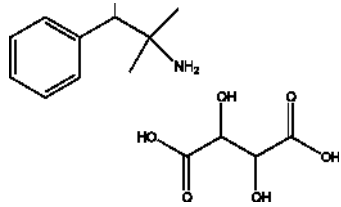
PENTOREX TARTRATE

Therapeutic Function: Anorexic

Chemical Name: Benzeneethanamine, α,α,β-trimethyl-, tartrate (1:1)

Common Name: Pentorex tartrate; Phenpentermine tartrate

Structural Formula:



Chemical Abstracts Registry No.: 434-43-5 (Base); 22876-60-4

Trade Name	Manufacturer	Country	Year Introduced
Liprodene	Anphar-Rolland	-	-
Modatrop	Nordmark	-	-

Raw Materials

2-Phenylbutanone-3
Sodium cyanide
Sulfuric acid
Methyl magnesium bromide
Acetic acid

Manufacturing Process

To a solution of 105.6 g of 2-phenylbutanone-3 in 110 ml ether was added dropwise a solution of methylmagnesium bromide (prepared from 19.4 g magnesium and 94.7 g methyl bromide in 400 ml of ether) for 60-90 min. Then the mixture was refluxed for 1 hour. After cooling to the mixture was added diluted sulfuric acid and then extracted with ether. Organic layer was dries with sodium sulfate. After evaporation of ether the 2-phenyl-3-methylbutanol was distilled, B.P. 116-118°C/20 mm, yield 105 g, n_d^{22} 1.5152.

To 25.5 g of NaCN at 10-20°C ware added dropwise under stirring 64 ml of glacial acetic acid and ten at 20°C a mixture of 70 ml concentrated sulfuric acid and 64 ml of glacial acetic acid. To the prepared mixture at 20-25°C was added dropwise 82 g of 2-phenyl-3-methylbutanol. The mixture was stirred at 45-50°C for 10-20 min and then at 75°C for 30 min. To the reaction mixture was added 750 ml of water. The acids was neutralized with sodium carbonate. Product was extracted with ether and distilled. Boiling point of (dimethylbenzylcarbinyl)formamide 173-176°C/0 mm, yield 63 g.

52.3 g of (dimethylbenzylcarbinyl)formamide, 245 ml concentrated hydrochloric acid and 196 ml of water were refluxed for 6 hours. The unreacted compounds was extracted with ether. The residuum was stirred with sodium hydroxide and extracted with ether. By distillation was obtained 48.2 g of 2-amino-2-methyl-3-phenylbutane; B.P. 109-111°C/20 mm.

Hydrochloride of 2-amino-2-methyl-3-phenylbutane have melting point 164-166°C.

In practice it is usually used as tartrate salt.

References

Brevet Special de Medicament 931,804, April 17, 1963; Assigned to Nordmak Werke Gesellschaft mit Beschraenkter Haftung, residant en Allemagne

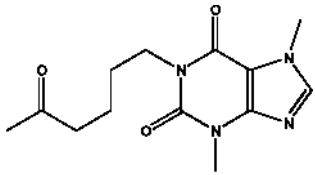
PENTOXIFYLLINE

Therapeutic Function: Vasodilator

Chemical Name: 3,7-Dihydro-3,7-dimethyl-1-(5-oxohexyl)-1H-purine-2,6-dione

Common Name: Oxpentifylline; Vazofirin

Structural Formula:



Chemical Abstracts Registry No.: 6493-05-6

Trade Name	Manufacturer	Country	Year Introduced
Trental	Albert Roussel	W. Germany	1972
Torental	Hoechst	France	1974
Trental	Hoechn	UK	1975
Trental	Albert Pharma	Italy	1976
Trental	Hoechst	Japan	1977
Agapurin	Spofa	Czechoslovakia	-
Techlon	Sawai	Japan	-

Raw Materials

1-Bromo-5-hexanone
Theobromine sodium

Manufacturing Process

A solution of 35.4 g of 1-bromohexanone-5 in 200 ml of ethanol was gradually mixed at the reflux temperature with vigorous stirring with 39.7 g of theobromine-sodium in 100 ml of water. After 3 hours reflux the unreacted theobromine was filtered off with suction, the filtrate was evaporated to dryness, the residue was dissolved in water and the solution was extracted with chloroform. The chloroform was distilled off and 1-(5'-oxohexyl)-3,7-

dimethylxanthine was obtained as residue; after recrystallization from isopropanol, it melted at 102°C to 103°C (about 25% yield, calculated on the reacted theobromine).

References

Merck Index 7002
Kleeman and Engel p. 701
PDR p. 947
OCDS Vol. 2 p. 466 (1980)
I.N. p. 746
Mohler, W., Reiser, M. and Popendiker, K.; US Patent 3,737,433; June 5, 1973; assigned to Chemische Werke Albert A.G. (W. Germany)

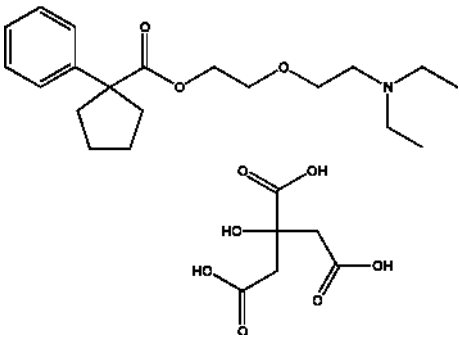
PENTOXYVERINE CITRATE

Therapeutic Function: Antitussive

Chemical Name: Cyclopentanecarboxylic acid, 1-phenyl-, 2-(2-(diethylamino)ethoxy)ethyl ester, citrate (1:1)

Common Name: Carbapentane citrate; Carbetopentane citrate; Pentoxiverini citras; Pentoxyverine citrate

Structural Formula:



Chemical Abstracts Registry No.: 23142-01-0; 77-23-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Asthma	Nichiiko	-	-
Carbex	Etna	-	-

Raw Materials

Sodium amide	Phenylacetonitrile
Sulfuric acid	1,4-Dibromobutane

Thionyl chloride 2-(2-Diethylaminoethoxy)ethanol

Manufacturing Process

1-Phenylcyclopentane carbonitrile was obtained by treatment of phenylacetonitrile with sodium amide and 1,4-dibrombutane.

1-Phenyl-1-cyclopentane carboxylic acid was produced in the result of reaction of 1-phenylcyclopentane carbonitrile with sulfuric acid.

1-Phenyl-1-cyclopentanecarbonyl chloride was obtained by treatment of 1-phenyl-1-cyclopentane carboxylic acid with thionyl chloride.

A mixture of 0.5 mol of 1-phenyl-1-cyclopentanecarbonyl chloride and of 0.5 mol of 2-(2-diethylaminoethoxy)ethanol (herein-after referred to as the amino alcohol) in 300 ml of toluene is heated under reflux for 20 h. The mixture is thereafter made alkaline by means of an aqueous solution of caustic soda and decanted; the toluenic layer is washed with water and concentrated in vacuo. The residue is distilled under high vacuum. After two fractional distillations, the 2-(2-diethylaminoethoxy)ethyl 1-phenylcyclopentane-carboxylate is obtained, in 85% yield. Boiling point 164°C/0.1 mm. Hg.

References

Morren H.; GB Patent No. 753,779; August 1, 1956
Kleemann A., Engel J.; Pharmazeutische Wirkstoffe, GeorgThieme Verlag Stuttgart. New York, 1982

PEPLOMYCIN SULFATE

Therapeutic Function: Antineoplastic

Chemical Name: 3-[(S)-1'-Phenylethylamino]propylaminobleomycin sulfate

Common Name: -

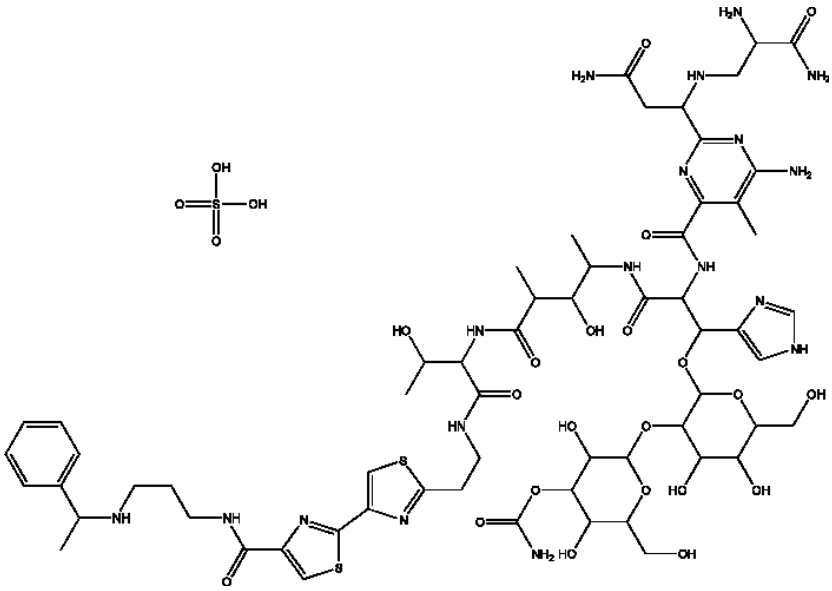
Chemical Abstracts Registry No.: 68247-85-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Pepleo	Nippon Kayaku, Co.	Japan	1981

Raw Materials

Bleomycinic acid
N-[(S)-1'-Phenylethyl]-1,3-diaminopropane
Sulfuric acid

Structural Formula:



Manufacturing Process

In 400 ml of dimethylformamide was dissolved 15.0 g of bleomycinic acid (copper-containing form). To the solution kept at 0°C by cooling were added 1.1 ml of N-methylmorpholine and 10.3 g of 6-chloro-1-p-chlorobenzenesulfonyloxybenzotriazole (CCBT) as an activating compound. The mixture was stirred for 5 minutes at 0°C, then admixed with 5.3 g of N-[(S)-1'-phenylethyl]-1,3-diaminopropane and further stirred for 1 hour.

After termination of the reaction by adding 200 ml of a 25% aqueous acetic acid solution, the reaction mixture was mixed with 5 liters of cold acetone to precipitate the reaction product. The precipitate was collected by filtration, washed with acetone, and dissolved in 500 ml of distilled water. The resulting aqueous solution was immediately adjusted to pH 6.0 and poured into a column containing 2 liters of CM-Sephadex C-25 (NH_4^+type) packed in 0.05 M aqueous ammonium chloride solution to adsorb bleomycins.

Using aqueous ammonium chloride solution, elution was performed by passing through the column 20 liters of eluent in which the concentration of ammonium chloride was continually increased from 0.05 to 1.0 M. The unreacted bleomycinic acid was found in the effluent at the ammonium chloride concentration of about 0.05 M and NK631 at the ammonium chloride concentration of about 0.45 M. Both fractions, which showed UV absorption at 292 nm;, were separately collected.

The NK631-containing fraction was poured into a resin column containing 2.6 liters of Amberlite XAD-2. The column was then washed thoroughly with water and eluted with 0.01 N hydrochloric acid in methanol-water (4:1 v/v). A total

of 2.5 liters of the blue fraction, which showed UV absorption at 292 mμ, was collected. After evaporating off the methanol from the eluent fraction, the concentrate was adjusted to pH 6.0 with Dowex 44 (OH^- type, an anion-exchange resin composed of a copolymer of epichlorohydrin and ammonia) and was freeze-dried to obtain 16.1 g (92% yield) of NK631 dihydrochloride (copper-containing form) in the form of blue amorphous powder.

By similar treatment, 280 mg of the unreacted bleomycinic acid (copper-containing form) were recovered.

In 200 ml of distilled water was dissolved 10.0 g of the NK631 dihydrochloride (copper-containing form). The solution was poured into a column containing 600 ml of Amberlite XAD-2 packed in distilled water. The column was washed successively with 2 liters of an aqueous solution containing 5% of EDTA-Na_2, 2.5 liters of a 5% aqueous sodium sulfate solution, and 630 ml of distilled water.

The column was then eluted with 0.0025 N sulfuric acid in methanol-water mixture (1:1 v/v). A total of 900 ml of fractions containing a substance which showed UV absorption at 290 mμ was collected. After removal of methanol by distillation, the residual liquid was adjusted to pH 6.0 with Dowex 44 (OH^- type) and freeze-dried to obtain 9.3 g (95% yield) of NK631 monosulfate (copper-free form) in the form of pale yellowish-white amorphous powder.

References

Merck Index 7011
DFU 6 (2) 101 (1981)
DOT 17 (8) 331 (7981)
Takita, T., Fujii, A., Fukuoka, T., Muraoka, Y., Yoshioka, O. and Umezawa, H.; US Patent 4,195,018; March 25, 1980; assigned to Nippon Kayaku K.K.
Umezawa, H., Maeda, K., Takita, T., Nakayama, Y., Fujii, A. and Shimada, N.; US Patent 3,846,400; November 5, 1974; assigned to Zaidan Hojin Biseibutsu Kagaku Kenkyu Kai.

PERGOLIDE MESYLATE

Therapeutic Function: Dopamine agonist

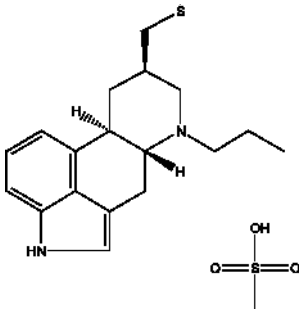
Chemical Name: Ergoline, 8-β-((methylthio)methyl)-6-propyl-, methanesulfonate (1:1)

Common Name: Pergolide mesilate

Chemical Abstracts Registry No.: 66104-23-2; 66104-22-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Celance	Eli Lilly	-	-
Permax	Eli Lilly	-	-
Nopar	Lilly	-	-

Structural Formula:



Raw Materials

9,10-Dihydrolysergol
Propionic anhydride
Dimethyl disulfide
Sodium hydroxide
Sodium iodide
Lithium aluminum hydride
Tri-n-butylphosphine

Manufacturing Process

Dimethyl disulfide (73.6 ml, 0.79 mol) and tri-n-butylphosphine (79.6 ml, 0.32 mol) were added to a solution of 9,10-dihydrolysergol in (8.1 g, 0.032 mol) in the 150 ml of anhydrous DMF and were stirred at room temperature for 6 hours under a nitrogen atmosphere. Dimethyl disulfide of the reaction mixture was removed under vacuo. A solution of the residue in ethyl acetate was extracted with 3.7% HCl (aq.). The aqueous layer was basified with ammonium hydroxide to a pH of 10 and then extracted with ethyl acetate. Removal of ethyl acetate followed by a silica gel column purification eluting with 10% MeOH/CH_2Cl_2 gave5.5.g of D-6-methyl-8β-(methylthiomethyl)ergoline (60%).

A solution of D-6-methyl-8β-(methylthiomethyl)ergoline (0.4 g, 0.0014 mol) and NaI (0.63 g, 0.0042 mol) in 10 ml of propionic anhydride was refluxed for 40 hours. The reaction mixture was guenched with a 10% Na_2CO_3 solution and extracted by ethyl acetate. The combined organic layers were washed with a saturated brine solution, dried with magnesium sulfate and concentrated to produce oil. The oil was purified by silica gel column, eluting with 10% MeOH/CH_2Cl_2 to give 0.33 g of D-1,6-dipropionyl-8β-(methylthiomethyl)ergoline.

$LiAlH_4$ (0.6 g, 0.0156 mol) was slowly added to a solution of D-1,6-dipropionyl-8β-(methylthiomethyl)ergoline in the 20 ml anhydrous THF at 0°C under nitrogene atmosphere. The mixture was stirred at 0°C for 30 min and then at room temperature for 4 hours. The reaction was cooled to 0°C and 0.6 ml of water was slowly added. The mixture was stirred at 0°C for 10 min and 1.8 ml of 15% NaOH (aq.) and 2.5 ml of water were added respectively. The mixture was stirred for 30 min at room temperature and then filtered. Excess of the solvent was removed under reduced pressure to give 150 mg of 8β-((methylthio)methyl)-6-propyl-ergoline or pergolide (yield: 68%). Ergoline,

8-((methylthio)methyl)-6-propyl-, monomethanesulfonate, (8β)- may be prepared by mixing of components in solution.

References

Wu E.S.C., Wu M.; US Patent No. 6,388,079, May 14; Assigned to Scinopharm Singapore Pte Ltd., Singapore (SG)

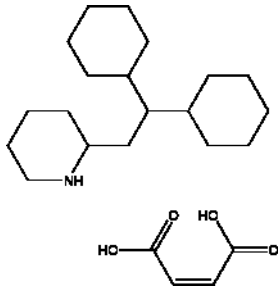
PERHEXILINE MALEATE

Therapeutic Function: Coronary vasodilator

Chemical Name: 2-(2,2-Dicyclohexylethyl)piperidine maleate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 6724-53-4; 6621-47-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Pexid	Merrell-Tourade	France	1973
Pexid	Merrell	W. Germany	1974
Pexid	Merrell	Italy	1974
Pexid	Merrell	UK	1975
Corzepin	Prodes	Spain	-
Daprin	Gerardo Ramon	Argentina	-

Raw Materials

Ethyl formate
α-Picoline
Sodium hydroxide
Maleic acid
Cyclohexylmagnesium bromide
Hydrogen chloride
Hydrogen

Manufacturing Process

1,1-Dicyclohexyl-2-(2'-pyridyl)ethanol hydrochloride (5 grams) was dehydrated by heating with 25 ml of concentrated hydrochloric acid at steam bath temperature for 10 minutes. 70 ml of water were added to the reaction mixture to give the crystalline hydrochloride salt. The product, 1,1-dicyclohexyl-2-(2'-pyridyl)ethylene hydrochloride, was recrystallized from methanol-ethyl acetate to yield a white solid melting at 150°-151.5°C.

1,1-Dicyclohexyl-2-(2'-pyridyl)ethylene hydrochloride (15 grams) in 150 ml of ethanol was hydrogenated in the presence of platinum oxide at about 60 pounds per square inch of hydrogen pressure. The product, 1,1-dicyclohexyl-2-(2'-piperidyl)ethane hydrochloride, crystallized from a mixture of methanol and methyl ethyl ketone as a white solid melting at 243° to 245.5°C.

The hydrochloride salt was neutralized with 10% sodium hydroxide solution and the free base so produced was dissolved in ether. The ether solution was dried over anhydrous magnesium sulfate. Addition of an excess of maleic acid in methanol to the solution yielded the acid maleate salt which melted at 188.5°-191°C.

The starting material was obtained by reacting ethyl formate with cyclohexylmagnesium bromide to give dicyclohexylcarbinol. That is oxidized to dicyclohexylketone and then reacted with α-picoline.

References

Merck Index 7026
Kleeman and Engel p. 703
DOT 10 (8) 299 (1974)
I.N. p. 747
REM p. 854
Richardson-Merrell Inc.; British Patent 1,025,578; April 14, 1966
Horgan, S.W., Palopoli, F.P. and Schwoegler, E.J.; US Patent 4,069,222; January 17, 1978; assigned to Richardson-Merrell Inc.

PERICIAZINE

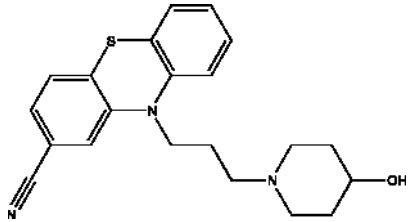
Therapeutic Function: Neuroleptic

Chemical Name: 10H-Phenothiazine-2-carbonitrile, 10-(3-(4-hydroxypiperidino)propyl)-

Common Name: Periciazine; Pericyazine

Chemical Abstracts Registry No.: 2622-26-6

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Aolept	Bayer Vital	-	-
Neuleptil	Rhone-Poulenc Rorer	-	-
Neuleptil	Vitoria	-	-
Neuleptil	Gerot	-	-
Neuleptil	Alkaloid	-	-
Nemactil	Rhone-Poulenc Rorer	-	-
Neulactil	Rhone-Poulenc Rorer	-	-
Neuperil	Orion	-	-
Neuleptil	Aventis Pharma B.V.	-	-

Raw Materials

Hydrochloric acid
Sodium hydroxide
4-Hydroxypiperidine
2-Cyano-10-(3-methanesulfonyloxypropyl) phenthiazine

Manufacturing Process

2-Cyano-10-(3-methanesulfonyloxypropyl)phenthiazine and 4-hydroxypiperidine in toluene were heated under reflux with stirring. The reaction mixture was allowed to cool and water was added. The resulting toluene solution layer was decanted and washed twice with water. The toluene solution was then stirred with 5% hydrochloric acid. The hydrochloride of the desired phenthiazine base precipitated in gummy condition in the aqueous layer. This was decanted and treated with sodium hydroxide (density 1.33). It was then extracted three times with ethyl acetate. The extracts were dried over sodium sulfate, filtered and concentrated in vacuum. A resinous product was obtained. This product was dissolved in a mixture of benzene and cyclohexane and chromatographed on a column containing alumina. The chromatographed product was eluted successively with mixtures of benzene and cyclohexane and then with benzene and finally with a mixture of benzene and ethyl acetate. The eluates were evaporated to yield a crude product. This product was recrystallised from aqueous ethanol (40% water) and yielded 2-cyano-10-[3-(4-hydroxy-1-piperidyl)propyl]phenthiazine as white crystals.

References

Jacob R.M., Robert J.G.; US Patent No. 3,150,129; Sept. 22, 1964; Assigned: Rhone-Poulenc S.A., Paris, France, a corporation of France

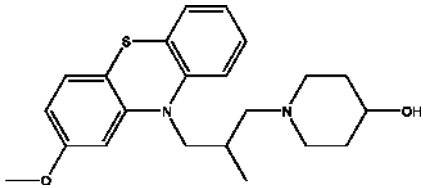
PERIMETHAZINE

Therapeutic Function: Tranquilizer

Chemical Name: 1-[3-(2-Methoxyphenothiazin-10-yl)-2-methylpropyl]-4-piperidinol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 13093-88-4

Trade Name	Manufacturer	Country	Year Introduced
Leptryl	Roger Bellon	France	1970

Raw Materials

3-Methoxy-10-(3-chloro-2-methylpropyl)phenthiazine
4-Hydroxypiperidine

Manufacturing Process

A solution of 3-methoxy-10-(3-chloro-2-methylpropyl)phenthiazine (9.65 grams) and 4-hydroxypiperidine (6.1 grams) in xylene (10 cc) is heated under reflux for 5 hours. After cooling the mixture is diluted with ether (60 cc) and the basic compounds are extracted by agitation with water (30 cc) and 4 N hydrochloric acid (20 cc). The aqueous acid phase is made alkaline with 4 N sodium hydroxide solution (23 cc) and the liberated base is extracted with ether. The ethereal solution is washed with water (60 cc) and dried over sodium sulfate. Finally the solvent is distilled off on a water-bath.

The solid residue obtained is recrystallized from a mixture (15:85) of benzene and cyclohexane and there is obtained 3-rnethoxy-10-[2-methyl-3-(4-hydroxy-1-piperidyl)-propyl]-phenthiazine (5.7 grams) as a white crystalline powder, MP 137°-138°C.

References

Merck Index 7030
Kleeman and Engel p. 704
DOT 6 (4) 190 (1970)

I.N. p. 748
Jacob, R.M. and Robert, J.G.; US Patent 3,075,976; January 29, 1963; assigned to Societe des Usines Chimiques Rhone-Poulenc, France

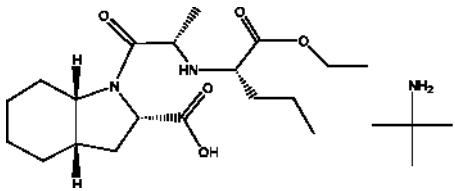
PERINDOPRIL ERBUMINE

Therapeutic Function: Antihypertensive

Chemical Name: 1H-Indole-2-carboxylic acid, octahydro, 1-{2-[(1-ethoxycarbonyl)butyl)amino]-1-oxopropyl}-, (2S-(1(R*(R*)),2-α,3a-β,7a-β))-, compd. with 2-methyl-2-propanamine (1:1)

Common Name: Perindopril erbumine

Structural Formula:



Chemical Abstracts Registry No.: 107133-36-8; 82834-16-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Aceon	Solvay Pharmaceuticals Inc.	USA	-
Acertil	Les Laboratoires Servier	France	-
Coverex	Egis Pharmaceuticals Ltd.	Hungary	-
Coversum	Les Laboratoires Servier	France	-
Coversum	Itherapia	Germany	-
Coversyl	Servier	France	-
Coversyl	Serdia Pharmaceuticals (India) Ltd.	India	-
Coversyl	Paranova Oy	Finland	-
Perigard	Glenmark Pharmaceuticals Ltd.	India	-
Perindopril Erbumine	Les Laboratoires Servier	France	-
Prestarium	Les Laboratoires Servier	France	-
Prexanil	Servier Pharma	France	-

Raw Materials

2-Carboxyindole
Sodium hydroxide
Rhodium
Sulfuric acid
(+)-α-Methylbenzylamine
Pyruvic acid

Palladium on charcoal	Triethylamine
4-Toluenesulfonic acid	Tin
L-Norvaline	Thionyl chloride
1-Hydroxybenzotriazole	Dicyclohexylcarbodiimide
Hydrogen	

Manufacturing Process

Heat 5 kg of 2-carboxyindole suspended in ethanol in the presence of sulfuric acid to boiling for 8 hours. Evaporate off take up the crystalline mass with hexane. After filtering off and drying, 5.3 kg of 2-ethoxycarbonylindole crystals are obtained. Melting point: 123°-125°C.

Suspend, in a reactor, 10 kg of 2-ethoxycarbonylindoline obtained previously in 110 liters of hydrochloric ethanol. Next, add 20 kg of granulated tin. Keep stirring for approximately 2 days at room temperature. Evaporate off the ethanol, take up the residue with water and add 110 liters of toluene. Stir for approximately 20 min. Alkalify with aqueous ammonia. Separate off the aqueous phase and extract once again with 150 liters of toluene. Combine the toluene phases and wash them with water. Separate off the toluene phases, filter. Remove the water by distilling the water-toluene azeotrope. Cool and pass through a stream of anhydrous HCl gas. Cool. Evaporate down and wash with pure toluene. Weight obtained of (R,S)-2-ethoxycarbonylindoline 10.11 kg. Yield: 84%.

2.15 kg of (R,S)-2-ethoxycarbonylindoline dissolved in ethanol are saponified with 12.5 liters of sodium hydroxide with stirring for 24 hours. After washing the alkaline solution, neutralize with concentrated hydrochloric acid. After filtering off, washing and drying, 1.57 kg of white crystals of the (R,S)-2-carboxyindoline are obtained. Yield: 86%. Melting point: 188°-189°C.

6.05 kg of (R,S)-2-carboxyindoline are added to a solution of 4.49 kg of (+)-α-methylbenzylamine in anhydrous ethanol. A white precipitated product is obtained which, after filtering off, is digested in refluxing isopropanol. After cooling, the solid is filtered off and washed with a little isopropanol. 1 kg of the obtained salt was dissolved in 5 liters of water and neutralizing with an aqueous hydrochloric acid solution. The precipitate is filtered off, washed with water and dried and (S)-2-carboxyindoline was prepared.

Place 25 kg of (S)-2-carboxyindoline, obtained previously, in 110 liters of methanol in a vessel. Keep stirred. Charge the rhodium (5% dry) catalyst into a mixer. Start up the stirring in a hydrogenator, charge the methanolic suspension of (S)-2-carboxyindoline by passing it through the mixer and rinse the assembly with water. Heat to 60°C and pressurize with hydrogen (30 bars). Filter off the catalyst on a single-plate filter. Collect the hydroalcoholic liquors in a reactor and evaporate the methanol off under vacuum. After concentrating, charge approximately 300 kg of dioxane. Heat to boiling and add water until a solution is obtained. Allow to cool. Filter off and dry. 22.3 kg of crystals of (2S,3aS,7aS)-2-carboxyoctahydroindole are obtained. Yield: 86.1%.

Place 35 kg of L-norvaline in approximately 300 kg of denatured ethanol in a reactor. Introduce approximately 60 kg of thionyl chloride, slowly and gradually. After stirring for a quarter of an hour, heat to reflux for 3 hours and

then evaporate off the ethanol under vacuum. Take up the residue with 300 liters of cyclohexane and heat to boiling. Allow to cool, filter, wash with cyclohexane and dry. 52.9 kg of ethyl L-norvalinate hydrochloride are obtained, that is a 97.6% yield.

Place 45 kg of ethyl N-norvalinate hydrochloride approximately 110 liters of water in a vessel equipped with a stirrer. Alkalify, then pour 23 kg of pyruvic acid very gradually into the solution obtained previously and stir the reaction mixture for 30 min. Place an aqueous suspension of charcoal containing 5% palladium and the alkaline solution of ethyl L-norvalinate obtained previously in a hydrogenation apparatus. Hydrogenate under pressure (30 bars) at room temperature for approximately one day. Filter under vacuum and evaporate the filtrate under reduced pressure, filter off and dry. Treat the residue obtained with ethanol; remove the insoluble material, consisting of sodium chloride, by filtration and rinse it with ethanol. Combine the ethanolic solutions; evaporate off the ethanol under reduced pressure and crystallize the residue from acetonitrile 34.3 kg of N-[(S)-1-carbethoxybutyl]-(S)-alanine are obtained, that is a 63.9% yield.

In a 30-liter reactor, reflux 12.5 kg of (2S,3aS,7aS)-2-carboxyperhydroindole, 50 kg of para-toluenesulfonic acid and 14.2 kg of benzyl alcohol and 38.4 kg of toluene, removing the water formed with the aid of a continuous separator. When no more water separates out, cool, filter off the precipitate of para-toluenesulfonate of the benzyl ester of (2S,3aS,7aS)-2-carboxyoctahydroindole formed, and dry. Yield: 91.3%.

Add approximately 3.5 kg of triethylamine to a suspension of approximately 5 kg of para-toluenesulfonate of the benzyl ester of (2S,3aS,7aS)-2-carboxyoctahydroindole in approximately 60 kg of ethyl acetate, followed by approximately 6 kg of 1-hydroxybenzotriazole, approximately 7.5 kg of the N-[(S)-1-carbethoxybutyl]-(S)-alanine and approximately 7.0 kg of dicyclohexylcarbodiimide. Stir, cooling slightly for approximately 3 hours, then filter off the dicyclohexylurea formed and wash the organic phase with water. The dried organic phase is evaporated to dryness and benzyl ester of (2S,3aS,7aS)-1-{2-[1-(ethoxycarbonyl)-(S)-butylamino]-(S)-propionyl}octahydroindole-2-carboxylic acid was obtained. Yield: 92.3%.

Dissolve, in a hydrogenator, 14 kg of benzyl ester of the (2S,3aS,7aS)-1-{2-[1-(ethoxycarbonyl)-(S)-butylamino]-(S)-propionyl}octahydroindole-2-carboxylic acid in cyclohexane. Add the charcoal containing 5% palladium and approximately 50 liters of water. Hydrogenate at ordinary temperature and pressure until the theoretical volume of hydrogen has been absorbed. Filter, wash the insoluble material with cyclohexane, separate off the organic phase and wash the aqueous phase again with cyclohexane. Isolate the (2S,3aS,7aS)-1-{2-[1-(ethoxycarbonyl)-(S)-butylamino]-(S)-propionyl}octahydroindole-2-carboxylic acid from the aqueous phase by freeze-drying.

In practice it is used combined with 2-methyl-2-propanamine.

References

Vincent M. et al.; US Patent No. 4,914,214; April 3, 1990; Assigned:Adir Et Cie, Neuilly-sur-Seine, France

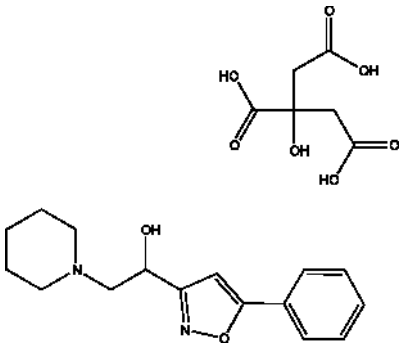
PERISOXAL CITRATE

Therapeutic Function: Antiinflammatory, Analgesic

Chemical Name: 3-(2-Piperidino-1-hydroxyethyl)-5-phenylisoxazole citrate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 2055-44-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Isoxal	Shionogi	Japan	1979

Raw Materials

Citric acid
3-(2-Methylthio-2-piperidinoacetyl)-5-phenylisoxazole
Sodium borohydride

Manufacturing Process

Crude crystals of 3-(2-methylthio-2-piperidinoacetyl)-5-phenilisoxazole (1.631 g) are suspended in 20 ml of methanol without being further purified and the suspension is stirred after a portionwise addition (in about 10 minutes) of 143 mg (3.78 mmol) of sodium borohydride at room temperature for about 30 minutes.

The methanol in the reaction mixture (pale yellow solution) is then removed by evaporation under reduced pressure to leave a residue which is subsequently dissolved in 30 ml of benzene. The benzene solution is shaken four times with 20 ml of 4 N hydrochloric acid each time to extract the basic substance. Each of the hydrochloric acid layers is washed once with 20 ml of benzene and combined together to be neutralized with potassium carbonate while being ice-cooled until it becomes basic (pH = 10).

The liberated crystalline substance is extracted twice with 50 ml of dichloromethane each time. After being separated, the dichloromethane layers are combined and washed once with 30 ml of water and dried over sodium sulfate. The solvent of the layer is removed by evaporation under reduced pressure to leave a crystalline residue (72.56 mg, 53% crude yield).

Recrystallization of this product from dichloromethane-ether (1:4) affords needles of 3-(2-piperidino-1-hydroxyethyl)-5-phenylisoxazole (701 mg, 51.3% as an overall yield calculated based on the starting material, melting point 104°C to 106°C. The product thus obtained may be reacted with citric acid to give the citrate.

References

Merck Index 7038
DFU 4 (4) 269 (1979)
I.N. p. 748
Hirai, S. and Kawata, K.; US Patent 3,939,167; February 17, 1976; assigned to Shionogi and Co., Ltd.

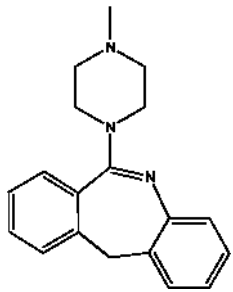
PERLAPINE

Therapeutic Function: Hypnotic

Chemical Name: 6-(4-Methyl-1-piperazinyl)-11H-dibenz[b,e]azepine

Common Name: 6-(4-Methyl-1-piperazinyl)morphanthridine

Structural Formula:



Chemical Abstracts Registry No.: 1977-11-3

Trade Name	Manufacturer	Country	Year Introduced
Hypnodin	Takeda	Japan	1974
Pipnodine	Takeda	Japan	-

Raw Materials

o-Aminodiphenylmethane
N-Methylpiperazine
Phosphorus oxychloride
Aluminum chloride
Phosgene

Manufacturing Process

The 5.6-dihydro-6-oxo-morphanthridine used as a starting material is usefully obtained in the following way. 30.2 grams of o-aminodiphenylmethane are dissolved in 65 ml of absolute toluene and, while stirring and at a temperature of between 0° and -10°C, 140 ml of 20% phosgene solution in toluene are added drop by drop. By bubbling phosgene slowly through it the milky mixture is heated within 30 minutes to reflux temperature, which is maintained during some 20 minutes. While stirring vigorously, dry nitrogen is passed into the boiling reaction mixture for 10 minutes. After evaporation of the solvent there are obtained by vacuum distillation 29.7 grams (86% of the theory of o-isocyanatodiphenylmethane of boiling point 169°C/12 mm Hg.

21.1 grams of aluminum chloride are heated in 110 ml of o-dichlorobenzene to 80°C and, while stirring, a solution of 29.7 grams of o-isocyanatodiphenylmethane in 60 ml of o-dichlorobenzene is added drop by drop, whereupon the temperature of the mixture rises to 120°C. This temperature is maintained for one hour while stirring. After cooling the reaction mixture is poured into 200 ml of 2 N hydrochloric acid, whereupon a brown precipitate is formed. After steam distillation the residue is isolated by filtration and crystallized from acetone/water. There are obtained 28.6 grams (97% of the theory) of 5,6-dihydro-6-oxo-morphanthridine of melting point 201°-203°C.

A mixture of 4.9 grams of 5,6-dihydro-6-oxo-morphanthridine, 37 ml of phosphorus oxychloride and 1.5 ml of dimethylaniline is heated for 3 hours at reflux, The viscous oil, obtained by evaporation of the reaction mixture in vacuo at 60°C, is diluted with 20 ml of absolute dioxane and, after adding 30 nil of N-methylpiperazine, heated for 4 hours at reflux. The resulting clear solution is evaporated in vacuo at 60°C to dryness. The residue is distributed between ether and ammonia water. The ethereal solution is separated, washed with water and then extracted with 1 N acetic acid. The acetic acid extract is mixed with ammonia water and then extracted with ether. The ethereal solution is washed with water, dried over sodium sulfate, filtered through alumina and evaporated.

The residue is caused to crystallize from ether/petroleum ether, and recrystallized from acetone/petroleum ether. 6.0 grams (88% of the theory) of 6-(4-methyl-1-piperazinyl)-morphanthridine of melting point 138°-138.5°C are obtained.

References

Merck Index 7040
Kleeman and Engel p. 705
OCDS Vol. 2 p. 425 (1980)
DOT 11 (2) 76 (1975)
I.N. p. 748

Schmutz, J., Hunziker, F. and Kunzle, F.M.; US Patent 3,389,139; June 18, 1968; assigned to Dr. A. Wander, SA, Switzerland

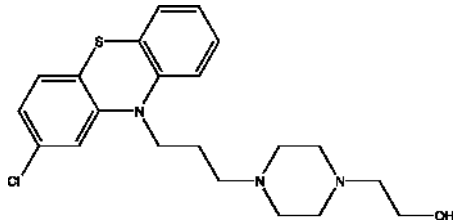
PERPHENAZINE

Therapeutic Function: Tranquilizer

Chemical Name: 4-[3-(2-Chlorophenothiazin-10-yl)propyl]-1-piperazineethanol

Common Name: Chlorpiprazine

Structural Formula:



Chemical Abstracts Registry No.: 58-39-9

Trade Name	Manufacturer	Country	Year Introduced
Trilafon	Schering	US	1957
Decentan	Merck	W. Germany	-
Etrafon	Schering	US	-
Fentazin	Allen and Hanburys	UK	-
F-Mon	Nippon Shinyaku	Japan	-
Peratsin	Farmos	Finland	-
Perfenil	Scalari	Italy	-
Perphenan	Taro	Israel	-
Phenazine	I.C.N.	Canada	-
Triavil	MSD	US	-
Trilifan	Cetrane	France	-
Triomin	Yamanouchi	Japan	-

Raw Materials

2-Bromoethanol
Piperazine
1-Bromo-3-chloropropane
2-Chlorophenothiazine

Manufacturing Process

A mixture of 155 parts of 2-chloro-10-(γ-chloropropyl)phenothiazine, 76 parts

of sodium iodide, 216 parts of piperazine and 2,000 parts of butanone is refluxed for 8 hours, concentrated and extracted with dilute hydrochloric acid. The extract is rendered alkaline by addition of dilute potassium carbonate and benzene or chloroform extracted. This extract is washed with water, dried over anhydrous potassium carbonate, filtered and evaporated. Vacuum distillation at 0.1 mm pressure yields 2-chloro-10-[γ-(N-piperazino)propyl]phenothiazine at about 214°-218°C.

A stirred mixture of 5 parts of 2-chloro-10-[γ-(N-piperazino)propyl]phenothiazine, 1.92 parts of 2-bromoethanol, 2.11 parts of potassium carbonate and 35 parts of toluene is refluxed for 5 hours. The mixture is treated with water and benzene and the organic layer is separated, washed with water, dried over anhydrous potassium carbonate, filtered and evaporated. The residue is distilled at about 240°-244°C and 0.15 mm pressure to yield 2-chloro-10-[γ-(N'-β-hydroxyethyl-N-piperazino)-propyl]phenothiazine according to US Patent 2,838,507.

The 2-chloro-10-(γ-chloropropyl)phenothiazine starting material is produced from 2-chlorophenothiazine and 1-bromo-3-chloropropane.

References

Merck Index 7044
Kleeman and Engel p. 705
PDR pp. 1217, 1617, 1655
OCDS Vol. 1 p. 383 (1977)
DOT 9 (6) 228 (1973)
I.N. p. 749
REM p. 1090
Cusie, J.W. and Hamilton, R.W.; US Patent 2,838,507; June 10, 1958; assigned to G.D. Searle and Co.
Sherlock, M.H. and Sperber, N.; US Patent 2,860,138; November 11, 1958; assigned to Schering Corporation

PERUVOSIDE

Therapeutic Function: Cardiotonic

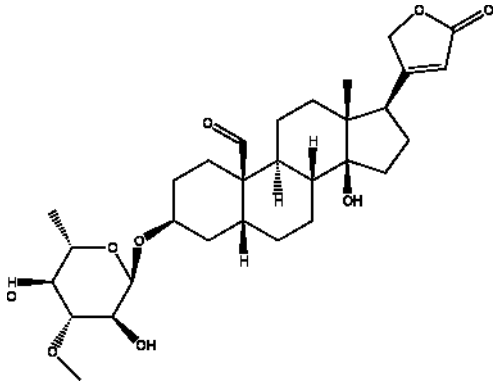
Chemical Name: Card-20(22)-enolide, 3-((6-deoxy-3-O-methyl-α-L-glucopyranosyl)oxy)-14-hydroxy-19-oxo-, (3β,5β)-

Common Name: Peruvoside

Chemical Abstracts Registry No.: 1182-87-2

Trade Name	Manufacturer	Country	Year Introduced
Peruvoside	Indena	-	-
Peruvoside	ZYF Pharm Chemical	-	-

Structural Formula:



Raw Materials

Fruits or seeds of ApocynaceaThevetia peruviana
Column of silica gel

Manufacturing Process

Peruvoside is obtained employing the fruit or seeds of ApocynaceaThevetia peruviana by the fermentation and the separation the extracted glucoside mixture by chromatography.

Two kilograms of the ground fruit of ApocynaceaThevetia peruviana is mixed with 100 g of grain chaff and moistened with 900 ml of hot water (approximately 60°C). The mixture is mixed with 20 ml of toluene and maintained at 45°-55°C in a closed vessel for 5 days. The thus fermented material is extracted six times with 1200 ml portions of acetone. The combined extracts are concentrated at 30°C under reduced pressure, until there remains about 600 ml of a dark colored aqueous concentrate. The latter is shaken out with an equal volume of petroleum ether. The organic phase is discarded after recovering the petroleum ether. The thus degreased aqueous concentrate is extracted six times with 500 ml portions of dichloromethane. The dichloromethane extracts are dried over sodium sulfate, combined, and concentrated to about 100 ml. Then the residue is stirred into 250 ml of petroleum ether. After standing overnight, the thus-separated crystallized product is vacuum-filtered, washed petroleum ether and dried at about 40°C. The thus obtained crude glycoside mixture (21 g) is dissolved in a mixture of chloroform/methanol and chromatographed on a column of silica gel. There is thus isolated a small amount of oil and fat, a total of 15.5 g of cerberine, acetylperuvoside and neriifolin, 2.2 g of pure peruvoside, MP: 160°-163°C; $[\alpha]_{22}^{d}$=70° (c = 1.3 in CH_3OH), corresponding to a yield 0.11%, based on the quantity of fruit of Thevetia peruviana employed as the starting material.

One kilogram of ground seeds of Thevetia peruviana is mixed with 300 g of grain chaff and moistened with 500 ml of hot water (60°C). After addition of 10 ml of toluene the mixture is allowed to stand in a sealed vessel for 5 days at 45°-55°C. Thereafter, the moist drug material is extracted six times with

500 ml portions of methanol. The extracts are concentrated at about 30°C to about 300 ml. Without degreasing, glycosides are extracted from this aqueous concentrate with three 300 ml portions followed by three 100 ml portions of chloroform. The chloroform extracts are concentrated at about 40°C to a volume of about 200 ml. This concentrate is then mixed with 500 ml of petroleum ether. After standing overnight, the crystallized product, which separated, is vacuum-filtered, washed with petroleum ether, and dried at 40°C. Yield of rude glycoside: 46.9 g. From this product, after the usual separation by chromatography, 5.1 g of pure peruvoside is obtained, MP: 161°-164°C. Yield 0.51%, based on the weight of the non-degreased seeds of Thevetia peruviana.

References

Balsam et al.; US Patent No. 3,713,980; Jan. 30, 1973; Assigned to Merck Patent Gesellshaft mit beschrankter Haftung, Darmstadt, Germany

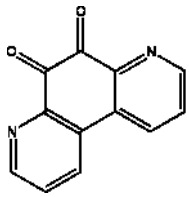
PHANQUINONE

Therapeutic Function: Antiamebic

Chemical Name: 4,7-Phenanthroline-5,6-quinone

Common Name: Fanquinonum; Phanchinonum; Phanquinone; Phanquone

Structural Formula:



Chemical Abstracts Registry No.: 84-12-8

Trade Name	Manufacturer	Country	Year Introduced
Phanquinone	Yick-Vic Chemicals and Pharmaceuticals (HK) Ltd.	-	-
Phanquinone	ZYF Pharm Chemical	-	-

Raw Materials

Sulfuric acid
6-Methoxy-4:7-phenanthroline
Nitric acid
Caustic soda

Manufacturing Process

2 parts of 6-methoxy-4:7-phenanthroline are mixed with 10 parts by volume of concentrated sulfuric acid and while cooling with a mixture of ice and sodium chloride, with 6 parts by volume of fuming nitric acid (density = 1.51), and the whole is heated for 2 h at 120°C. The reaction solution is poured on to ice, its pH value is adjusted to 7 by means of a 10 N solution of caustic soda, after standing for 2 h the whole is filtered with suction to remove the precipitate which separates, and the latter is washed with hot water. After recrystallising the product from methyl alcohol and drying it at 100°C under 0.1 mm pressure, there are obtained 1.8 parts (i.e. 90 % of the calculated yield) of 4:7-phenanthroline-5:6-quinone in the form of pale yellow crystals melting at 295°C.

References

GB Patent No. 688,802; March 11, 1953; Assigned: CIBA Limited, a body corporate, Basle, Switzerland

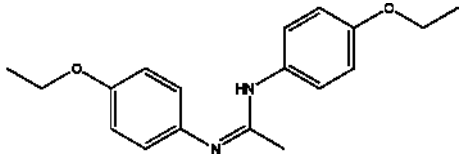
PHENACAINE

Therapeutic Function: Local anesthetic

Chemical Name: Ethanimidamide, N,N'-bis(4-ethoxyphenyl)-

Common Name: Fenacaine; Phenacaine; Tanicaine

Structural Formula:



Chemical Abstracts Registry No.: 101-93-9

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

Raw Materials

Hydrogen chloride
Phenacetin (4-ethoxyacetanilide)

Manufacturing Process

Phenacetin (4-ethoxyacetanilide) was treated with slowly current of gaseous

hydrogen chloride for 15 hours at 150°C. On cooling the product was poured into 20 volumes of water and heated. Then it was cooled to room temperature, filtered off and excess of alkali was added. The precipitated crude product was at first re-crystallized from 60% ethanol, then from benzene-ligroin to give pure acetamidine as a white needles; MP: 121°C.

References

Tauber E.; D.R. Patent No. 79,868; March 16, 1894

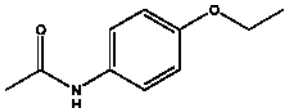
PHENACETIN

Therapeutic Function: Analgesic

Chemical Name: Acetamide, N-(4-ethoxyphenyl)-

Common Name: Acetophenetidin

Structural Formula:



Chemical Abstracts Registry No.: 62-44-2

Trade Name	Manufacturer	Country	Year Introduced
Phenacetin	Environmental Health and Safety	-	-

Raw Materials

4-Ethoxyaniline
Acetic anhydride
Sodium hydrosulfite

Manufacturing Process

A mixture of 10 g of 4-ethoxyaniline and 8.6 g of acetic anhydride in 28 g of dry benzene was refluxed for 4 hours. To the reaction mixture was added a small amount of $Na_2S_2O_4$. After cooling the phenacetin was crystallized; yield 12.5 g (96%), M.P. 136°C.

References

Merck Index, Monograph number: 7344, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.

Friedlander, Berichte, 1893, 25, 178
Lumiere A., 1906, [3], 33, 785

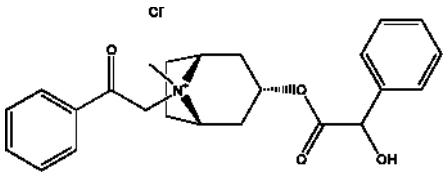
PHENACTROPINIUM CHLORIDE

Therapeutic Function: Antihypertensive

Chemical Name: α-Hydroxybenzeneacetic acid 8-methyl-8-[(2-oxo-2-phenyl)-ethyl]-8-azoniabicyclo[3.2.1]-oct-3-yl ester chloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 3784-89-2

Trade Name	Manufacturer	Country	Year Introduced
Trophenium	American Cyanamid (AHP)	US	1961
Trophenium	Duncan Flockhart	UK	-

Raw Materials

Homatropine
Phenacyl chloride

Manufacturing Process

330 g (1.2 M) of homatropine were dissolved in 1 liter of dry methyl ethyl ketone and gently refluxed on a water-bath during the gradual addition of a solution of 204 g (1.32 M) redistilled phenacyl chloride in 200 ml of the same solvent. After 10 to 15 minutes 1 g of previously prepared homatropine phenacyl chloride was added to avoid formation of a supersaturated solution of the quaternary compound. Reflux was continued for 9 hours, then the thick suspension was allowed to cool, filtered and washed with 200 ml methyl ethyl ketone to yield 490 g (95%) slightly creamy solid, MP 188°C to 191°C.

For purification the crude quaternary salt was dissolved in hot ethyl alcohol (2 ml/g) and warm dry acetone (8 ml/g) was stirred into the clear filtrate. On cooling, 387 g (78 % recovery) of a pure white powder, MP 195°C to 197°C, were obtained, in which the ionizable chlorine assayed at 99.7% of the theoretical value.

References

Merck Index 7067
I.N. p. 752
Johnston, R.G. and Spencer, K.E.V.; US Patent 2,828,312; March 25, 1958; assigned to T. and H. Smith, Ltd. (UK)

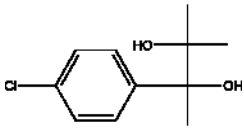
PHENAGLYCODOL

Therapeutic Function: Tranquilizer

Chemical Name: 2-(4-Chlorophenyl)-3-methyl-2,3-butanediol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 79-93-6

Trade Name	Manufacturer	Country	Year Introduced
Ultran	Lilly	US	1975
Felixyn	Radiumpharma	Italy	-

Raw Materials

Sodium cyanide
Hydrogen chloride
Ethanol
Magnesium
p-Chloroacetophenone
Sodium hydroxide
Methyl iodide

Manufacturing Process

To a mixture of 460 g of p-chloroacetophenone, 350 ml of ether and 500 ml of water are added 410 g of sodium cyanide, with vigorous stirring. The reaction mixture is cooled to about 5°C to 10°C and 700 ml of concentrated hydrochloric acid are added at such a rate that no hydrogen cyanide is formed and the temperature of the mixture does not rise above 10°C. After the addition of the acid is complete, the reaction mixture is stirred for about three hours at room temperature, and allowed to separate into an aqueous and an organic phase. The organic phase is removed from the aqueous phase, and the aqueous phase and any salt which may have separated in the course of the reaction are washed with about 300 ml of ether. The combined ether washings and organic phase are dried over anhydrous magnesium sulfate, and

the ether is removed by evaporation in vacuo at room temperature. The residue is poured with stirring into 800 ml of concentrated hydrochloric acid kept at about 0°C by cooling with solid carbon dioxide. The acid mixture is saturated with gaseous hydrogen chloride at 0°C, and stirred at room temperature overnight. The resulting precipitate of p-chloroatrolactamide is removed by filtration, washed by slurrying with water and dried. After recrystallization from ethanol, p-chloroatrolactamide melts at about 105°C to 107°C.

A mixture of 200 g of p-chloroatrolactamide and 1 liter of 25% sodium hydroxide solution is refluxed with stirring for about sixteen hours. The reaction mixture is then poured over cracked ice and diluted with water to a volume of about 3 liters. The aqueous solution is washed with two 1 liter portions of ether, and acidified with concentrated hydrochloric acid, whereupon a precipitate of p-chloroatrolactic acid forms. The precipitated acid is removed by filtration, and is dissolved in 500 ml of ether, washed with two 250 ml portions of water and dried. The ether is removed by evaporation. p-chloroatrolactic acid thus prepared melts at about 117°C to 120°C.

A mixture of 185 g of p-chloroatrolactic acid, 600 ml of ethanol and 60 ml of concentrated sulfuric acid is refluxed for about twelve hours. About half the solvent is then removed by evaporation in vacuo at room temperature, the residue is poured over cracked ice, and diluted with water to a volume of about 2 liters. The ethyl p-chloroatrolactate formed in the reaction is extracted with two 1 liter portions of ether. The combined ether extracts are washed with successive 200 ml portions of water, 5% sodium carbonate solution, and water, and are dried over anhydrous magnesium sulfate. The dried ether solution is subjected to fractional distillation, and the fraction boiling at about 90°C to 100°C at a pressure of 0.1 mm of mercury, is collected. The distillate consists of ethyl p-chloroatrolactate.

To a solution of 2 mols of methylmagnesium iodide in 1.5 liters of ether are added with vigorous stirring 107 g (0.5 mol) of ethyl p-chloroatrolactate. The reaction mixture is stirred for about sixteen hours, and is then decomposed by the addition of about 320 ml of saturated aqueous ammonium chloride solution. After standing, the ether layer is decanted from the mixture and the aqueous phase and the precipitated salts are washed with several 500 ml portions of ether. The combined ether solution and washings are washed with successive 500 ml portions of 5% ammonium chloride solution and water, are dried over anhydrous magnesium sulfate, and are evaporated to dryness in vacuo. The crystalline residue consisting of 2-p-chlorophenyl-3-methyl-2,3-butanediol, is recrystallized from a mixture of benzene and petroleum ether.

2-p-chlorophenyl-3-methyl-2,3-butanediol thus prepared melts at about 66°C to 67°C.

References

Merck Index 7070
Kleeman and Engel p. 709
OCDS Vol. 1 p. 219 (1977)
I.N. p. 752
Mills, J.; US Patent 2,812,363; November 5, 1957; assigned to Eli Lilly and Co.

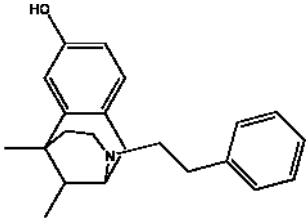
PHENAZOCINE

Therapeutic Function: Narcotic analgesic

Chemical Name: 2,6-Methano-3-benzazocin-8-ol, 1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(2-phenylethyl)-

Common Name: Fenatsokin; Phenazocine; Phenobenzorphan; Xenagol

Structural Formula:



Chemical Abstracts Registry No.: 127-35-5

Trade Name	Manufacturer	Country	Year Introduced
Phenazocine	SmithKline French (GSK)	-	-

Raw Materials

3,4-Lutidine
Methyl iodide
Hydrobromic acid
Lithium aluminum hydride
Palladium on barium
Acetic anhydride
Ethereal solution of p-methoxybenzylmagnesium chloride

Manufacturing Process

25.0 g 3,4-lutidine methyl iodide in 60 ml of dry ethyl ether is stirred while 400 ml of a 0.3958 N ethereal solution of p-methoxybenzylmagnesium chloride is added at room temperature. The mixture is stirred for 30 minutes and then decomposed with a solution of 100 ml of water containing 25 g of ammonium chloride and 10 ml of concentrated ammonium hydroxide. The layers are separated. The organic layer is extracted with a solution of 75 ml of water and 17 ml of concentrated hydrochloric acid. The extracts are neutralized and taken into ether. The volatiles are evaporated to leave a light yellow oil, the dehydro base.

The oily residue is then hydrogenated at 17 p.s.i. of hydrogen with 5% palladium-on-barium sulfate in 100 ml of 2 N hydrochloric acid for six hours. The reaction mixture is filtered, made alkaline and taken through ether to give the tetrahydro base as a clear oil.

The oily tetrahydro base (about 10.0 g) in 150 ml of 48% hydrobromic acid is heated at 135°C for 24 hours, and then quenched in an ice Treating with base

and taking through chloroform gives a brown residue of the isomeric mixture of 2'-hydroxy-2,5,9-trimethyl-6,7-benzmorphan.

This residue is triturated with ether, cooled and the resulting slurry filtered. The solid product is dissolved in a minimum of dry ethanol and made acid with ethereal hydrogen chloride. The cooled mixture is filtered to give the hydrochloride salt of the N-methyl-iso-benzmorphan, MP: 279-282°C, after recrystallization from ethanol. The base melts at 215°C.

The ethereal filtrate is evaporated. A residue is neutralized to give the crude normal N-methyl-benzmorphan isomer, MP: 229-230°C. The hydrochloride salt of this isomer is formed, MP: 196-198°C, as a hydrate. A mixture of 10.0 g of the N-methyl-iso-benzmorphan isolated above in 15 ml of acetic anhydride is heated on the steam bath for about an hour, then quenched in an ice slurry. The mixture is then neutraliized and taken through ether to give the O-acetate derivative, iso-2'-acetoxy-2,5,9-trimethyl-6,7-benzomorphan. The crude acetate (9.5 g) is reacted with 5.0 g of cyanogen bromide in 100 ml of chloroform at reflux for several hours. The volatiles are removed in vacuo to leave a residue, which is refluxed in 150 ml of dilute hydrochloric acid for 24 hours. The mixture is cooled, neutralized and taken through chloroform to give the desired base with two methyl groups as a viscous syrup which crystallized slowly, MP: 173-175°C from methanol. The base, 6.5 g, is reacted with 5.0 g of phenylacetyl chloride in the presence of an excess of sodium carbonate in water. The mixture is stirred for several hours, diluted with water and taken into ether to give the N-phenacetylated compound. This compound in ether (250 ml) is reacted with an excess of 1.5 M ethereal lithium aluminum hydride at reflux overnight. The reaction mixture is evaporated to dryness, after quenching carefully with water and hydrobromic acid, to give the crude 2'-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan hydrobromide salt which is optionally recrystallized from ethanol, MP: 272-273°C. The hydrobromide salt in the normal series melts at 170-173°C. The base is isolated by neutralizing of the hydrobromide salt in an ether alkali mixture, with following separating and evaporating the organic solvent.

References

Gordon M. et al.; US Patent No. 2,959,594; November 8, 1960; Assigned to Smith Kline and French Laboratories, Philadelphia, Pa., a corporation of Pennsylvania

PHENAZOPYRIDINE HYDROCHLORIDE

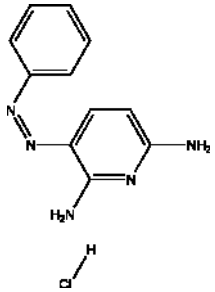
Therapeutic Function: Urinary analgesic, Antiseptic, Diagnostic aid

Chemical Name: 2,6-Pyridinediamine, 3-(phenylazo)-, monohydrochloride

Common Name: Phenazopyridine hydrochloride; Azopirin

Chemical Abstracts Registry No.: 94-78-0 (Base); 136-40-3

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Phenazopyridine Hydrochloride	AroKor Holdings Inc.	-	-
Azopirin	Barcymex	-	-
Cystamine	Mc-Clung	-	-
Phenazopyridine Hydrochloride	Xi'an Boojie Pharmaceutical and Chemical Technology Co., Ltd.	-	-
Phenazopyridine Hydrochloride	Azide Chemical Co., Ltd.	-	-
Prodium	Breckenridge	-	-
Sedural	Teva	-	-
Urisept	Kahira	-	-
Urophenyl	Nadeau	-	-
Urologin	Delta	-	-

Raw Materials

Phenyldiazene
2,6-Diaminopyridine

Manufacturing Process

Phenyldiazene chloride reacted with 2,6-diaminopyridine and in the result 2,6-diamino-3-(phenylazo)pyridine was obtained.

In practice it is usually used as monohydrochloride.

References

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

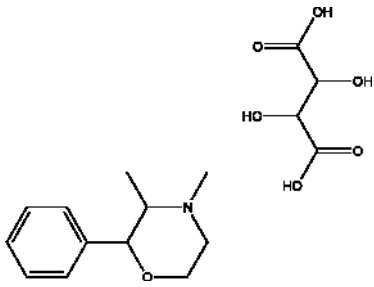
PHENDIMETRAZINE TARTRATE

Therapeutic Function: Antiobesity

Chemical Name: 3,4-Dimethyl-2-phenylmorpholine bitartrate

Common Name: 3,4-Dimethyl-2-phenyltetrahydro-1,4-oxazine bitartrate

Structural Formula:



Chemical Abstracts Registry No.: 50-58-8; 634-03-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Plegine	Ayerst	US	1961
Statobex	Lemmon	US	1972
Bacarate	Tutag	US	1972
Prelu-2	Boehringer Ingelheim	US	1980
Sprx 105	Tutag	US	1980
Obezine	Western Research	US	1981
X-Trozine	Rexar	US	1981
Hyrex-105	Hyrex	US	1983
Adipost	Ascher	US	1983
Slyn-LL	Edwards	US	1983
Trimcaps	Mayrand	US	1983
Adipo II	Sig	US	-
Adphen	Ferndale	US	-
Amphasub	Palmedico	US	-
Anoxine T	Winston Pharm.	US	-
Arcotrol	Arco	US	-
Bacarate	Reid-Provident	US	-
Bontril	Carnrick	US	-
Di-Ap-Trol	Foy	US	-
Dyrexan	Trimen	US	-
Ephemet	Canright	US	-
Fringanor	Sobio	France	-
Melfiat	Reid-Rowell	US	-
Neo-Nilorex	A.V.P.	US	-

Trade Name	Manufacturer	Country	Year Introduced
Obe-Del	Marlop	US	-
Obepar	Parmed	US	-
Obesan	SCS Pharmalab	S. Africa	-
Obex-LA	Rio Ethicals	S. Africa	-
Pan-Rexin	Pan American	US	-
Phenazine	Jenkins	US	-
Reducto	Arcum	US	-
Reton	Tri-State	US	-
Stodex	Jalco	US	-
Symetra	Westerfield	US	-
Trimstat	Laser	US	-
Wehless	Hauck	US	-
Weightrol	N. Amer. Pharm.	US	-
X-Trozine	Rexar	US	-

Raw Materials

Propiophenone
2-Methylaminomethanol
Bromine
Formic acid

Manufacturing Process

A mixture of 61 grams 1-phenyl-1-oxo-2-(N-methyl-N-ethanolamino)-propane hydrochloride and 100 cc 98-100% formic acid was refluxed at the boiling point at atmospheric pressure for 45 minutes on an oil bath. Thereafter, the oil bath temperature was increased to 180°C and as much of the excess unreacted formic acid as possible was distilled off. A vigorous evolution of carbon dioxide developed during the distillation, which ceased after approximately 45 additional minutes. The honey-yellow syrup which remained as the distillation residue was worked up by admixing it with about six volumes of water and adjusting the aqueous mixture to alkaline reaction with concentrated sodium hydroxide. An oily phase separated out which was extracted with ether. The ether extract was washed with water and dried over potassium carbonate. The solvent was distilled off and the distillation residue was fractionally distilled in vacuo. The base boils at 132°-133°C at 12 mm. The yield was 93% of theory. Reaction with tartaric acid gave the final product.

The starting material is produced by reacting propiophenone with bromine and then reacting the α-bromopropiophenone produced with 2-methylaminomethanol.

References

Merck Index 7088
Kleeman and Engel p. 711
PDR pp. 633, 679, 778, 928, 948, 992, 1448, 1450, 1807
OCDS Vol. 1 p. 260 (1977) and 2, 261 (1980)
I.N. p. 754
REM p. 892

Heel, W. and Zeile, K.; US Patent 2,997,469; August 22, 1961; assigned to C.H. Boehringer Sohn, Germany

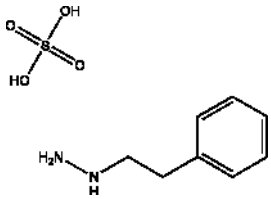
PHENELZINE SULFATE

Therapeutic Function: Psychostimulant

Chemical Name: (2-Phenethyl)hydrazine sulfate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 156-51-4; 51-71-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Nardil	Parke Davis	US	1959
Nardelzine	Substantia	France	-

Raw Materials

Phenethyl bromide
Hydrazine hydrate

Manufacturing Process

To a refluxing solution containing 147.5 grams of 85% hydrazine hydrate in 500 cc of ethanol was added, during a period of 5 hours, 92.5 grams of phenethylbromide (0.50 mol) in 150 cc of ethanol. Stirring and refluxing were continued for two hours. The ethanol was removed by distillation and the residue extracted repeatedly with ether. The ether was dried with potassium carbonate and the product base collected by distillation, BP 74°C/0.1 mm, yield 52.3 grams (77%). The base is reacted with sulfuric acid in propanol to give the sulfate.

References

Merck Index 7089
Kleeman and Engel p. 711

PDR p. 1368
OCDS Vol. 1 p. 74 (1977)
I.N. p. 754
REM p. 1096
Biel, J.H.; US Patent 3,000,903; September 19, 1961; assigned to Lakeside Laboratories, Inc.

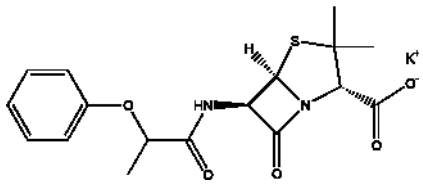
PHENETHICILLIN POTASSIUM

Therapeutic Function: Antibacterial

Chemical Name: 3,3-Dimethyl-7-oxo-6-[(1-oxo-2-phenoxypropyl)amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid potassium salt

Common Name: Penicillin MY

Structural Formula:



Chemical Abstracts Registry No.: 132-93-4; 147-55-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Syncillin	Bristol	US	1959
Ro-Cillin	Rowell	US	1960
Chemiphen	Squibb	US	1960
Semopen	Massengill	US	1960
Dramcillin-S	White	US	1960
Maxipen	Roerig	US	1960
Darcil	Wyeth	US	1960
Alpen	Schering	US	1960
Altocillin	Caber	Italy	-
Bendralan	Antibioticos	Spain	-
Broxil	Beecham	UK	-
Metilpen	Boniscontro-Gazzone	Italy	-
Optipen	C.S.L.	Australia	-
Pen-200	Pfizer	W. Germany	-
Peniplus	Fumouze	France	-
Penopen	Pliva	Yugoslavia	-
Penorale	Lusofarmaco	Italy	-
Synthecilline	Bristol	France	-
Synthepen	Meiji	Japan	-

Raw Materials

α-Phenoxypropionic acid
Isobutyl chloroformate
6-Aminopenicillanic acid
Potassium 2-ethylhexanoate

Manufacturing Process

Triethylamine (1.5 ml) was added to a cold solution (10°C) of α-phenoxypropionic acid (1.66 g, 0.01 mol) in 15 ml of pure dioxane, with stirring and cooling to 5°C to 10°C while isobutyl chloroformate (1.36 g, 0.01 mol) in 5 ml of dioxane was added dropwise. Then the mixture was stirred for ten minutes at 5°C to 8°C. A solution of 6-amino-penicillanic acid (2.16 g, 0.01 mol) in 15 ml of water and 2 ml of triethylamine was then added dropwise while the temperature was maintained below 10°C. The resulting mixture was stirred in the cold for 15 minutes then at room temperature for 30 minutes, diluted with 30 ml of cold water and extracted with ether which was discarded. The cold aqueous solution was then covered with 75 ml of ether and acidified to pH 2 with 5 N H_2SO_4. After shaking, the ether layer containing the product 6-(α-phenoxypropionamido)penicillanic acid, was dried for ten minutes over anhydrous sodium sulfate and filtered. Addition of 6 ml of dry n-butanol containing 0.373 g/ml of potassium 2-ethylhexanoate precipitated the potassium salt of the product as a colorless oil which crystallized on stirring and scratching and was collected, dried in vacuo and found to weigh 2.75 g, to melt at 217°C to 219°C.

References

Merck Index 7093
Kleeman and Engel p. 712
OCDS Vol. 1 p. 410 (1977)
I.N. p. 755
Beecham Research Laboratories, Ltd.; British Patent 877,120; September 13, 1961

PHENFORMIN

Therapeutic Function: Antidiabetic

Chemical Name: N-(2-Phenylethyl)imidodicarbonimidic diamide

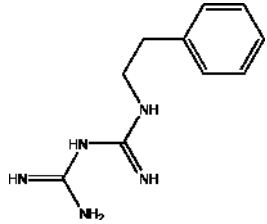
Common Name: Phenethyldiguanide

Chemical Abstracts Registry No.: 114-86-3

Raw Materials

β-Phenylethylamine
Hydrogen chloride
Dicyandiamide

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
DBI	Geigy	US	1959
Meltrol	U.S.V. Pharm.	US	1971
Adiabetin	Arcana	Austria	-
Antipond	Arcana	Austria	-
Cronoformin	Guidotti	Italy	-
De Be J	Isa	Brazil	-
Debeone	U.S.V.	US	-
Diabis	Funk	Spain	-
Dibein	Pharmacia	Sweden	-
Dibophen	Polfa	Poland	-
Insoral	U.S.V.	US	-
Kataglicina	Marxer	Italy	-
Prontoformin	Guidotti	Italy	-

Manufacturing Process

15.76 g of β-phenylethylamine hydrochloride and 8.4 g of dicyandiamide were ground and intimately mixed. The mixture was heated in an oil bath in a 3-neck flask fitted with a thermometer and stirrer, and the mixture began to melt at a bath temperature of 125°C and was completely fluid at 130°C. Further heating at 145°C to 150°C initiated an exothermic reaction and the temperature of the fusion mixture (156°C) exceeded the oil bath temperature (150°C) by 6°. Heating was continued for one hour at bath temperature of 148°C to 150°C. The reaction mixture was cooled, dissolved in about 100 cc of methanol and filtered. The methanol filtrate was concentrated under reduced pressure, cooled and the product (β-phenylethylbiguanide hydrochloride) filtered off and recrystallized from 95% isopropanol.

References

Merck Index 7099
OCDS Vol. 1 p. 75 (1977)
I.N. p. 755
Shapiro, S.L. and Freedman, L.; US Patent 2,961,377; November 22, 1960; assigned to US Vitamin and Pharmaceutical Corp.

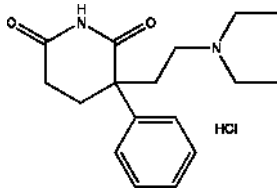
PHENGLUTARIMIDE HYDROCHLORIDE

Therapeutic Function: Anticholinergic, Antiparkinsonian

Chemical Name: Glutarimide, 2-(2-(diethylamino)ethyl)-2-phenyl-, hydrochloride

Common Name: Phenglutarimide hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 1674-96-0; 1156-05-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Ciba 10870	Ciba Pharmaceutical Products, Inc.	-	-

Raw Materials

Acetic acid — Acetic anhydride
Sulfuric acid — Hydrochloric acid
Potassium salt of 2-phenyl-2-(β-diethylaminoethyl)-pentane-1,5-diacid mononitrile

Manufacturing Process

350 parts by weight of the potassium salt of 2-phenyl-2-(β-diethylaminoethyl)-pentane-1,5-diacid mononitrile are dissolved with heating in 700 parts by volume of glacial acetic acid, 850 parts by volume of acetic anhydride are added, and then 250 parts by volume of concentrated sulfuric acid introduced portionwise. The temperature of the reaction mixture in this operation rises to 120-130°C. When the reaction subsides, the whole is finally maintained for a further 15 min on the boiling water bath. The solvent is removed on the water bath under reduced pressure, the residue poured onto ice and caustic soda solution, and the whole extracted with chloroform. The chloroform solution washed with water, dried over potassium carbonate and the solvent evaporated. The crystalline residue, consisting of 3-phenyl-3-(β-diethylaminoethyl)-2,6-dioxopiperidine. After recrystallization from a mixture of ethyl acetate and ligroin, melts at 118-120°C.

The hydrochloride (produced by dissolving the base in ethyl acetate and adding an equivalent quantity of hydrochloric acid gas dissolved in ethyl

acetate) melts, after recrystallization from a mixture of methyl alcohol and ethyl acetate, at 168-172°C.

References

Hoffmann K., Tadmann E.; US Patent No. 2,664,424; Dec. 29, 1953; Assigned to Ciba Pharmaceutical Products, Inc., Summit, N.J.

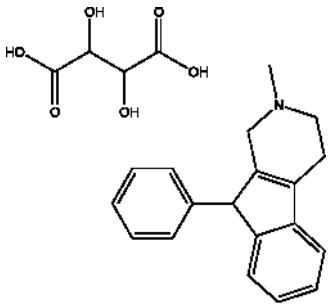
PHENINDAMINE TARTRATE

Therapeutic Function: Antihistaminic

Chemical Name: 2,3,4,9-Tetrahydro-2-methyl-9-phenyl-1H-indeno[2,1,c]pyridine tartrate

Common Name: 2-Methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene tartrate

Structural Formula:



Chemical Abstracts Registry No.: 569-59-5; 82-88-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Thephorin	Roche	US	1947
Nolahist	Carnrick	US	-
Nolamine	Carnrick	US	-
Pernovin	Chinoin	Hungary	-
PV-Tussin	Reid-Rowell	US	-

Raw Materials

Acetophenone
Formaldehyde
Hydrogen bromide
Potassium thiocyanate
Methylamine
Sodium hydroxide
Hydrogen

Manufacturing Process

A mixture of 750 grams of 1-methyl-3-benzoyl-4-hydroxy-4-phenylpiperidine and 2,500 cc of 48% hydrobromic acid is refluxed for about 20 minutes. It is then poured into 8 liters of water. An oily precipitate appears which on standing crystallizes. It is filtered and crystallized from about 3.5 liters of alcohol. 2-Methyl-9-phenyl-2,3-dihydrel-pyridindene hydrobromide, MP 201°-203°C, is obtained.

A mixture of 680 grams of 2-methyl-9-phenyl-2,3-dihydrol-pyridindene hydrobromide, 6,000 cc of water and about 100 grams of Raney-nickel catalyst is hydrogenated at room temperature and at about 1,000 lb pressure for a period of three hours. The catalyst is filtered. The clear filtrate is treated with a solution of 240 grams potassium thiocyanate in 400 cc of water. A heavy solid precipitates from which the supernatant liquid is decanted.

The residue is dissolved in 10 liters of boiling alcohol with stirring in the presence of nitro gen. The solution is cooled to room temperature under nitrogen, and then allowed to stand overnight. 2-Methyl-9-phenyl-tetrahydro-1-pyridindene thiocyanate separates in crystals of MP 188°-189°C. From the concentrated filtrate an additional amount is obtained. The corresponding free base, prepared by treating the slightly soluble thiocyanate in aqueous suspension with sodium hydroxide and extracting with ether, has a MP of 90°-91°C. It forms a tartrate of MP 160°C.

The starting material was prepared by reacting acetophenone, methylamine and formaldehyde followed by treatment of the intermediate with sodium hydroxide.

References

Merck Index 7103
Kleeman and Engel p. 713
PDR pp. 781, 1448
I.N. p. 756
Plati, J.T. and Wenner, W.; US Patent 2,470,108; May 17,1949; assigned to Hoffmann-La Roche Inc.

PHENIPRAZINE

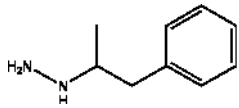
Therapeutic Function: Antihypertensive

Chemical Name: (1-Methyl-2-phenylethyl)hydrazine

Common Name: -

Chemical Abstracts Registry No.: 55-52-7

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Catron	Lakeside	US	1959
Catroniazide	Lakeside		-

Raw Materials

1-Phenyl-2-propylidenylhydrazine
Acetic acid
Hydrogen

Manufacturing Process

A solution containing 741 g (5.0 mols) of 1 -phenyl-2-propylidenylhydrazine, 300 g (5.0 mols) of glacial acetic acid and 900 cc of absolute ethanol was subjected to hydrogenation at 1,875 psi of hydrogen in the presence of 10 g of platinum oxide catalyst and at a temperature of 30°C to 50°C (variation due to exothermic reaction). The catalyst was removed by filtration and the solvent and acetic acid were distilled. The residue was taken up in water and made strongly alkaline by the addition of solid potassium hydroxide. The alkaline mixture was extracted with ether and the ether extracts dried with potassium carbonate. The product was collected by fractional distillation, BP 85°C (0.30 mm); yield 512 g (68%).

The hydrochloride salt was formed in a mixture of 1:10 isopropyl alcohol:diisopropyl ether and recrystallized from acetonitrile, yield 87%, MP 124°C to 125°C.

References

Merck Index 7105
OCDS Vol. 1 p. 74 (1977)
I.N. p. 757
Biel, J.H.; US Patent 2,978,461; April 4, 1961; assigned to Lakeside Laboratories, Inc.

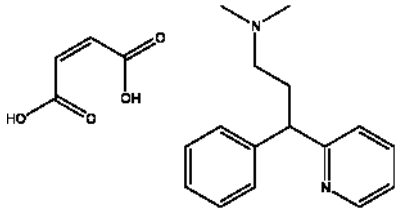
PHENIRAMINE MALEATE

Therapeutic Function: Antihistaminic

Chemical Name: N,N-Dimethyl-γ-phenyl-2-pyridine-propanamine maleate

Common Name: Prophenpyridine

Structural Formula:



Chemical Abstracts Registry No.: 132-20-7; 86-21-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Trimeton Maleate	Schering	US	1948
Avil	Albert Roussel	W. Germany	-
Citra Forte	Doyle	US	-
Daneral	Hoechst	UK	-
Dristan	Whitehall	US	-
Fenamine	Fawns and McAllan	Australia	-
Fiogesic	Sandoz	US	-
Inhiston	Upjohn	US	-
Poly-Histine	Bock	US	-
Ru-Tuss	Boots	US	-
S.T. Forte	Scot-Tussin	US	-
Triaminic	Dorsey	US	-
Tussirex	Scot-Tussin	US	-

Raw Materials

2-Benzylpyridine
β-Dimethylaminoethyl chloride
Potassium amide
Maleic acid

Manufacturing Process

According to US Patent 2,676,964: to 1.0 mol of potassium amide in 3 liters of liquid ammonia, is added 1.0 mol of 2-benzylpyridine. After 15 minutes, 1.1 mols of β-dimethylaminoethyl chloride are added. The ammonia is allowed to evaporate and the reaction product decomposed with water and ether extracted. The ether layer is dried over sodium sulfate and after evaporation the residue is distilled, giving the 3-phenyl-3-(2-pyridyl)-N,N-dimethylpropylamine, BP 139°-142°C/1-2 mm. The maleate is produced by reaction with maleic acid.

References

Merck Index 7106

Kleeman and Engel p. 713; PDR pp. 674, 688, 692, 849, 1583, 1662, 1899
OCDS Vol. 1 p. 77 (1977)
I.N. p. 757
REM p. 1131
Sperber, N., Papa, D. and Schwenk, E.; US Patent 2,567,245; September 11, 1951; assigned to Schering Corporation
Sperber, N., Papa, D. and Schwenk, E.; US Patent 2,676,964; April 27, 1954; assigned to Schering Corporation

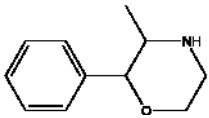
PHENMETRAZINE

Therapeutic Function: Antiobesity

Chemical Name: 3-Methyl-2-phenylmorpholine

Common Name: Oxazimdrine

Structural Formula:



Chemical Abstracts Registry No.: 134-49-6; 1707-14-8 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Preludin	Boehringer Ingelheim	US	1956
Anorex	Pfizer	US	-
Cafilon	Yamanouchi	Japan	-
Marsin	Ikapharm	Israel	-

Raw Materials

Bromopropiophenone
Hydrogen
Benzyl ethanolamine
Hydrogen chloride

Manufacturing Process

10 grams of β-phenyl-α-methyl-β,β'-dihydroxy-diethylamine hydrochloride (produced by hydrogenation in the presence of palladium and charcoal of β-phenyl-α-methyl-β-keto-β'-hydroxy-N-benzyl-diethylamine hydrochloride obtained from bromopropiophenone by reacting with benzyl-ethanolamine), are warmed with 10% hydrochloric acid for 6 hours on a water bath.

After working up in the usual manner, the hydrochloride of the 2-phenyl-3-methyl-morpholine crystallizes out from methanolic hydrochloric acid and acetone, MP = 182°C, according to US Patent 2,835,669.

References

Merck Index 7108
Kleeman and Engel p. 714
PDR p. 678
OCDS Vol. 1 p. 260 (1977)
I.N. p. 757
REM p. 892
Thoma, O.;US Patent 2,835,669; May 20, 1958; assigned to C.H. Boehringer Sohn, Germany
Siemer, H. and Hengen, O.; US Patent 3,018,222; January 23, 1962; assigned to Ravensberg GmbH, Germany

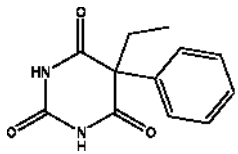
PHENOBARBITAL

Therapeutic Function: Anticonvulsant, Antiepileptic, Hypnotic, Sedative

Chemical Name: Barbituric acid, 5-ethyl-5-phenyl-

Common Name: Phenobarbital; Fenemal; Fenobarbital; Fenobarbiton; Phenylethylbarbituric acid

Structural Formula:



Chemical Abstracts Registry No.: 50-06-6

Trade Name	Manufacturer	Country	Year Introduced
Phenobarbital	Inter-Chemical Ltd.	-	-
Phenobarbital	Zxchem	-	-
Dormital	Acromax	-	-
Hypnogen	Fragner	-	-
Leonal	Leo	-	-
Noctinal	Faes	-	-
Sedabar	Saunders	-	-
Sednotic	Medical Arts	-	-
Sedo	Avicopharma	-	-
Sedonal	Assia	-	-

Raw Materials

Urea
Phenylethylmalonic diethyl ester
Sodium
Ethanol absolute
Sulfuric acid

Manufacturing Process

528 g phenylethyl malonic diethyl ester is dissolved in 500 ml of absolute alcohol. There is then added 140 g urea to the mixture. To this mixture is then added a solution of 57.5 g sodium in 1000 ml absolute alcohol, at such rate that one-half the solution is added during the first hour, a quarter the second hour; an eighth the third hour, and the final eighth during the 4 hours. Then the alcohol is distilled from the reaction mixture. When the alcohol has all been removed, 250 ml xylol is added to the mixture. The reaction mixture is cooled to room temperature and 3 L of water added. The xylene layer was separated and the water solution washed with another 200 ml portion of xylene There is then added to the water solution a 10% excess of a 50% by weight solution of sulfuric acid. The phenobarbital is precipitated as nearly white fluffy crystals, which are filtered off. When dried, they showed 100% phenobarbital by titration. This product may be purified by recrystallization. The unreacted ester in the xylene solution was recovered by distilling off the xylene, and then the phenylethyl malonic ester.

References

Inman M.T., Bitler W.P.; US Patent No. 2,358,072; Sept. 12, 1944; Assigned to Kay-Fries Chemicals, Inc., West Haverstraw, N.Y., a corporation of New York

PHENOPERIDINE HYDROCHLORIDE

Therapeutic Function: Analgesic

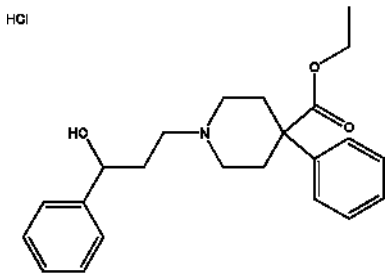
Chemical Name: 1-(3-Hydroxy-3-phenylpropyl)-4-phenyl-4-piperidinecarboxylic acid ethyl ester hydrochloride

Common Name: 3-(4-Carboethoxy-4-phenylpiperidino)-1-phenyl-1-propanol hydrochloride

Chemical Abstracts Registry No.: 3627-49-4; 562-26-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Operidine	Janssen	US	1965
Lealgin	Leo	Sweden	-
R-1406	Le Brun	France	-

Structural Formula:



Raw Materials

Hydrogen
Phenylacetonitrile
Benzoylethylene
Bis-chloroethyl toluene sulfonyl amide

Manufacturing Process

The starting materials for the overall process are phenylacetonitrile with bis-chloroethyl toluene sulfonyl amide. These react to give a product which hydrolyzes to normeperidine (4-carboethoxy-4-phenylpiperidine). Condensation of that material with benzoylethylene gives the ketone: β-(4-carboethoxy-4-phenylpiperidino)propiophenone.

A reaction mixture was prepared containing 4 grams of β-(4-carboethoxy-4-phenylpiperidino)-propiophenone hydrochloride, 100 ml of methanol and about 0.5 gram of platinum oxide catalyst. The mixture was placed in a low pressure hydrogenation apparatus and was hydrogenated at a temperature of about 27°C and a pressure of about 3.5 atmospheres of hydrogen to convert the keto group of the β-(4-carboethoxy-4-phenylpiperidino)-propiophenone to a hydroxy group, and to form 3-(4-carboethoxy-4-phenylpiperidino)-1-phenyl-1-propanol hydrochloride. After the hydrogenation was complete, the catalyst was separated from the reaction mixture by filtration, and the filtrate was evaporated to dryness in vacuo leaving a residue containing 3-(4-carboethoxy-4-phenylpiperidino)-1-phenyl-l-propanol hydrochloride. The residue was digested with ethyl acetate thereby causing 3-(4-carboethoxy-4-phenylpiperidino)-1-phenyl-1-propanol hydrochloride to crystallize. This compound melted at about 188°-189°C after being recrystallized three times from an ethyl acetate-methanol solvent mixture, according to US Patent 2,951,080.

References

Merck Index 7125
Kleeman and Engel p. 715
OCDS Vol. 1 p. 302 (1977)
I.N. p. 759
Pohland, A.; US Patent 2,951,080; August 30, 1960; assigned to Eli Lilly and Company

Cutler, F.A., Jr. and Fisher, J.F.; US Patent 2,962,501; November 29, 1960; assigned to Merck and Co., Inc.

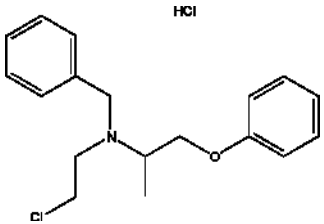
PHENOXYBENZAMINE HYDROCHLORIDE

Therapeutic Function: Adrenergic blocker

Chemical Name: N-(2-Chloroethyl)-N-(1-methyl-2-phenoxyethyl) benzenemethanamine hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 63-92-3; 59-96-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Dibenzyline	SKF	US	1953
Dibenzyran	Rohm Pharma	W. Germany	-

Raw Materials

1-Phenoxy-2-propanol
Ethanolamine
Hydrogen chloride
Thionyl chloride
Benzyl chloride

Manufacturing Process

Step 1: In a 500 ml flask equipped with gas inlet tube, dropping funnel and reflux condenser is placed 139 grams of 1-phenoxy-2-propanol. A stream of dry air is bubbled through the alcohol while 55 grams of thionyl chloride is added dropwise with external cooling. The stream of dry air is continued for about six hours or until most of the hydrogen chloride has been expelled and then another 55 grams of thionyl chloride is added. The reaction mixture is allowed to stand twenty-four hours, a few drops of pyridine are added and the mixture heated 4 hours on the steam bath. The cooled reaction mixture is poured into water, the crude product is washed with dilute sodium bicarbonate solution and finally taken up in benzene. The benzene is distilled at ordinary pressure and the residue distilled in vacuo to yield 60-70% of 1-phenoxy-2-chloropropane, BP 93°-94°C/5 mm.

Step 2: To 494 grams of ethanolamine, heated to approximately 150°C in a 500 ml flask equipped with stirrer, condenser and dropping funnel, is added 465 grams of 1-phenoxy-2-chloropropane with mechanical stirring. The reaction mixture is then heated to reflux for 3 hours, cooled and poured into a liter of water. The organic layer is extracted into ether and the ether solution is extracted with dilute hydrochloric acid. The aqueous acid solution is then made alkaline with 40% sodium hydroxide solution and the organic base is extracted into ether. Removal of the ether leaves N-(phenoxyisopropyl)-ethanolamine which, after recrystallization from hexane, melts at 70.5°-72°C.

Step 3: To 43 grams of N-(phenoxyisopropyl)ethanolamine dissolved in 500 ml of alcohol in a 1,000 ml flask equipped with stirrer and condenser is added 28 grams of benzyl chloride and 18.5 grams of sodium bicarbonate. The mixture is stirred and refluxed for 10 hours and then approximately half the alcohol is removed by distillation. The remaining solution is poured into 500 ml of water and the organic material extracted with 3 100-ml portions of ether. The combined ether extracts are washed with water, dried over anhydrous potassium carbonate and filtered. After removal of the ether, the residue is distilled in vacuo to yield N-(phenoxyisopropyl)-N-benzylethanolamine, BP 163°-168°C/0.2 mm.

Step 4: A solution of 20 grams of the above amino alcohol is dissolved in 50 ml of dry chloroform and treated with dry hydrogen chloride until acid. Then a solution of 9 grams of thionyl chloride in 50 ml of dry chloroform is added and the reaction mixture is heated on a water bath at 50°-60°C for 2 hours. Most of the chloroform is removed by distillation under reduced pressure. Addition of ether to the residue causes the product to crystallize. After recrystallization from a mixture of alcohol and ether, the N-(phenoxyisopropyl)-N-benzyl-β-chloroethylamine hydrochloride melts at 137.5°-140°C.

References

Merck Index 7134
Kleeman and Engel p. 716
PDR p. 1713
OCDS Vol. 1 p. 55 (1977)
I.N. p. 760
REM p. 905
Kerwin, J.F. and Ullyot, G.E.; US Patent 2,599,000; June 3, 1952; assigned to Smith, Kline and French Laboratories

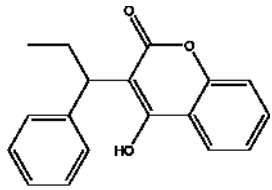
PHENPROCOUMON

Therapeutic Function: Anticoagulant

Chemical Name: 4-Hydroxy-3-(1-phenylpropyl)-2H-1-benzopyran-2-one

Common Name: 3-(1-Phenylpropyl)-4-hydroxycoumarin

Structural Formula:



Chemical Abstracts Registry No.: 435-97-2

Trade Name	Manufacturer	Country	Year Introduced
Liquamar	Organon	US	1958
Falithrom	Fahlberg-List	E. Germany	-
Fencumar	Medica	Finland	-
Marcumar	Roche	W. Germany	-

Raw Materials

Methanol
Sodium
Sodium hydroxide
Diethyl-(1'-phenylpropyl)malonate
Acetylsalicylic acid chloride

Manufacturing Process

8.3 parts by weight of powdered sodium in 300 parts by volume of benzene, 100 parts by weight of diethyl (1'-phenylpropyl)-malonate and 72 parts by weight of acetylsalicylic acid chloride are reacted together to form diethyl 1-(o-acetoxybenzoy1)-1-(1'-phenylpropyl)malonate, which boils at 195°-198°C/0.03 mm Hg.

10.3 parts of weight of diethyl 1-(o-acetoxybenzoyl)-1-(1'-phenylpropyl)-malonate are dissolved in 60 parts by volume of absolute ether and to this solution are added portion. wise at 10°C, while stirring, 2.6 parts by weight of sodium methylate. The reaction mixture is stirred for 4 hours, whereupon it is poured into ice water. The ether solution is washed neutral with ice water. After having distilled off the ether, a thick oil consisting of 3-carbethoxy-3-(1'-phenylpropyl)-4-oxo-dihydrocoumarinis obtained. This compound crystallized in butyl oxide and has a MP of 108°-109°C.

The 3-carbethoxy-3-(1'-phenylpropyl)-4-oxo-dihydrocoumarinmay be hydrolyzed and decarboxylated as follows. The crude product is heated to 85°C for 1/2 hour with 100 parts by volume of 5% aqueous sodium hydroxide, while agitating or stirring. To remove traces of undissolved oil, the cooled solution is treated with 1 part by weight of charcoal, whereupon it is filtrated and acidified to Congo reaction with dilute sulfuric acid. The 3-(1'-phenylpropyl)-4-hydroxycoumarin formed is separated off and recrystallized in 80% ethanol, whereupon it melts at 178°-179°C according to US Patent 2,701,804.

References

Merck Index 7139
Kleeman and Engel p. 718
I.N. p. 761
REM p. 827
Hegedus, B. and Grussner, A.; US Patent 2,701,804; February 8, 1955; assigned to Hoffmann-La Roche Inc.
Schroeder, C.H. and Link, K.P.; US Patent 2,872,457; February 3, 1959; assigned to Wisconsin Alumni Research Foundation
Preis, S., West, B.D. and Link, K.P.; US Patent 3,239,529: March 8, 1966; assigned to Wisconsin Alumni Research Foundation

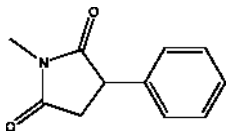
PHENSUXIMIDE

Therapeutic Function: Anticonvulsant

Chemical Name: 1-Methyl-3-phenyl-2,5-pyrrolidinedione

Common Name: N-Methyl-α-phenylsuccinimide

Structural Formula:



Chemical Abstracts Registry No.: 86-34-0

Trade Name	Manufacturer	Country	Year Introduced
Milontin	Parke Davis	US	1953
Lifene	Debat	France	-
Petimid	Dincel	Turkey	-
Succitimal	Katwijk	Netherlands	-

Raw Materials

Phenylsuccinic anhydride
Methyl amine
Acetyl chloride

Manufacturing Process

10 grams of phenylsuccinic anhydride is dissolved in 250 ml of absolute ether and the solution is treated with dry methylamine until a precipitate ceases to form. After standing for ½ hour the ether is decanted off and the residue is

washed with 40 ml of water by decantation. The mixture is filtered and the precipitate washed with 10 ml of water. By acidification of the filtrate, a white precipitate is obtained. After drying it weighs 8 grams and melts at 136°-140°C. The two precipitates are combined and recrystallized from aqueous alcohol to give β-N-methylphenylsuccinamic acid which melts at 158°-160°C.

9 grams of β-N-methylphenylsuccinamic acid and 200 ml of acetyl chloride are heated together on a steam bath for ½ hour. The excess acetyl chloride is removed by distillation and 50 ml of water are added to the thick residue. After allowing for hydrolysis of the excess acetyl chloride the water is decanted and the yellow residue dissolved in 75 ml of ether. The resulting solution is treated with charcoal twice and dried over anhydrous magnesium sulfate. On partial evaporation of the ether a white solid precipitates. There is obtained 4 grams of N-methyl-α-phenylsuccinimide which melts at 71°-73°C.

References

Merck Index 7140
Kleeman and Engel p. 718
PDR p. 1367
OCDS Vol. 1 p. 226 (1977)
I.N. p. 762
REM p. 1080
Miller, C.A. and Long, L.M.; US Patent 2,643,258; June 23, 1953; assigned to Parke, Davis and Company

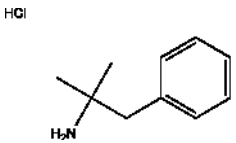
PHENTERMINE HYDROCHLORIDE

Therapeutic Function: Antiobesity

Chemical Name: α,α-Dimethylbenzeneethanamine hydrochloride

Common Name: α-Benzylisopropylamine hydrochloride; Phenyl-tert-butylamine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 1197-21-3; 122-09-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Wilpo	Dorsey	US	1961
Linyl	Roussel	France	1962
Fastin	Beecham	US	1973

Trade Name	Manufacturer	Country	Year Introduced
Adipex-P	Lemmon	US	1976
Ona Mast	Mast	US	1980
Obestin	Ferndale	US	1980
Oby-Trim	Rexar	US	1982
Duromine	Riker	UK	-
Ex-Adipos	Eurand	Italy	-
Ionamin	Pennwalt	UK	-
Jonakraft	Kraft Pharm	US	-
Lipopil	Roussel Maestretti	Italy	-
Minobese	Restan	S. Africa	-
Mirapront	Bracco	Italy	-
Netto-Longcaps	Heyden	W. Germany	-
Panbesy	Asperal	Belgium	-
Panshade	Pan American	US	-
Parmine	Parmed	US	-
Phentermine	Schein	US	-
Phentermyl	Diethelm	W. Germany	-
Regulin	Kwizda	Austria	-
Span R/D	Metro Med	US	-
Teramine	Legere	US	-

Raw Materials

Isobutyryl chloride
Ammonia
Hydrogen chloride
Bromine
Calcium hydroxide
Sodium
Benzyl bromide
Benzene
Potassium hydroxide

Manufacturing Process

Preparation of isobutyrophenone: In a 12 liter, 3-necked flask, 1,280 grams of aluminum chloride was covered with 2,000 cc of dry thiophene-free benzene and a solution of 919 grams of isobutyryl chloride, (BP 92°-94°C) in 1 liter of benzene was added slowly with stirring. After heating for 3 hours at reflux, the solution was cooled and poured over a mixture of 1 liter of concentrated hydrochloric acid and 5 kg of ice. The benzene layer was separated, the aqueous layer extracted with benzene, and the combined benzene solutions were washed, dried and concentrated in vacuo. The residue was distilled rapidly to give 1,051 grams of isobutyrophenone, boiling at 81°-89°C at 1 mm, yield 83.4%.

Preparation of 1,3-Diphenyl-2,2-Dimethylpropanone-1: Sodamide was prepared from 12.5 grams of sodium added in small portions to 600 cc of liquid ammonia with 1 gram of hydrous ferric chloride as catalyst. The ammonia was replaced by 200 cc of dry toluene and without delay a solution of 74 grams of isobutyrophenone and 76.5 grams of benzyl bromide in 200 cc of benzene was slowly added with stirring. The reaction mixture was heated on a boiling water bath for 48 hours. Water was then added, the organic layer separated and the product isolated by distillation. The 1,3-diphenyl-2,2-

dimethylpropanone-1 boiled from 142°-143°C at a pressure of 3 mm, n_D^{20}1.5652.

Preparation of α,α-Dimethyl-β-Phenylpropionamide: Sodamide was prepared from 7.6 grams of sodium in 350 cc of liquid ammonia with 0.9 gram of hydrous ferric chloride. The ammonia was replaced by 250 cc of toluene, the mixture was heated to 60°C and 71.4 grams of 1,3-diphenyl-2,2-dimethyl propanone-1 dissolved in 150 cc of toluene was added. The mixture was stirred and heated on a steam bath for 5 hours. A clear red color appeared in 15 minutes and disappeared after about an hour. After cooling, water was added, the organic layer was washed, dried, and concentrated to give 36.5 grams of α,α-dimethyl-β-phenyl propionamide which crystallized slowly after the addition of an equal volume of petroleum ether. The product melted at 62°C after crystallization from benzene-petroleum ether.

Preparation of Di-(β-Phenyl-α,α-Dimethylethyl)Urea: 3.5 grams of α,α-dimethyl-β-phenylpropionamide in 420 cc of water was added to a solution of 87.5 grams of potassium hydroxide and 35 grams of bromine in 350 cc of water. After 2 hours at 60°C, the product was obtained on crystallization from ethanol, melting at 184°C.

Preparation of ω-Phenyl-tert-Butylamine: 24 grams of the urea derivative obtained as indicated above, were well mixed with 96 grams of calcium hydroxide in a flask immersed in an air bath and provided with a dropping funnel the stem of which reached the bottom of the flask. The mixture was heated to 240°-260°C (inside temperature) for 7 hours during which time 86 cc of water was slowly added. The vapors were collected in a receiver cooled with ice. After extraction with ether and distillation, the product was obtained as a colorless liquid boiling from 80°-84°C at 9 mm according to US Patent 2,590,079.

The ether solution may be dried and saturated with hydrogen chloride and the precipitated hydrochloride recrystallized from a mixture of 50 parts alcohol and 100 parts of acetone.

The pure hydrochloride is thus obtained as a white crystalline substance having a MP of 195°-196°C, according to US Patent 2,408,345.

References

Merck Index 7141
Kleeman and Engel p. 719
PDR pp. 660, 1033, 1034, 1246, 1450, 1606, 1999
OCDS Vol. 1 p. 72 (1977)
I.N. p. 762
REM p. 892
Shelton, R.S. and Van Campen, M.G., Jr.; US Patent 2,408,345; September 24, 1946; assigned to The Wm. S. Merrell Company
Abell, L.L., Bruce, W.F. and Seifter, J.; US Patent 2,590,079; March 25, 1952; assigned to Wyeth Incorporated

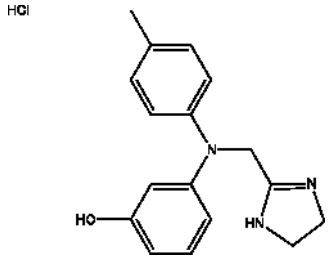
PHENTOLAMINE HYDROCHLORIDE

Therapeutic Function: Adrenergic blocker

Chemical Name: 3-[[(4,5-Dihydro-1H-imidazol-2-yl)methyl](4-methylphenyl) amino]phenol hydrochloride

Common Name: 2-(m-Hydroxy-N-p-tolylanilinomethyl)-2-imidazoline hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 73-05-2; 50-60-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Regitine	Ciba	US	1952
Regitine	Ciba Geigy	Japan	-
Regitine	Ciba	UK	-

Raw Materials

Hydrogen chloride
N-(p-Methylphenyl)-m'-hydroxyphenylamine
2-Chloromethylimidazoline HCl

Manufacturing Process

199.24 parts of N-(p-methylphenyl)-m'-hydroxyphenylamine and 77.52 parts of 2-chloromethylimidazoline hydrochloride are heated for sixteen hours in an oil bath having a temperature of 150°C, while stirring and introducing a current of nitrogen. The viscous contents of the flask are then cooled to about 100°C, mixed with 400 parts by volume of hot water, and stirred for a short time.

After further cooling to about 60°C, 200 parts by volume of water and 500 parts by volume of ethyl acetate at 60°C are added, and the aqueous layer is separated. The excess of starting material may be recovered from the ethyl acetate.

The aqueous portion is chilled in a cooling chamber at -10°C, whereupon the

hydrochloride of 2-[N-(p-methylphenyl)-N-(m'-hydroxyphenyl)-aminomethyl]-imidazoline crystallizes. Upon being concentrated and cooled the mother liquor yields a further quantity of the hydrochloride. The combined quantities of hydrochloride are treated with a small quantity of cold water, dried with care, and washed with ethyl acetate. The product is then crystallized from a mixture of alcohol and ethyl acetate, and there is obtained a hydrochloride melting at 239°-240°C.

References

Merck Index 7143
Kleeman and Engel p. 719
PDR p. 809
OCDS Vol. 1 p. 242 (1977)
I.N. p. 762
REM p. 906
Miescher, K., Marxer, A. and Urech, E.; US Patent 2,503,059; April 4, 1950; assigned to Ciba Pharmaceutical Products, Inc.

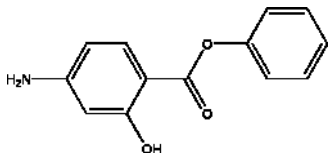
PHENYL AMINOSALICYLATE

Therapeutic Function: Antibacterial (tuberculostatic)

Chemical Name: 4-Amino-2-hydroxybenzoic acid phenyl ester

Common Name: Fenamisal

Structural Formula:



Chemical Abstracts Registry No.: 133-11-9

Trade Name	Manufacturer	Country	Year Introduced
Pheny-Pas-Teb-Amin	Purdue Frederick	US	1959
Fenil-PAS	Farmabion	Spain	-

Raw Materials

p-Nitrosalicylic acid
Phosphorus oxychloride
Phenol
Hydrogen

Manufacturing Process

183 g of p-nitrosalicylic acid are dissolved in 564 g of phenol by heating to 140°C to 150°C on an oil bath. When all the p-nitrosalicylic acid is dissolved, 153 g of phosphorus oxychloride are run in, drop by drop, over a period of about 2 hours, while maintaining the temperature at about 150°C. The still warm mixture is run into 2 liters of water with agitation. The precipitate formed is filtered off, washed with water until phenol is removed and then dried.

There are thus obtained 250 g of 2-hydroxy-4-nitrophenylbenzoate which melts at 154°C to 155°C.

In a hydrogenation autoclave are introduced 92 g of 2-hydroxy-4-nitrophenylbenzoate preceded by 200 cc of ethyl acetate; Raney nickel, obtained from 30 g of alloy, is added with 300 cc of ethyl acetate. Hydrogenation under pressure (100 to 120 kg) at ordinary temperature is carried out during a period of about 12 hours. The nickel is filtered off and the ethyl acetate is removed by distillation on the water bath under a vacuum of 300 mm. There is thus obtained 80 g of crude damp 2-hydroxy-4-amnophenylbenzoate which after recrystallization from isopropyl alcohol melts at 153°C.

References

Merck Index 7151
OCDS Vol. 2 p. 89 (1980)
I.N. p. 415
Freire, SA.; US Patent 2,604,488; July 22, 1952; assigned to Soc. des Usines Chimiques Rhone-Poulenc (France)

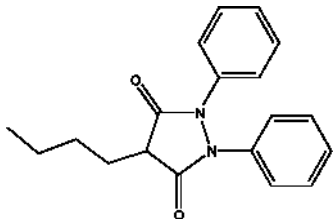
PHENYLBUTAZONE

Therapeutic Function: Antiinflammatory, Antiarthritic

Chemical Name: 4-Butyl-1,2-diphenyl-3,5-pyrazolidinedione

Common Name: 3,5-Dioxo-1,2-diphenyl-4-n-butylpyrazolidine

Structural Formula:



Chemical Abstracts Registry No.: 50-33-9

Trade Name	Manufacturer	Country	Year Introduced
Butazolidin	Geigy	US	1952
Butazolidin	Ciba Geigy	France	1954
Azolid	U.S.V. Pharm.	US	1971
Acrizeal	S.S. Pharm	Japan	-
Alkabutazona	Lovens	Denmark	-
Anuspiramin	Farbios	Spain	-
Artropan	Polifarma	Italy	-
Bulentin	Sanwa	Japan	-
Butacal	Langley	Australia	-
Butacote	Geigy	UK	-
Butadion	Streuli	Switz.	-
Butadiona	Miquel	Spain	-
Butadyne	Bio-Chimique	Canada	-
Butalan	Lancet	Australia	-
Butalgin	Fawns and McAllan	Australia	-
Butalgina	Esteve	Spain	-
Butaluy	Miluy	Spain	-
Butaphen	Mulda	Turkey	-
Butapirazol	Polfa	Poland	-
Butarex	Adams	Australia	-
Butartril	Chiesi	Italy	-
Butazina	Vis	Italy	-
Butazone	DDSA	UK	-
Butiwas Simple	Wassermann	Spain	-
Butoroid	Virax	Australia	-
Butrex	SCS Pharmalab	S. Africa	-
Carudol	Lab. Franc. Therap.	France	-
Chembuzone	Chemo-Drug	Canada	-
Demoplas	Adenylchemie	W. Germany	-
Digibutina	Bicsa	Spain	-
Diossidone	Eliovit	Italy	-
Ecobutazone	I.C.N.	Canada	-
Elmedal	Thiemann	W. Germany	-
Equi Bute	Fort Dodge Labs	US	-
Eributazone	Eri	Canada	-
Fenibutasan	Santos	Spain	-
Fenibutol	Atral	Portugal	-
Flexazone	Berk	UK	-
IA-But	Inter-Alia Pharm.	UK	-
Intalbut	Inter-Alia Pharm.	UK	-
Kadol	Midy	Italy	-
Merizone	Meriot	Canada	-
Neo-Zoline	Neo	Canada	-
Neuplus	Toyo	Japan	-
Novobutazone	Novopharm	Canada	-
Novophenyl	Novopharm	Canada	-

Trade Name	Manufacturer	Country	Year Introduced
Panazone	Propan-Lipworth	S. Africa	-
Phenbutazol	Smallwood	Canada	-
Phenyl Betazone	Barlow Cote	Canada	-
Phenylone	Medic	Canada	-
Pilazon	Kobayashi	Japan	-
Pirarreumol	Hermes	Spain	-
Praecirheumin	Pfleger	W. Germany	-
Rectofasa	Lifasa	Spain	-
Reumasyl	Leiras	Finland	-
Reumazin	Mohan	Japan	-
Reumuzol	Farmos	Finland	-
Reupolar	Farmos	Finland	-
Rheumaphen	Reiss	W. Germany	-
Schemergen	Azusa	Japan	-
Sedazole	Toho	Japan	-
Servizolidin	Servipharm	Switz.	-
Shigrodin	Ikapharm	Israel	-
Spondyril	Dorsch	W. Germany	-
Tetnor	Drugs, Ltd.	UK	-
Tevcodyne	Tevcon	US	-
Therazone	Western Serum	US	-
Ticinil	De Angeli	Italy	-
Todalgil	Lopez-Brea	Spain	-
Tokugen	Sawai	Japan	-
Uzone	Kempthorne Prosser	New Zealand	-
Wescozone	Saunders	Canada	-
Zolidinium	Kwizda	Austria	-

Raw Materials

Hydrazobenzene
Diethyl-n-butyl malonate
Sodium
Ethanol

Manufacturing Process

7.6 parts of sodium are dissolved in 190 parts by volume of absolute alcohol; 65 parts of diethyl-n-butyl malonate and 65 parts of hydrazobenzene are added. The alcohol is slowly distilled off and the reaction mixture heated for 12 hours at a bath temperature of 150°C and finally in vacuo, until no more alcohol comes off.

The product is dissolved in water, clarified with a little animal charcoal and 15% hydrochloric acid is slowly added until an acid reaction to Congo red paper is produced. 1,2-Diphenyl-3,5-dioxo-4-n-butyl-pyrazolidine separates as an oil, which rapidly become crystalline. It crystallizes from alcohol as colorless needles with a MP of 105°C.

References

Merck Index 7157
Kleeman and Engel p. 720
PDR pp. 830, 891, 1606, 1999
OCDS Vol. 1 p. 236 (1977) and 2, 388, 474 (1980)
I.N. p. 763
REM p. 1120
Stenzl, H.; US Patent 2,562,830; July 31, 1951; assigned to J.R. Geigy AG, Switzerland

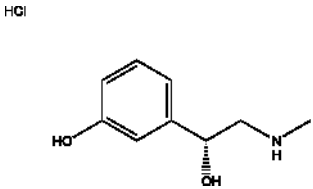
PHENYLEPHRINE HYDROCHLORIDE

Therapeutic Function: Adrenergic

Chemical Name: (R)-3-Hydroxy-α-[(methylamino)methyl]benzenemethanol hydrochloride

Common Name: m-Methylaminoethanolphenol hydrochloride; Metaoxedrin

Structural Formula:



Chemical Abstracts Registry No.: 61-76-7

Trade Name	Manufacturer	Country	Year Introduced
Neosynephrine	Badrial	France	1953
Mydfrin	Alcon	US	1979
Nostril	Boehringer Ingelheim	US	1982
Adrianol	Anasco	W. Germany	-
Atrohist	Adams	US	-
Bromphen	Schein	US	-
Codimal	Central	US	-
Comhist	Norwich Eaton	US	-
Congespirin	Bristol-Myers	US	-
Coryban	Pfipharmecs	US	-
Dallergy	Laser	US	-
Deconsal	Adams	US	-
Decontabs	Zenith	US	-
Degest	Barnes Hind	US	-
Derizene	Hollister-Stier	US	-

Trade Name	Manufacturer	Country	Year Introduced
Donatussin	Laser	US	-
Dristan	Whitehall	US	-
Dura-Vent	Dura	US	-
E.N.T.	Springbok	US	-
Entex	Norwich Eaton	US	-
Extendryl	Fleming	US	-
Fenilfar	Farmila	Italy	-
Histalet	Reid-Rowell	US	-
Histamic	Metro Med	US	-
Histaspan	U.S.V. Pharm.	US	-
Histor	Hauck	US	-
Hycomine	Du Pont	US	-
Isonefrine	Tubi Lux Pharma	Italy	-
Isophrine	Broemmel	US	-
Isotropina	Tubi Lux Pharma	W. Germany	-
Korigesic	Trimen	US	-
Matafa-Lind	Anasco	US	-
Naldecon	Bristol	Spain	-
Nasophen	Premo	US	-
Neosinefrina	Reunidos	US	-
Newphrine	Vitarine	US	-
Nostril	Boehringer Ingelheim	US	-
Pediacof	Winthrop-Breon	US	-
Phenergan	Wyeth	US	-
Protid	La Salk	US	-
PV-Tussin	Reid-Rowell	US	-
Quelidrine	Abbott	US	-
Rinisol	Farmos	Finland	-
Ru-Tuss	Boots	US	-
Singlet	Lakeside	US	-
S-T Forte	Scot-Tussin	US	-
Synasal	Texas Pharm	US	-
Tear-Efrin	Tilden Yates	US	-
Tussar	U.S.V. Pharm.	US	-
Tussirex	Scot-Tussin	US	-
Tympagesic	Adria	US	-
Visopt	Sigma	Australia	-
Zeph	Scott and Turner	Australia	-

Raw Materials

Hydrogen
m-Hydroxymethylaminoacetophenone
Hydrogen chloride

Manufacturing Process

4.5 g of the hydrochloride of m-hydroxymethylaminoacetophenone are

dissolved in a small amount of water; to the solution a solution of colloidal palladium obtained from palladiumchloride is added, and the mixture is treated with hydrogen.

After diluting the reaction liquid with acetone it is filtered, and the residue obtained after the evaporation of the filtrate in vacuo, and complete drying over pentoxide of phosphorus is then dissolved in absolute alcohol, and to this is added about the same volume of dry ether, until turbidity just commences to occur. After a short time the hydrochloride of the m-hydroxyphenylethanol-methylamine will separate out as a colorless mass of crystals at a melting point of 142°C to 143°C.

References

Merck Index 7167
PDR pp. 555, 562, 570, 677, 688, 701, 727, 784, 855, 865, 880, 928, 991, 1246, 1272, 1276, 1404, 1447, 1606, 1662, 1735, 1807, 1813, 1824, 1899, 1923, 1973, 1999
OCDS Vol. 1 p. 63 (1977); 2, 265 (1980) and 3, 20 (1984)
I.N. p. 764
REM p. 889
Legerlotz, H.; US Patent 1,932,347; October 24, 1933; assigned to Frederick Stearns and Co.

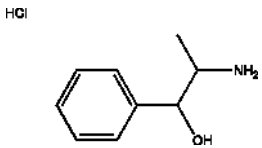
PHENYLPROPANOLAMINE HYDROCHLORIDE

Therapeutic Function: Nasal decongestant, Anorexic

Chemical Name: α-(1-Aminoethyl)benzenemethanol hydrochloride

Common Name: dl-Norephedrine hydrochloride; 2-Amino-1-phenyl-1-propanol hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 154-41-6; 14838-15-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Propadrine	MSD	US	1941
Dexatrim	Thompson	US	1980
Dietac	Menley and James	US	1980
Obestat	Lemmon	US	1980
Permatrim	Lee	US	1980

Trade Name	Manufacturer	Country	Year Introduced
Nobese	O'Neal Jones	US	1981
Dexatrim Extra	Thompson	US	1981
Propagest	Carnrick	US	1982
Acutr im	Ciba Geigy	US	1983
Help	Verex	US	1983
Appedrine	Thompson	US	-
Bromphen	Schein	US	-
Codimal	Central	US	-
Comtrex	Bristol-Myers	US	-
Congespirin	Bristol-Myers	US	-
Control	Thompson	US	-
Corvban-D	Pfipharmecs	US	-
Co-Tylenol	McNeil	US	-
Cremacoat	Vicks	US	-
Decontabs	Zenith	US	-
Dietrim	Legere	US	-
Dimetane-D.C.	Robins	US	-
Dura Vent	Dura	US	-
E.N.T.	Springbok	US	-
Entex	Norwich Eaton	US	-
Fiogesic	Sandoz	US	-
Head and Chest	Procter and Gamble	US	-
Histaminic	Metro Med	US	-
Hycomine	Du Pont	US	-
Korigesic	Trimen	US	-
Kronohist	Ferndale	US	-
Monydrin	Draco	Sweden	-
Naldecon	Bristol	US	-
Nolamine	Carnrick	US	-
Ornade	SKF	US	-
Poly-Histine	Bock	US	-
Prolamine	Thompson	US	-
Rhindecon	McGregor	US	-
Rhinolar	McGregor	US	-
Ru-Tuss	Boots	US	-
Sinubid	Parke Davis	US	-
Sinulin	Carnrick	US	-
Tinaroc	Remeda	Finland	-
Triaminic	Dorsey	US	-
Tuss-Ornade	SKF	US	-

Raw Materials

Benzaldehyde
Nitroethane
Sodium bisulfite
Hydrogen
Hydrogen chloride

Manufacturing Process

In one route as described in US Patent 2,151,517, 10.7 kg of technical benzaldehyde is vigorously agitated with a solution of 11.0 kg of sodium bisulfite in 50.0 liters of water until the formation of the addition-product is complete. Simultaneously, 8.25 kg of nitroethane is dissolved in a solution of 4.5 kg of caustic soda in 20.0 liters of water and the resultant warm solution is added with vigorous stirring to the magma of benzaldehyde sodium bisulfite. The mixture is agitated for 30 minutes and then allowed to stand overnight.

The aqueous portion of the mixture is now siphoned off from the supernatant layer of oily phenylnitropropanol and replaced with a fresh solution of 11.0 kg of sodium bisulfite in 50.0 liters of water. The mixture of phenylnitropropanol and bisulfite solution is now vigorously agitated for 15 minutes in order to remove and recover small amounts of unreacted benzaldehyde, and is then again allowed to stratify. This time, the phenylnitropropanol is siphoned off and filtered to remove a small amount of resinous material. The aqueous solution of sodium bisulfite remaining behind is reacted with benzaldehyde, as described above, thus making the process continuous.

The 1-phenyl-2-nitropropanol thus obtained is a colorless oil, specific gravity 1.14 at 20°C, odorless when pure, volatile with steam and boiling at 150° to 165°C under a pressure of 5 mm of mercury. It is soluble in alcohol, ether, acetone, chloroform, carbon tetrachloride, benzene and glacial acetic acid. The yield of 1-phenyl-2-nitropropanolobtained by this procedure is 17.1 to 17.7 kg.

It is hydrogenated and converted to the hydrochloride in subsequent steps. The hydrogen chloride has a melting point of 192°-194°C.

In an alternative route described in US Patent 3,028,429 propiophenone may be reacted with an alkyl nitrite to give isonitrosopropiophenone which is then hydrogenated and finally converted to the hydrochloride.

References

Merck Index 7189
Kleeman and Engel p. 721
PDR pp. 674, 688, 702, 727, 781, 784, 850, 854, 865, 875, 1033, 1084, 1246, 1277, 1388, 1404, 1431, 1454, 1583, 1606, 1719, 1730, 1735, 1805, 1807, 1869, 1999
I.N. p. 766
REM p. 889
Kamlet, J.; US Patent 2,151,517 March 21, 1939
Wilbert, G. and Sosis, P.; US Patent3,028,429; April 3, 1962; assigned to Nepera Chemical Co., Inc.

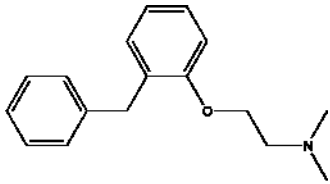
PHENYLTOLOXAMINE

Therapeutic Function: Antihistaminic

Chemical Name: N,N-Dimethyl-2-[2-(phenylmethyl)phenoxy]ethanamine

Common Name: Bistrimin

Structural Formula:



Chemical Abstracts Registry No.: 92-12-6; 6152-43-8 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Bristalin	Bristol	US	1952
Bristamine	Banyu	Japan	-
Codipront	Mack	W. Germany	-
Ephepect	Bolder	W. Germany	-
Floxamine	Durst	US	-
Fluidol	Metadier-Tours	France	-
Histionex	Strasenburgh	US	-
Netux	Roussel	France	-
Pholtex	Riker	UK	-
Quadrahist	Schein	US	-
Rinurel	Warner	UK	-
Tussionex	Pennwalt	US	-

Raw Materials

o-Benzylphenol
Methanol
Sodium
Dimethylaminoethyl chloride

Manufacturing Process

Sodium methylate is made by dropping 11.7 g of sodium strips into 199 ml of absolute methanol in a 1-liter three-necked flask. 93.9 g of o-benzylphenol are dissolved in 200 ml of dry toluene and added to the sodium methylate solution. The solution is distilled until the boiling point of toluene is reached. At the end of the distillation, enough toluene is added to restore the original volume of solvent.

109.5 g of dimethylaminoethyl chloride hydrochloride and 200 ml of toluene are placed in a 1-liter Erlenmeyer flask, cooled in an ice bath, and decomposed with 167.5 g of 20% sodium hydroxide solution. The toluene and water layers are separated, and the water layer is extracted again with 50 ml of toluene. The toluene layers are combined, washed with saturated salt solution, and dried over anhydrous potassium carbonate.

The dried dimethylaminoethyl chloride solution is poured into the toluene solution of the sodium salt of o-benzylphenol, heated to reflux, and refluxed 16 hours. After refluxing, enough water is added to the mixture to dissolve the precipitated solid. The layers are separated, and the toluene layer is further washed with water until the water extract is just slightly alkaline. The toluene solution is then made acid with 6N hydrochloric acid and extracted with water until no cloudiness is produced when the extract is made alkaline. The acidic aqueous extract is washed with ether, then made alkaline with 20% sodium hydroxide solution, and extracted into ether. The ether solution is washed several times with water, then with saturated salt solution, and is dried over anhydrous potassium carbonate. The dried solution is filtered and distilled. The product distills at 143.5°C/1 mm; 69.7 g of pale yellow oil are recovered.

57.1 g of the free base are dissolved in ether and precipitated with dry HCl. 66.0 g of crude hydrochloride are recovered. The hydrochloride is dissolved in 130 ml of reagent acetone by boiling, filtered hot, and allowed to cool. The crystalline material obtained on cooling is filtered, washed with a little acetone, washed with ether, and dried in vacuo. 44.8 g, MP 119.5°C to 121°C, are recovered from the first crop of crystals. Ethyl acetate may also be used as the solvent for recrystallization.

References

Merck Index 7197
Kleeman and Engel p. 721
PDR p. 1606
OCDS Vol. 1 p. 115 (1977);
I.N. p. 766
Binkley, S.B. and Cheney, L.C.; US Patent 2,703,324; March 1, 1955; assigned to Bristol Laboratories, Inc.

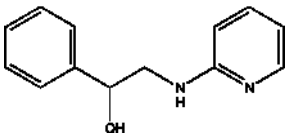
PHENYRAMIDOL

Therapeutic Function: Analgesic, Muscle relaxant

Chemical Name: α-[(2-Pyridinylamino)methyl]benzenemethanol

Common Name: Fenyramidol

Structural Formula:



Chemical Abstracts Registry No.: 553-69-5; 326-43-2 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Analexin	Mallinckrodt Inc.	US	1960
Cabral	Kali-Chemie	W. Germany	1962
Fenprin	RBS	Italy	1962
Anabloc	Irbi	Italy	-
Aramidol	A.B.C.	Italy	-
Bonapar	Minerva-Chemie	Netherlands	-
Evasprine	Millot	France	-
Firmalgil	Firma	Italy	-
Miodar	I.S.M.	Italy	-
Pheniramidol	Pulitzer	Italy	-
Vilexin	Vitrum	Sweden	-

Raw Materials

2-Aminopyridine
Lithium amide
Styrene oxide

Manufacturing Process

A mixture containing 188 g (0.20 mol) of 2-arninopyridine, 0.55 g of lithium amide and 75 cc of anhydrous toluene was refluxed for 1.5 hours. Styrene oxide (12.0 g = 0.10 mol) was then added to the reaction mixture with stirring over a period of ten minutes. The reaction mixture was stirred and refluxed for an additional 3.5 hours. A crystalline precipitate was formed during the reaction which was removed by filtration, MP 170°C to 171°C. 1.5 g. The filtrate was concentrated to dryness and a dark residue remained which was crystallized from anhydrous ether; yield 6.0 g. Upon recrystallization of the crude solid from 30 cc of isopropyl alcohol, 2.0 g of a light yellow solid was isolated; MP 170° to 171°C.

References

Merck Index 7203
Kleeman and Engel p. 399
OCDS Vol. 1 p. 165 (1977)
I.N. p. 422
Biel, J.H.; US Patent 3,040,050; June 19, 1962; assigned to Lakeside Laboratories, Inc.

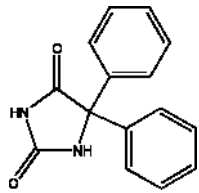
PHENYTOIN

Therapeutic Function: Antiepileptic

Chemical Name: 5,5-Diphenyl-2,4-imidazolidinedione

Common Name: Diphenylhydantoin

Structural Formula:



Chemical Abstracts Registry No.: 57-41-0

Trade Name	Manufacturer	Country	Year Introduced
Dilantin	Parke Davis	US	1938
Ditan	Mallard	US	1980
Aleviatin	Dainippon	Japan	-
Citrullamon	Sudmedica	W. Germany	-
Didan	Canfield	US	-
Difhydan	Leo	Sweden	-
Dihydan	Carrion	France	-
Dihydantoin	Orion	Finland	-
Dintoina	Recordati	Italy	-
Diphentyn	I.C.N.	Canada	-
Enkefal	Leiras	Turkey	-
Epanutin	Parke Davis	W. Germany	-
Epinat	Nyegaard	Norway	-
Fenantoin	A.C.O.	Sweden	-
Hydantin	Medica	Finland	-
Hydantol	Fujinaga	Japan	-
Lehydan	Leo	Sweden	-
Novophenytoin	Novopharm	Canada	-
Phenhydan	Desitin	W. Germany	-
Pyoredol	Roussel	France	-
Solantyl	Roussel	France	-
Tacosal	Helvepharm	Switz.	-
Zentropil	Nordmark	W. Germany	-

Raw Materials

Benzophenone
Potassium cyanide
Ammonium carbonate

Manufacturing Process

10 g of benzophenone (1 mol), 4 g of potassium cyanide (1.22 mols) and 16 g of ammonium carbonate (3.3 mols) are dissolved in 100 cc of 60% (by volume) ethyl alcohol and the mixture warmed under a reflux condenser without stirring at 58° to 62°C. After warming the mixture for 10 hours a

partial vacuum is applied and the temperature is raised enough to permit concentration of the reaction mixture to two-thirds of its initial volume.

A slight excess of mineral acid, such as sulfuric or hydrochloric acid is added to acidify the mixture which is then chilled and the solid which separates is filtered off. It is then treated with an aqueous solution of dilute sodium hydroxide to dissolve the hydantoin from the solid unreacted benzophenone. After filtration, the alkaline extract is then acidified to cause the separation of solid pure diphenylhydantoin which is filtered off and dried. It melts at 293° to 296°C.

A net yield of about 95% is obtained by the procedure described above. If the time of warming the reaction mixture is increased three-or four-fold, practically 100% net yields are obtained. The same high net yields are also obtained by heating for even longer periods of time. For example, by heating for 90 hours, a 100% net yield, or 67% gross yield, is obtained.

References

Merck Index 7204
Kleeman and Engel p. 722
PDR pp. 1334, 1337
DOT 9 (6) 245 (1973)
I.N. p. 767
REM p. 1081
Henze, H.R.; US Patent 2,409,754; October 22, 1946; assigned to Parke, Davis and Company

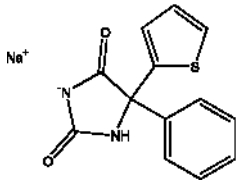
PHETHENYLATE SODIUM

Therapeutic Function: Anticonvulsant

Chemical Name: 5-Phenyl-5-(2-thienyl)-2,4-imidazolidinedione monosodium salt

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 510-34-9

Trade Name	Manufacturer	Country	Year Introduced
Thiantoin	Lilly	US	1950

Raw Materials

Phenyl-(2-thienyl)ketone
Potassium cyanide
Ammonium carbonate

Manufacturing Process

The 5-phenyl-5-(2-thienyl)hydantoin is prepared by heating a mixture of 5.64 g (0.03 mol) of phenyl-(2-thienyl)ketone, 3.25 g (0.03 mol) of potassium cyanide and 10.2 g (0.09 mol) of ammonium carbonate in 75 cc of 50% ethanol for 28 hours at a temperature of about 110°C. An additional 3.25 g of potassium cyanide and 3 g of ammonium carbonate are added and the mixture heated for 24 hours at about 110°C.

The reaction mixture is removed and about half of the liquid evaporated, an oil separating during the process. The mixture is acidified with concentrated hydrochloric acid and extracted with two 100 cc portions of ether. The extracts, which contain the 5-phenyl-5-(2-thienyl)hydantoin, are combined and the combined ether extracts are shaken with two 25 cc portions of 5% potassium hydroxide solution. The alkaline solution, which dissolves the 5-phenyl-5-(2-thienyl)hydantoin to form the potassium salt thereof, is acidifed with hydrochloric acid and heated to expel ether.

By the process of purification, 4.3 g of 5-phenyl-5-(2-thienyl)hydantoin is obtained, and from the ether layer, 2.2 g of unreacted ketone. The yield of the 5-phenyl-5-(2-thienyl)hydantoin is about 56%. The melting point of the purified 5-phenyl-5-(2-thienyl)hydantoinis about 256°C to 257°C.

References

Merck Index 7206
Spurlock, J.J.; US Patent 2,366,221; January 2, 1945

PHOLEDRINE SULFATE

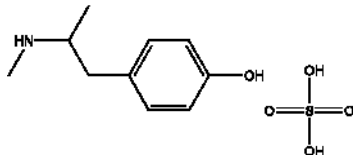
Therapeutic Function: Sympathomimetic, Mydriatic, Analeptic, Vasopressor

Chemical Name: Phenol, p-(2-(methylamino)propyl)- sulfate

Common Name: Foledrine; Methylparedrine; Pholedrine sulfate

Chemical Abstracts Registry No.: 370-14-9 (Base); 6114-26-7

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Pholedrine Sulfate	ZYF Pharm Chemical	-	-
Paredrinol	Sigma-Aldrich	-	-
Pressitan	Allard	-	-
Pulsotyl	CHINOIN - BUDAPES	-	-

Raw Materials

p-Methoxybenzylmethylketone
Hydrogen
Nickel

Manufacturing Process

100 g β-(methoxyphenyl)isopropylamine prepared, for example by reduction of p-methoxybenzylmethylketone with hydrogen and nickel catalyst in presence of ammonia or by Mannix's method, 250 ml ethanol and calculated quantity of solution of formaldehyde and 70 g activated aluminum shaving were heated for 6 hours by stirring. The mixture was filtered, the solvent was removed in vacuum and the residue was dissolved in ethanol contained hydrochloric acid. The prepared hydrochloride of β-(p-methoxyphenyl)isopropylmethylamine had MP: 174°C.

In practice it is usually used as sulfate.

References

Knoll A.-G.; D.R. Patent No. 665,793; May 27, 1936; Assigned to Chemishe Fabriken in Ludvigshafen, Rhein, Germany
Knoll A.-G.; D.R. Patent No. 674,753; May 27, 1936; Assigned to Chemishe Fabriken in Ludvigshafen, Rhein, Germany

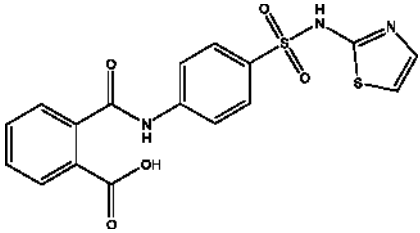
PHTHALYLSULFATHIAZOLE

Therapeutic Function: Antibacterial (intestinal)

Chemical Name: 2-[[[4-[(2-Thiazolylamino)sulfonyl]phenyl]amino] carbonyl]benzoic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 85-73-4

Trade Name	Manufacturer	Country	Year Introduced
Sulfathalidine	MSD	US	1946
Talidine	Clin Midy	France	1948
AFI-Ftalyl	A.F.I.	Norway	-
Colicitina	Panthox and Burck	Italy	-
Enterosteril	Ripari-Gero	Italy	-
Ftalysept	Ferrosan	Denmark	-
Gelotamide	Choay	France	-
Lyantil	Syntex Daltan	France	-
Novosulfina	Medosan	Italy	-
Phtalazol	Geistlich	Switz.	-
Phthalazol	Knoll	Australia	-
Sulfatalyl	Pharmacia	Sweden	-
Talisulfazol	Chemiek	E. Germany	-
Thalazole	May and Baker	UK	-

Raw Materials

Phthalic anhydride
Sulfathiazole

Manufacturing Process

5 g of phthalic anhydride was added to a boiling suspension of 10 g of sulfathiazole in 100 cc of alcohol. The mixture was then refluxed for 5 minutes after the addition was complete at which time all of the solids were in solution. The solution was then cooled and diluted with an equal volume of water, The white solid precipitate which formed was filtered and recrystallized from dilute alcohol, yielding 2-N^4-phthalylsulfanilamidothiazole,which decomposes above 260°C, according to US Patent 2,324,015.

References

Merck Index 7261
Kleeman and Engel p. 723
OCDS Vol. 1 p. 132 (1977)
I.N. p. 769

Moore, M.L.; US Patent 2,324,013; July 13, 1943; assigned to Sharp and Dohme, Incorporated
Moore, M.L.; US Patent 2,324,014; July 13, 1943; assigned to Sharp and Dohrne, Incorporated
Moore, M.L.; US Patent 2,324,015; July 13, 1943; assigned to Sharp and Dohme, Incorporated

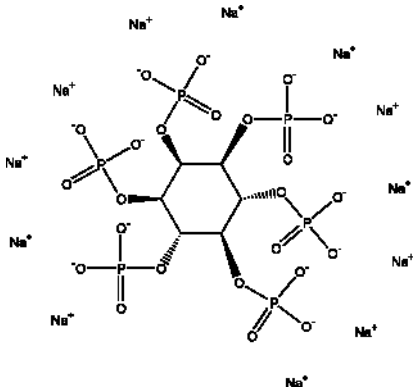
PHYTATE SODIUM

Therapeutic Function: Hypocalcemic

Chemical Name: myo-Inositol hexakis(dihydrogen phosphate) sodium salt

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 83-86-3 (Acid)

Trade Name	Manufacturer	Country	Year Introduced
Rencal	Squibb	US	1962
Iliso	Made	Spain	-

Raw Materials

Corn steep water
Lime
Cation exchange resin

Manufacturing Process

Cereal grains are particularly rich in phytates; corn steep water produced in the wet milling of corn, is one of the best sources of such material. To recover the phytate from corn steep water it is customary to neutralize the same with

an alkaline material, suitably lime, causing the phytate to precipitate as a crude salt which can be removed readily by filtration. This material contains substantial amounts of magnesium, even though lime may have been employed as precipitant, and traces of other metallic ions, as well as some proteinaceous materials and other contaminants from the steep water. It may be partially purified by dissolving in acid and reprecipitating but, nevertheless, such commercial phytates do not represent pure salts. They always contain some magnesium, appreciable amounts of iron and nitrogenous materials, and traces of heavy metals, such as copper.

Heretofore, no economical method for preparing pure phytic acid was known. The classical method was to dissolve calcium phytate in an acid such as hydrochloric acid, and then add a solution of a copper salt, such as copper sulfate to precipitate copper phytate. The latter was suspended in water and treated with hydrogen sulfide, which formed insoluble copper sulfide and released phytic acid to the solution. After removing the copper sulfide by filtration, the filtrate was concentrated to yield phytic acid as a syrup.

The phytic acid in the form of a calcium phytate press cake may however be contacted with a cation exchange resin to replace the calcium with sodium to yield phytate sodium.

References

Merck Index 7269
I.N. p. 25
Baldwin, A.R., Blatter, L.K. and Gallagher, D.M.; US Patent 2,815,360; December 3, 1957; assigned to Corn Products Refining Co.

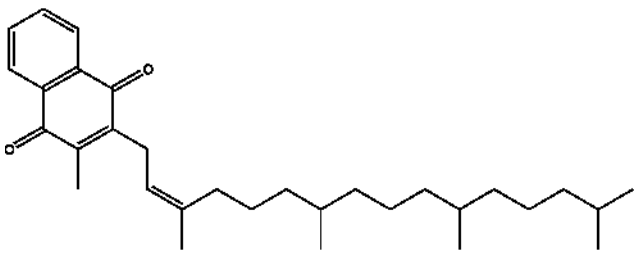
PHYTONADIONE

Therapeutic Function: Prothrombogenic vitamin

Chemical Name: 2-Methyl-3-(3,7,11,15-tetramethyl-2-hexadecenyl)-1,4-naphthalenedione

Common Name: Vitamin K; Phytomeanadion; Phylloquinone

Structural Formula:



Chemical Abstracts Registry No.: 84-80-0

Trade Name	Manufacturer	Country	Year Introduced
Mephyton	MSD	US	1941
Konakion	Roche	US	1959
Aquamephyton	MSD	US	1960
Mono-Kay	Abbott	US	1961
Eleven-K	Nippon Shinyaku	Japan	-
Hymeron	Yamanouchi	Japan	-
Kanavit	Spofa	Czechoslovakia	-
Kativ-N	Takeda	Japan	-
Kayeine	Kanto	Japan	-
Kaywan	Eisai	Japan	-
K-Eine	Hokuriku	Japan	-
Keipole	Kyowa	Japan	-
Kennegin	Kowa	Japan	-
Kephton	Toyo Jozo	Japan	-
Kinadione	Chugai	Japan	-
Kisikonon	Kyorin	Japan	-
K-Top Wan	Sawai	Japan	-
Monodion	Maruko	Japan	-
Nichivita-K	Nichiiko	Japan	-
One-Kay	Mohan	Japan	-
Synthex P	Tanabe	Japan	-
Vita-K	Kobayashi	Japan	-
Vitamine K1	Delagrange	France	-

Raw Materials

2-Methyl-1,4-naphthohydroquinone
Phytol
Hydrogen

Manufacturing Process

11 parts by weight of 2-methyl-1,4-naphthohydroquinone, 30 parts by volume of water-free dioxane and 1.5 parts by volume of boron trifluoride etherate are heated to 50°C. While agitating and introducing nitrogen, 10 parts by weight of phytol dissolved in 10 parts by volume of dioxane are added in the course of 15 minutes. Thereupon, the dark colored reaction mixture is stirred for 20 additional minutes at 50°C, cooled down and 60 parts by volume of ether are added. The reaction mixture is washed first with water, then with a mixture of 3 parts of N-sodium hydroxide and 2 parts of a 2.5% solution of sodium hydrosulfite and again with water. The aqueous extracts are washed with ether. The ether solutions are collected, dried over sodium sulfate and concentrated, toward the end under reduced pressure.

The waxlike condensation product so obtained is mixed with 60 parts by volume of petroleum ether (boiling limits 30°C to 40°C) and agitated with hydrogen in the presence of a little active palladium lead catalyst (Pd-$CaCO_3$

catalyst, the activity of which is reduced by the addition of lead and quinoline). During the operation, the condensation product separates in the form of a voluminous white precipitate. The latter is separated by filtration in the absence of air while adding an inert coarse-grained adsorption agent (for example, aluminum silicate salt for filter purposes), and washed with cooled petroleum ether. Thereupon, the 2-methyl-3-phytyl-1,4-naphthohydroquinone is extracted from the filter cake by means of ether, the ethereal solution is concentrated to 100 parts by volume and the reaction product is oxidized by stirring the solution with 6.6 parts by weight of silver oxide during 30 minutes. The solution is filtered through sodium sulfate, the latter is rinsed with ether and the solvent is evaporated. There are obtained 5.7 parts by weight of 2-methyl-3-phytyl-1,4-naphthoquinone (vitamin K1) in the form of a golden yellow oil.

References

Merck Index 9834
Kleeman & Engel p. 724
PDR pp. 1140, 1488
I.N. p. 770
REM p. 1011
Isler, O. and Doebel, K.; US Patent 2,683,176; July 6, 1954; assigned to Hoffmann-La Roche, Inc.

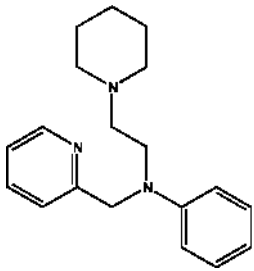
PICOPERINE

Therapeutic Function: Antitussive

Chemical Name: N-(2-Piperidinoethyl)-N-(2-pyridylmethyl)aniline

Common Name: Picoperamidine

Structural Formula:



Chemical Abstracts Registry No.: 21755-66-8

Trade Name	Manufacturer	Country	Year Introduced
Coben	Takeda	Japan	1971

Raw Materials

N-(2-Pyridylmethyl)aniline
Sodium amide
2-Piperidinoethyl chloride

Manufacturing Process

To a simultaneously stirred and refluxed suspension of 5.6 parts by weight of sodamide in 60 parts by volume of anhydrous toluene, there is added dropwise a solution of 18.4 parts by weight of N-(2-pyridylmethyl)aniline in 20 parts by volume of anhydrous toluene. After the addition is complete, the mixture is refluxed for two hours under constant stirring.

To the resulting mixture there is added dropwise a solution of 14.9 parts by weight of 2-piperidinoethyl chloride in 20 parts by volume of anhydrous toluene and the whole mixture is stirred and refluxed for another two hours. After cooling, water is added carefully to decompose the unreacted sodamide, the separated toluene layer is dried over anhydrous sodium sulfate and the solvent removed under reduced pressure.

The residual oil is subjected to distillation under reduced pressure, the fraction boiling in the range of 185°C to 198°C/4 mm Hg being collected. Purification of the fraction by redistillation under reduced pressure gives 22.5 parts by weight of N-(2-piperidinoethyl)-N-(2-pyridylmethyl)-aniline which boils at 195°C to 196°C/4 mm Hg. Yield 76.3%.

References

Merck Index 7285
DOT 8 (5) 185 (1972)
I.N. p. 771
Mitano, S. and Kase, Y.; US Patent 3,471,501; October 7, 1969; assigned to Takeda Chemical Industries, Ltd.

PICOSULFATE SODIUM

Therapeutic Function: Laxative

Chemical Name: 4,4'-(2-Pyridinylmethylene)bisphenol-bis(hydrogen sulfate) (ester) disodium salt

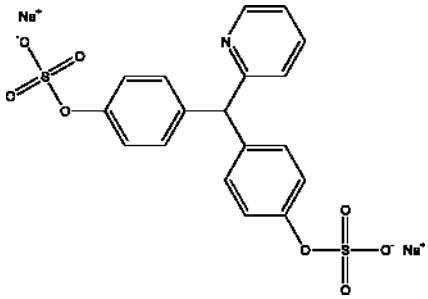
Common Name: Picosulfol

Chemical Abstracts Registry No.: 10040-45-6

Raw Materials

2-Pyridine aldehyde
Sodium hydroxide
2-Chlorophenol
Chlorosulfonic acid

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Guttalax	De Angelini	Italy	1967
Laxoberal	Thomae	W. Germany	1972
Laxoberal	W.B. Pharm.	UK	1975
Laxoberon	Teijin	Japan	1980
Contumax	Casen	Spain	-
Evacuol	Almirall	Spain	-
Gocce Euchessina	Antonetto	Italy	-
Gocce Lassative Aicardi	Aicardi	Italy	-
Laxante Azoxico	Bescansa	Spain	-
Laxidogol	Dolorgiet	W. Germany	-
Picolax	Falqui	Italy	-
Skilax	Prodes	Spain	-
Trali	Sintyal	Argentina	-

Manufacturing Process

Preparation of 3,3'-Dichloro-4,4'-Dioxy-Diphenyl-(2-Pyridyl)-Methane: 75 g (0.7 mol) of 2-pyridinaldehyde are dropped during about 1 hour to a homogeneous mixture [obtained between 0° and 10°C from 107 ml of concentrated sulfuric acid and 292.9 g (2.28 mols) of 2-chlorophenol], maintaining the temperature between 0° and 5°C. The mixture is stirred for ½ hour at this temperature, which is then allowed to rise spontaneously, taking care not to exceed 30°C. After stirring for 1½ hours, the mixture is maintained overnight at room temperature, then it is dissolved, with external cooling, with a 10% sodium hydroxide solution, filtered with charcoal and neutralized with 5% hydrochloric acid. The precipitate obtained, consisting of crude product, filtered, washed with water, dried, triturated with ether and dried again, weighs 211 g.

The isomer 2,4'-dioxy-3,3'-dichloro-diphenyl-(2-pyridyl)-methane is removed by thoroughly washing with 430 ml of 95°C boiling alcohol, obtaining 167 g of isomer-free product (yield 69%). The 3,3'-dichloro-4,4'-dioxy-diphenyl-(2-pyridyl)-methane is a white solid, crystallizing from 95% alcohol; MP 212° to 215°C.

Preparation of 4,4'-Dioxy-Diphenyl-(2-Pyridyl)-Methane: 100 g of 3,3'-dichloro-4,4'-dioxydiphenyl-(2-pyridyl)-methane, obtained as above described, are dissolved in 660 ml of 10% sodium hydroxide and 49 g of Raney-nickel alloy are added to the solution with vigorous stirring, at room temperature and during 4 hours. The mixture is stirred overnight at room temperature, then it is filtered and brought to pH 5 with 10% acetic acid. The precipitate obtained, filtered, washed and dried is then dissolved in 1,500 ml of 95°C boiling alcohol to eliminate the insoluble salts. The residue obtained after the evaporation of the alcoholic solution weighs 74 g (yield 92%). The yield in respect to 2-pyridinaldehyde is 63.5%. The compound is a white solid, crystallizing from 95% alcohol; MP 248° to 250.5°C, according to US Patent 3,558,643.

Preparation of Disodium 4,4'-Disulfoxy-Diphenyl-(2-Pyridyl)-Methane: In ½ hour, 102 g chlorosulfonic acid are added to a solution of 100 g 4,4'-dihydroxydiphenyl-(2-pyridyl)methane in 750 ml of anhydrous pyridine, the temperature being maintained at between 0° and 5°C. Towards the end of the addition of acid, a precipitate is formed which is slowly redissolved during subsequent agitation.

Upon completion of the addition, the mixture is agitated for 7 hours at ambient temperature. The solution is then poured into 3 liters of water/ice obtaining a clear solution of dark yellow color which is rendered alkaline upon phenolphthalein with 30% NaOH and extracted with ethyl ether to eliminate the majority of the pyridine. The mixture is filtered with active charcoal, the pH adjusted to 8 with hydrochloric acid 1:1 and extracted with chloroform to remove the 4,4'-dihydroxydiphenyl-(2-pyridyl)-methane which has not reacted.

The aqueous solution is then concentrated to dryness at an outside temperature of 40° to 45°C and at low pressure. The residue, obtained by drying in a vacuum at 40° to 45°C is triturated in a mortar with ethyl ether and, after filtration, is extracted with 3,400 ml boiling absolute ethanol. The ethanol extract is separated from the undissolved part by filtration, cooled and the product which crystallizes by cooling is filtered and dried at 40°C in a vacuum. In that manner the disodium (4,4'-disulfoxy-diphenyl)-(2-pyridyl)methane bi-hydrate is obtained, which takes the form of a white solid, according to US Patent 3,528,986.

References

Merck Index 7286
Kleeman & Engel p. 725
DOT 8 (8) 302 (1972)
I.N. p. 771
Pala, G.; US Patent 3,528,986; September 15, 1970; assigned to Istituto de Angeli S.p.A., Italy
Pala, G.; US Patent 3,558,643; January 26, 1971; assigned to Istituto de Angeli S.p.A., Italy

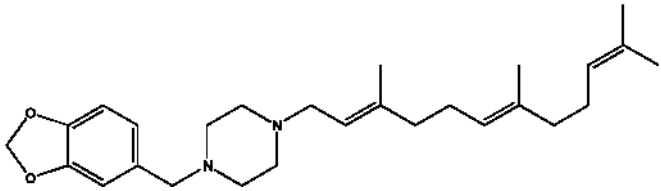
PIFARNINE

Therapeutic Function: Antiulcer

Chemical Name: 1-(1,3-Benzodioxol-5-ylmethyl)-4-(3,7,11-trimethyl-2,6,10-dodecatrienyl)piperazine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 56208-01-6

Trade Name	Manufacturer	Country	Year Introduced
Pifazin	Pierrel	Italy	1983

Raw Materials

1-Bromo-3,7,11-trimethyl-2,6,10-dodecatriene
Piperonylpiperazine
Triethylamine

Manufacturing Process

A solution of 45 mmols of 1-bromo-3,7,11-trimethyl-2,6,10-dodecatriene (obtained from synthetic farnesol, commercially available and containing four isomers) in 10 ml of benzene was added dropwise at 0°C to a stirred solution of 45 mmols of piperonylpiperazine in 60 ml of benzene containing 5 g of triethylamine. The mixture was stirred for 2 hours and then the precipitated triethylammonium bromide was filtered off. The benzene solution was washed first with water and then with K_2CO_3 solution and finally dried (K_2CO_3). Removal of benzene under reduced pressure gave a crude oily residue which was dissolved in acetone and treated at 5°C to 8°C with a slight excess of 37% HCl solution. The precipitated hydrochloride was filtered, washed with acetone and with absolute ethanol. The corresponding base was purified on a silica gel column and the purity of all fractions was checked by thin layer chromatography and gas liquid chromatography. Thin layer chromatography on silica gel gave three spots in the solvent system ethylacetate-petrol ether 1:1. Gas liquid chromatography showed three peaks indicating the presence of four possible isomers. The pure product was a colorless oil.

References

Merck Index 7299
DFU 2 (12) 829 (1977)
Kleeman and Engel p. 725
I.N. p. 772
Zumin, S.T., Riva, M. and Iafolla, G.; US Patent 3,875,163; April 1, 1975; assigned to Pierrel S.p.A. (Italy)

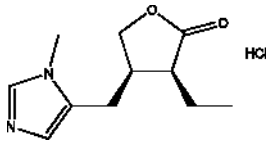
PILOCARPINE HYDROCHLORIDE

Therapeutic Function: Cholinergic

Chemical Name: 2(3H)-Furanone, 3-ethyldihydro-4-[(1-methyl-1H-imidazol-5-yl)methyl]-, (3S-cis)-, monohydrochloride

Common Name: Pilocarpine hydrochloride; Pilokarpin hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 54-71-7; 92-13-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Andre Carpine	Andre Laboratries Pvt. Ltd.	India	-
Pilokarpine hydrochloride	Merck KGaA	Germany	-
Pilokarpine hydrochloride	Boehringer Ingelheim Pharma KG	Germany	-
Pilokarpine hydrochloride	Sigma	-	-

Raw Materials

Sodium hydride	Ethyl diethylphosphonoethoxyacetate
Palladium on carbon	1-Methylimidazole-5-aldehyde
Diisobutylaluminum hydride	2-Diethylphosphonobutyric acid
Hydrogen chloride	4-Dimethylaminopyridine

Manufacturing Process

The 1-methylimidazole-5-aldehyde is easily accessible from sarcosine methyl ester hydrochloride and dimethylamino-2-azaprop-2-en-1-

ylidenedimethylammonium.

0.14 mol of ethyl diethylphosphonoethoxyacetate is slowly added dropwise with stirring and under inert gas to a suspension of 0.14 mol of NaH (paraffin-free) in 250 ml of abs. THF, the mixture is stirred for 1 h at 20°C and a solution of 0.093 mol of 1-methylimidazole-5-aldehyde in 100 ml of abs. THF is added dropwise. After stirring at 20°C for 10 min, the solvent is distilled off in vacuo, the residue is taken up in a little H_2O, and the solution is acidified with 1 N HCl and washed several times with ether. The aqueous phase is rendered alkaline using 2 N NaOH with cooling (0°-5°C) and extracted several times with CH_2Cl_2. After drying of the organic extracts with Na_2SO_4, the solvent is removed in vacuo and 2-ethoxy-3-[(1-methyl-1H-imidazol-5-yl)methyl]-acrilic acid ethyl ester. Yield: 99% of theory.

122 ml of 45% diisobutylaluminum hydride solution (328 mmol) are slowly added dropwise under inert gas, with stirring and ice cooling, to a solution of 137 mmol of 2-ethoxy-3-[(1-methyl-1H-imidazol-5-yl)methyl]-acrilic acid ethyl ester in 600 ml of abs. C_6H_6. Stirring of the mixture is continued for a further 30 min at 0°-5°C and 600 ml of CH_3OH, then 100 ml of H_2O, are slowly added. The hydroxide precipitate is filtered off with suction and washed several times with hot CH_3OH. After drying of the combined filtrates the solvents are distilled off in vacuo and the residue is crystallized using C_2H_5OH. 2-ethoxy-3-[(1-methyl-1H-imidazol-5-yl)methyl]-prop-2-en-1-ol was obtained. Yield: 100% of theory. The crude product is pure enough for the subsequent reaction. Recrystallization of an analytical sample from CH_3OH/acetone: melting point 129°C.

A solution of 58 mmol of 2-ethoxy-3-[(1-methyl-1H-imidazol-5-yl)methyl]-prop-2-en-1-ol in 116.6 ml of HCl (= 116.6 mmol) is stirred at 30°-35°C for 1.5 h and concentrated in vacuo at the same temperature. The residual HCl is removed by distillation with $CHCl_3$ in vacuo. After seeding, the residue crystallizes at 20°C (15 h) 1-hydroxy-3-[(1-methyl-1H-imidazol-5-yl)methyl]-propan-2-one hydrochloride. The crystallizate is filtered off with suction, washed with a little CH_3OH and dried in vacuo. Yield: 86% of theory; melting point 190°C.

About 80-90% of the equivalent amount of $NaOCH_3$ solution in CH_3OH is slowly added dropwise at 20°C with stirring and exclusion of moisture to a suspension of 21.24 mmol of 1-hydroxy-3-[(1-methyl-1H-imidazol-5-yl)methyl]-propan-2-one hydrochloride in 80 ml of CH_3OH, in the course of which the pH of 6.5 is not to be exceeded. The solvent is distilled off in vacuo at a maximum of 30°C and the residue of 1-hydroxy-3-[(1-methyl-1H-imidazol-5-yl)methyl]-propan-2-one is purified by flash chromatography (silica gel; $CHCl_3$/CH_3OH). Yield: 100% of theory; viscous, orange-colored oil.

Catalytic amounts of 4-dimethylaminopyridine and a solution of 21.3 mmol of 1-hydroxy-3-[(1-methyl-1H-imidazol-5-yl)methyl]-propan-2-one in 80 ml of CH_2Cl_2 are added to a solution of 26.44 mmol of 2-diethylphosphonobutyric acid in 40 ml of purified CH_2Cl_2. After cooling to 0°-5°C, a solution of 23.5 mmol of dicyclohexylcarbodiimide in 60 ml of CH_2Cl_2 is added dropwise and the mixture is stirred for 1 h at 0°-5°C and for 2 h at 20°C. The crystallized

dicyclohexylurea is filtered off with suction and the filtrate is washed with H_2O and saturated $NaHCO_3$ solution. After drying of the organic phase the solvent is distilled off at 30°C in vacuo and the residue of 2-diethoxy-phosphoryl)-butyric acid 3-[(1-methyl-1H-imidazol-5-yl)methyl]-2-oxo-propyl ester is purified by flash chromatography (silica gel; ethyl acetate/CH_3OH). Yield: 95% of theory of a viscous, orange-colored oil.

A mixture of 5 mmol each of 80% NaH and 15-crown-5 in 50 ml of absol. toluene is stirred at 20°C under inert gas for 10 min and a solution of 5 mmol of 2-diethoxy-phosphoryl)-butiric acid 3-[(1-methyl-1H-imidazol-5-yl)methyl]-2-oxo-propyl ester in 50 ml of absol. toluene is then added dropwise. Stirring is continued for a further 15 min under inert gas and the mixture is hydrolyzed with a little water until phase separation is detectable. After separating off the organic phase, the aqueous layer is saturated with NaCl and extracted several times with $CHCl_3$. The combined organic phases are the solvent is distilled off at 40°C in vacuo and the residue 3-ethyl-4-[(1-methyl-1H-imidazol-5-yl)methyl]-5H-furan-2-one is purified twice by flash chromatography (silica gel; ethyl acetate/CH_3OH). Yield: 52% of theory; virtually colorless oil.

1.36 mmol of 3-ethyl-4-[(1-methyl-1H-imidazol-5-yl)methyl]-5H-furan-2-one in 15.5 ml of CH_3OH are hydrogenated for 5 h at 50 bar and 60°C using 210 mg of Pd/carbon (10%). After filtering off the catalyst and distilling off the solvent at 30°C in vacuo, the oily residue (about 250 mg) is treated with 10 ml of 1 N HCl and the mixture is stirred for 3 h at 20°C. The hydrochloric acid is distilled off in vacuo at 35°-40°C, the oily residue is taken up in a little CH_3OH and ether is added. The precipitate of pilocarpine hydrochloride is recrystallized from CH_3OH/ether. Yield: 73% of theory; melting point 210°C.

References

Reimann E.; US Patent No. 5,530,136; Jan. 25, 1996; Assigned: Merck Patent Gesellschaft Mit Beschrankter Haftung, Darmsstadt, Germany
Reuther G.R.; US Patent No. 5,059,531; Oct. 22, 1991; Assigned: Merck Patent Gesellschaft Mit Beschrankter Haftung, Darmsstadt, Germany
Courtois D. et al.; US Patent No. 5,569,593; Oct. 29, 1996; Assigned: Nestec S.A.,Vevey, Switzerland

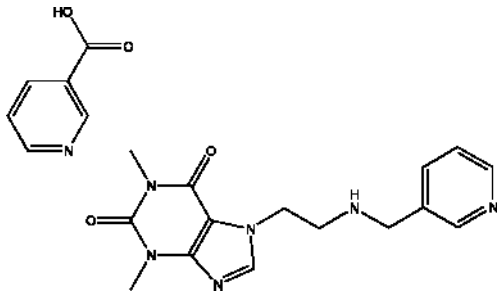
PIMEFYLLINE NICOTINATE

Therapeutic Function: Coronary vasodilator

Chemical Name: 3,7-Dihydro-1,3-dimethyl-7-[2-[(3-pyridinylmethyl)amino] ethyl]-1H-purine-2,6-dione nicotinate

Common Name: 7-(β-3'-Picolylaminoethyl)theophylline nicotinate

Structural Formula:



Chemical Abstracts Registry No.: 10058-07-8; 10001-43-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Teonicon	Bracco	Italy	1975
Teonicon	Neopharmed	Japan	-

Raw Materials

7-(2-Bromethyl)theophylline
3-Picolylamine
Nicotinic acid

Manufacturing Process

77 g 7-(β-bromoethyl)-theophylline (C.A. 50, 12071f) and 57.8 g 3-picolylamine in 750 ml toluene were refluxed 16 hours with vigorous agitation. The 3-picolylamine hydrobromide formed was filtered off, and the filtrate was evaporated in a vacuum to about one-third of its original volume. About 300 to 400 ml diisopropyl ether were added, and the solution was seeded with a few pure crystals of the desired product.

7-(β-3'-picolylaminoethyl)-theophylline crystallized over a period of a few hours. It was filtered off with suction, washed with a little diisopropyl ether, and dried. The yield of crude product was 69.3 g (82%), its MP 103° to 106°C. The MP was 111° to 112°C after recrystallization from isopropyl acetate. The compound was identified by microanalysis.

39.3 g 7-(β-3'-picolylaminoethyl)-theophylline were dissolved in 300 ml boiling isopropanol, and 15.4 g nicotinic acid were added to the solution in which the acid promptly dissolved. The nicotinate formed crystallized after a short time. It was filtered with suction and dried. The yield was 52.3 g (95.5%). The MP of 159° to 160°C was not significantly changed by recrystallization from ethanol.

References

Merck Index 7306

Kleeman & Engel p. 727
Suter, H. and Zutter, H.; US Patent 3,350,400; October 31, 1967; assigned to Eprova Limited, Switzerland

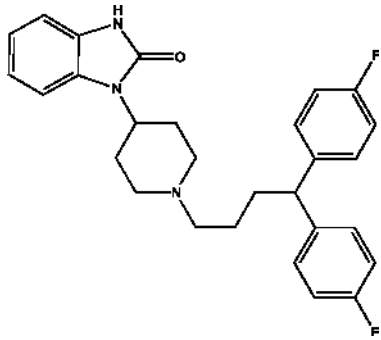
PIMOZIDE

Therapeutic Function: Antipsychotic

Chemical Name: 1-[1-[4,4-Bis(4-fluorophenyl)butyl]-4-piperidinyl]-1,3-dihydro-2H-benzimidazol-2-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 2062-78-4

Trade Name	Manufacturer	Country	Year Introduced
Orap	Janssen	W. Germany	1971
Opiran	Cassenne	France	1971
Orap	Janssen	UK	1971
Orap	Fujisawa	Japan	1974
Orap	Janssen	Italy	1977
Norofren	Dif-Dogu	Turkey	-
Oralep	Abic	Israel	-
Pimotid	Medica	Finland	-

Raw Materials

Thionyl chloride
Cyclopropyl-di-(4-fluorophenyl)-carbinol
Hydrogen
4-(2-Oxo-1-benzimidazolinyl)piperidine

Manufacturing Process

To a solution of 130 parts cyclopropyl-di-(4-fluorophenyl)-carbinol in 240 parts benzene are added dropwise 43 parts thionyl chloride. The whole is refluxed until no more gas is evolved. The reaction mixture is then evaporated. The residue is distilled in vacuo, yielding 4-chloro1,1-di-(4-fluorophenyl)-1-butene, boiling point 165°C to 167°C at 6 mm pressure; n_D^{20}: 1.5698; d_{20}^{20}:1.2151.

A solution of 61 parts 4-chloro-1,1-di-(4-fluorophenyl)-1-butene in 400 parts 2-propanol is hydrogenated at normal pressure and at room temperature in the presence of 5.5 parts palladium-on-charcoal catalyst 10% (exothermic reaction: temperature rises to about 30°C). After the calculated amount of hydrogen is taken up, hydrogenation is stopped. The catalyst is filtered off and the filtrate is evaporated. The oily residue is distilled in vacuo, yielding 1-chloro-4,4-di-(4-fluorophenyl)-butane, boiling point 166°C to 168°C at 6 mm pressure; n_D^{20}: 1.5425; d_{20}^{20}:1.2039.

To a mixture of 4.4 parts of 4-(2-oxo-1-benzimidazolinyl)-piperidine, 3.3 parts sodium carbonate, a few crystals of potassium iodide in 200 parts 4-methyl-2-pentanone are added portionwise 6.2 parts 1-chloro-4,4-di-(4-fluorophenyl)-butane. After the addition is complete, the whole is stirred and refluxed for 65 hours. After cooling the reaction mixture, there are added 70 parts water. The organic layer is separated, dried over potassium carbonate, filtered and evaporated. The solid residue is triturated in diisopropyl-ether, filtered off again and recrystallized from a mixture of 120 parts acetone and 80 parts 4-methyl-2-pentanone, yielding the crude product. After recrystallization of this crop from 80 parts acetone, 1-[4,4-di-(4fluorophenyl)-butyl]-4-(2-oxo-1-benzimidazolinyl)-piperidine is obtained, melting point 217°C to 219°C.

References

Merck Index 7310
Kleeman & Engel p. 727
PDR p. 1091
OCDS Vol. 2 p. 390 (1980)
DOT 5 (1) 36 (1969); 7 (5) 176 (1971); and 9 (6) 235 (1973)
I.N. p. 774
REM p. 1092
Janssen, P.A.J.; US Patent 3,196,157; July 20, 1965; assigned to Research Laboratorium Dr. C. Janssen N.V. (Belgium)

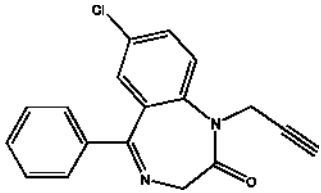
PINAZEPAM

Therapeutic Function: Antidepressant

Chemical Name: 7-Chloro-1,3-dihydro-5-phenyl-1-(2-propynyl)-2H-1,4-benzodiazepin-2-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 52463-83-9

Trade Name	Manufacturer	Country	Year Introduced
Domar	Zambeletti	Italy	1975
Duna	Zambeletti	Italy	-

Raw Materials

Propargyl bromide
2-Amino-5-chlorobenzophenone
Hydrazine hydrate
Phthalimidoacetyl chloride

Manufacturing Process

46.3 g (0.2 mol) of 2-amino-5-chlorobenzophenone were dissolved in 100 ml (1.28 mols) of propargyl bromide and the mixture refluxed for 4 hours. Thereafter, the whole was evaporated to dryness and the residue recrystallized from methanol to give 32.4 g (60.2%) of the desired 2-propargylamino-5-chlorobenzophenone; melting point 92°C to 93°C.

2.7 g (0.01 mol) of the 2-propargylamino-5-chlorobenzophenone obtained as above and 2.23 g (0.01 mol) of phthalimidoacetyl chloride were added to 30 ml of chloroform and the whole was refluxed overnight. Thereafter, the reaction mixture was evaporated to dryness and the residue recrystallized from methanol to give 2.66 g (58.3%) of the desired 2-(N-propargyl)phthalimidoacetamide-5-chlorobenzophenone. Melting point: 176°C.

A suspension of 22.8 g (0.05 mol) of 2-(N-propargyl)-phthalimidoacetamido-5-chlorobenzophenone in 250 ml ethanol containing 7.5 g hydrazine hydrate (0.15 mol) was heated under reflux for 2 hours, at the end of which time the reaction mixture was set aside overnight at ambient (25°C) temperature. Thereafter, the crystalline phthalyl hydrazide which had precipitated out was removed by filtration and washed with 3 x 50 ml aliquots of chloroform. The filtrate and washings were diluted with water and exhaustively extracted with chloroform. The chloroform extract was then evaporated and the residue washed with 100 ml hexane to promote crystallization. The crude 7-chloro-1-propargyl-3H-1,4-benzodiazepine-2(1H)-one was recrystallized from a methanol-water mixture to give 10.5 g (71.4%) of the pure product. Melting point: 140°C to 142°C.

References

Merck Index 7316
Kleeman & Engel p. 728
DOT 12 (4) 147 (1976)
I.N. p. 774
Podesva, C. and Vagi, K.; US Patent 3,842,094; October 15, 1974; assigned to Delmar Chemicals Ltd. (Canada)

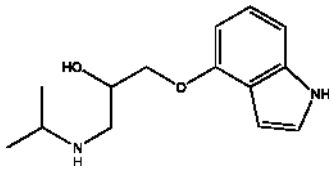
PINDOLOL

Therapeutic Function: Beta-adrenergic blocker

Chemical Name: 2-Propanol, 1-(1H-indol-4-yloxy)-3-((1-methylethyl)amino)-

Common Name: Pindolol: Prindolol

Structural Formula:



Chemical Abstracts Registry No.: 13523-86-9

Trade Name	Manufacturer	Country	Year Introduced
Betadren	Lagap	-	-
Cardilate	Teikoku	-	-
Lizenil	Nippon Kayaku	-	-

Raw Materials

Sodium amide
Hydrogen
Epichlorohydrin
Isopropylamine
Ammonia
Palladium on aluminum oxide
Sodium hydroxide
Tartaric acid

Manufacturing Process

4-Hydroxyindole is obtained by debenzylation of 4-benzyloxyindole with hydrogen in the presence of a 5% palladium catalyst on aluminium oxide.

10.0 g of 4-hydroxyindole and subsequently 7.4 ml of epichlorohydrin are added while stirring in an atmosphere of nitrogen to a solution of 2.73 g of sodium hydroxide in 65 ml of water. Stirring is effected at room temperature

for a further 15 h, the reaction mixture is extracted 4 times with 50 ml of methylene chloride and the combined organic layers which have been dried over magnesium sulfate are evaporated at reduced pressure. So 3-chloro-1-(4-indolyloxy)-2-propanol is obtained.

The 3-chloro-1-(4-indolyloxy)-2-propanol is dissolved in 50 ml of toluene and 50 ml of isopropylamine and heated to the boil for 45 h. Evaporation to dryness is effected in a vacuum, the residue is shaken out thrice between ethyl acetate and a 1 N tartaric acid solution and a 5 N sodium hydroxide solution is then added to the combined tartaric acid phases until an alkaline reaction is obtained. The alkaline solution is shaken out thrice with 50 ml of methylene chloride, the extracts are dried over magnesium sulfate and the solvent evaporated in vacuum. The residue is crystallized from ethyl acetate/ether to give the 4-(2-hydroxy-3-isopropylaminopropoxy)indole.

References

Troxler F., Hofmann A.; GB Patent No. 1,138,968; Jan. 13, 1966; Assigned: Sandoz Ltd., of Lichtstrasse 35, Basle, Switzerland, a Swiss Body Corporate

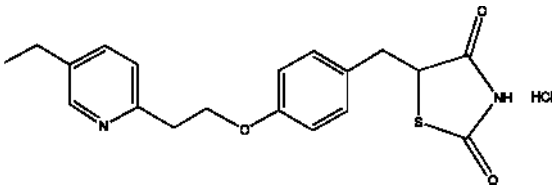
PIOGLITAZONE HYDROCHLORIDE

Therapeutic Function: Antidiabetic

Chemical Name: (+-)-2,4-Thiazolidinedione, 5-((4-(2-(5-ethyl-2-pyridinyl) ethoxy)phenyl)methyl), monohydrochloride

Common Name: Pioglitazone hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 112529-15-4; 111025-46-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Actos	Eli Lilly	USA	-
Actos	Takeda Pharmaceuticals	USA	-
Actos	Takeda Chemical Industry	Japan	-

Raw Materials

Palladium on carbon	2-(5-Ethyl-2-pyridyl)ethanol
Hydrogen bromide	Copper oxide
4-Fluoronitrobenzene	Sodium hydride
$NaNO_2$	Sodium methylate
Methyl acrylate	Sodium acetate

Manufacturing Process

To a solution of 2-(5-ethyl-2-pyridyl)ethanol (53.0 g) and 4-fluoronitrobenzene (47.0 g) in DMF (500 ml) was added portionwise under ice-cooling 60% sodium hydride in oil (16.0 g). The mixture was stirred under ice-cooling for one hour, then at room temperature for 30 min, poured into water and extracted with ether. The ether layer was washed with water and dried ($MgSO_4$). The solvent was evaporated off to give 4-[2-(5-ethyl-2-pyridyl)ethoxy]nitrobenzene as crystals (62.0 g, 62.9%). Recrystallization from ether-hexane gave colorless prisms, melting point 53°-54°C.

A solution of 4-[2-(5-ethyl-2-pyridyl)ethoxy]nitrobenzene (60.0 g) in methanol (500 ml) was hydrogenated at room temperature under one atmospheric pressure in the presence of 10% Pd-C (50% wet, 6.0 g). The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residual oil was dissolved in acetone (500 ml)-methanol (200 ml). To the solution was added a 47% HBr aqueous solution (152 g). The mixture was cooled, to which was added dropwise a solution of $NaNO_2$ (17.3 g) in water (30 ml) at a temperature not higher than 5°C. The whole mixture was stirred at 5°C for 20 min, then methyl acrylate (112 g) was added thereto and the temperature was raised to 38°C. Cuprous oxide (2.0 g) was added to the mixture in small portions with vigorous stirring. The reaction mixture was stirred until nitrogen gas evolution ceased, and was concentrated under reduced pressure. The concentrate was made alkaline with concentrated aqueous ammonia, and extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$) The solvent was evaporated off to leave methyl 2-bromo-3-{4-[2-(5-ethyl-2-pyridyl)ethoxy]phenyl}propionate as a crude oil (74.09 g, 85.7%).

A mixture of the crude oil of methyl 2-bromo-3-{4-[2-(5-ethyl-2-pyridyl)ethoxy]phenyl}propionate (73.0 g) thiourea (14.2 g), sodium acetate (15.3 g) and ethanol (500 ml) was stirred for 3 hours under reflux. The reaction mixture was concentrated under reduced pressure, and the concentrate was neutralized with a saturated aqueous solution of sodium hydrogencarbonate, to which were added water (200 ml) and ether (100 ml). The whole mixture was stirred for 10 min to yield 5-{4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl}-2-imino-4-thiazolidinone as crystals (0.3 g, 523.0%). Recrystallization from methanol gave colorless prisms, melting point 187°-188°C, dec.

A solution of 5-{4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl}-2-imino-4-thiazolidinone (23.5 g) in 2 N HCl (200 ml) was refluxed for 6 hours. The solvent was evaporated off under reduced pressure, and the residue was neutralized with a saturated aqueous solution of sodium hydrogencarbonate. The crystals (23.5 g, 97.5%) which precipitated were collected by filtration

and recrystallized from DMF-H_2O to give 5-{4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl}-2,4-thiazolidinedione as colorless needles (20.5 g, 86.9%), melting point 183°-184°C.

In practice it is usually used as hydrochloride salt.

References

Meguro K., Fujita T.; US Patent No. 4,687,777; August 18, 1987; Assigned: Takeda Chemical Industries, LTD., Osaka, Japan

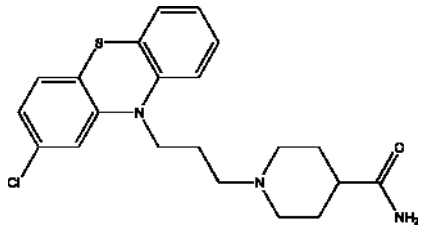
PIPAMAZINE

Therapeutic Function: Antiemetic

Chemical Name: 1-[3-(2-Chloro-10H-phenothiazin-10-yl)propyl]-4-pyridinecarboxamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 84-04-8

Trade Name	Manufacturer	Country	Year Introduced
Mornidine	Searle	US	1959
Nausidol	Gremy-Longuet	France	-

Raw Materials

4-Piperidinecarboxamide
2-Chloro-10-(γ-chloropropyl)phenothiazine

Manufacturing Process

To a stirred and refluxing suspension of 4.95 parts of 4-piperidinecarboxamide, 1 part of sodium iodide and 8.4 parts of potassium carbonate in 40 parts of butanone there are added in the course of 30 minutes 9.3 parts of 2-chloro-10-(γ-chloropropyl)phenothiazine in 40 parts of

butanone. Stirring and refluxing are continued for 12 hours after which the mixture is cooled and filtered. The filtrate is concentrated under vacuum to give a residue which is recrystallized from a mixture of 2-propanol and petroleum ether. The 1-[γ-(2'-chloro-10'-phenothiazine)propyl]piperidine-4-carboxamide thus obtained melts at approximately 139°C.

This base is dissolved in a small amount of 2-propanol and treated with a 25% solution of hydrogen chloride in 2-propanol. Upon treatment of this solution with anhydrous ether a hydrochloride precipitates as a white solid melting at about 196°C to 197°C with formation of bubbles.

References

Merck Index 7326
Kleeman & Engel p. 729
OCDS Vol. 1 p. 385 (1977)
I.N. p. 775
Cusic, J.W. and Sause, H.W.; US Patent 2,957,870; October 25, 1960; assigned to G.D. Searle & Co.

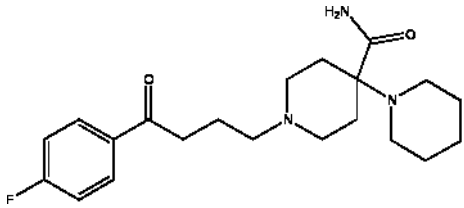
PIPAMPERONE

Therapeutic Function: Antipsychotic

Chemical Name: 1'-[4-(4-Fluorophenyl)-4-oxobutyl]-[1,4'-bipiperidine]-4'-carboxamide

Common Name: Floropipamide

Structural Formula:



Chemical Abstracts Registry No.: 1893-33-0

Trade Name	Manufacturer	Country	Year Introduced
Dipiperon	Janssen	W. Germany	1961
Dipiperon	Janssen-Le Brun	France	1968
Piperonil	Lusofarmaco	Italy	1970
Propitan	Eisai	Japan	-

Raw Materials

Piperidine hydrochloride	1-Benzyl-4-piperidone
Potassium cyanide	γ-Chloro-4-fluorobutyrophenone
Sulfuric acid	Hydrogen

Manufacturing Process

To a stirred solution of 130.4 parts of potassium cyanide and 243.2 parts of piperidine hydrochloride in a mixture of 800 parts of water and 320 parts of ethanol is added portionwise 378 parts of 1-benzyl-4-piperidone. After about one hour a solid starts to precipitate. Stirring is continued for 24 hours. The reaction mixture is filtered and the solid is recrystallized from 1,200 parts of diisopropyl ether. On cooling to room temperature a first crop of 1-benzyl-4-cyano-4-piperidinopiperidine melting at about 104°C to 106°C is obtained. By concentrating and further cooling of the mother liquor a second crop of the above compound is obtained.

A mixture of 14.1 parts of 1-benzyl-4-cyano-4-piperidinopiperidine and 40 parts of 90% sulfuric acid is heated on a steam bath for 10 minutes. Without further heating, the mixture is stirred until a temperature of about 20°C is obtained. The mixture is then poured into 150 parts of ice-water and the resultant solution is alkalized with excess ammonium hydroxide solution. The aqueous solution is decanted from the precipitated oil. On treating this oil with 80 parts of acetone, crystallization sets in. After one hour the solid is filtered off and dried to yield 1-benzyl-4-piperidinopiperidine-4-carboxamide melting at about 137.5°C to 140°C.

A mixture of 215 parts of 1-benzyl-4-piperidinopiperidine-4-carboxamide, 1,200 parts of isopropyl alcohol, 1,000 parts of distilled water and 157 parts of hydrogen chloride is debenzylated under atmospheric pressure and at a temperature of about 40°C in the presence of 40 parts of a 10% palladium-on-charcoal catalyst. After the calculated amount of hydrogen is taken up, hydrogenation is stopped. The mixture is filtered and the filtrate is evaporated. The semisolid residue is treated with a mixture of 80 parts of acetone and 80 parts of benzene and evaporated again. The residue is triturated in 200 parts of methanol and filtered, yielding the dihydrochloride of 4-piperidinopiperidine-4-carboxamide melting at about 299°C to 300.8°C with decomposition. A sample of 20 parts of the dihydrochloride is dissolved in 30 parts of water. The aqueous solution is alkalized with 15 parts of 44% sodium hydroxide and stirred for a short time. The solid obtained is filtered off yielding crude product. To separate the free base from organic and inorganic salts, it is extracted overnight in a Soxhlet apparatus with toluene. The toluene extract is evaporated and the solid residue is filtered off, yielding 4-piperidinopiperidine-4-carboxamide melting at about 118.5°C to 119.5°C.

To a mixture of 4.1 parts of 4-piperidinopiperidine-4-carboxamide, 6.4 parts of sodium carbonate, and a few crystals of potassium iodide in 100 parts of anhydrous toluene is added dropwise a solution of 5.6 parts of γ-chloro-4-fluorobutyrophenone and 40 parts of anhydrous toluene at a temperature of 30°C to 40°C. The mixture is stirred and refluxed for 48 hours. The reaction mixture is cooled and divided between 50 parts of water and 60 parts of chloroform. The combined organic layers - toluene and chloroform - are dried over potassium carbonate, filtered, and evaporated. The oily residue solidifies

on treatment with 80 parts of ether. After cooling for 30 minutes at 0°C, there is obtained 1-[γ-(4-fluorobenzoyl)propyl]-4-piperidinopiperidine-4-carboxamide melting at about 124.5°C to 126°C.

References

Merck Index 7327
Kleeman & Engel p. 729
OCDS Vol. 2 p. 388 (1980)
I.N. p. 775
Janssen, P.A.J.; US Patent 3,041,344; June 26, 1962; assigned to Research Laboratorium Dr. C. Janssen N.V. (Belgium)

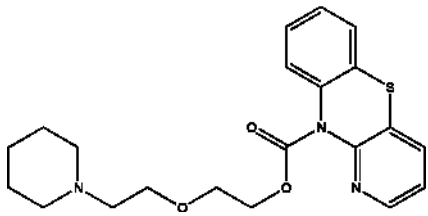
PIPAZETHATE

Therapeutic Function: Antitussive

Chemical Name: 10H-Pyrido[3,2-b][1,4]benzothiadiazine-10-carboxylic acid 2-(2-piperidinoethoxy)ethyl ester

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 2167-85-3; 6056-11-7 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Theratuss	Squibb	US	1962
Dipect	Draco	Sweden	-
Lenopect	Draco	Sweden	-
Selvigon	Homburg	W. Germany	-

Raw Materials

1-Azaphenothiazine carboxylic acid chloride
Piperidinoethoxy ethanol

Manufacturing Process

8.5 parts of 1-azaphenothiazine carboxylic acid chloride and 14 parts of piperidino-ethoxyethanol were introduced into 100 parts of chlorobenzene and the mixture boiled under reflux for 5 minutes. After cooling off the precipitated hydrochloride salt of piperidino-ethoxyethanol was filtered off on a suction filter. Water was added to the filtrate and the pH thereof adjusted to 5 to 6 with dilute HCl. The aqueous phase was then removed, a caustic soda solution added thereto and then extracted with ether. The ethyl extract was washed with water, then dried with potash and the ether distilled off. 9.4 parts of the piperidino-ethoxy-ethyl ester of 1-azaphenothiazine carboxylic acid were obtained. This product was dissolved in 20 parts of isopropanol and the solution neutralized with isopropanolic HCl. The monohydrochloride which precipitated out after recrystallization from isopropanol had a melting point of 160°C to 161°C.

References

Merck Index 7328
Kleeman & Engel p. 730
OCDS Vol. 1 p. 390 (1977)
I.N. p. 775
Schuler, W.A.; US Patent 2,989,529; June 20, 1961; assigned to Degussa (Germany)

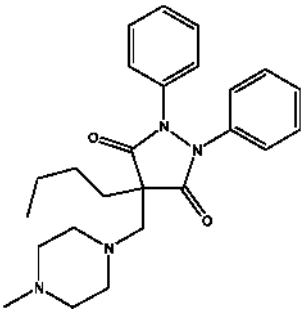
PIPEBUZONE

Therapeutic Function: Antiinflammatory

Chemical Name: 1,2-Diphenyl-3,5-dioxo-4-n-butyl-4-(N'-methylpiperazinomethyl)pyrazolidine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 27315-91-9

Trade Name	Manufacturer	Country	Year Introduced
Elarzone	Dausse	France	1973

Raw Materials

Phenylbutazone
Formaldehyde
N-Methylpiperazine

Manufacturing Process

77 g (0.25 mol) of phenylbutazone, 30 ml of a 30% strength solution of formaldehyde and 50 ml of ethyl alcohol are introduced into a 500 ml flask, 25 g (0.25 mol) of N-methylpiperazine are slowly added to this mixture which is stirred mechanically. The mixture is then heated for one hour on a water bath, left to cool, and crystallization started by scratching.

After being left in the refrigerator overnight the mixture, which has set solid, is triturated with 50 ml of isopropyl alcohol and the solid product filtered off and dried in vacuo over phosphorus pentoxide. 63 g (60% yield) of 1,2-diphenyl-3,5-dioxo-4-n-butyl-4-(N'-methylpiperazinomethyl)pyrazolidine are obtained, melting at 129°C after recrystallization from 150 ml of isopropyl alcohol.

References

Merck Index 7329
Kleeman & Engel p. 730
DOT 9 (11) 476 (1973)
I.N. p. 775
Dausse, S.A.; British Patent 1,249,047; October 6, 1971

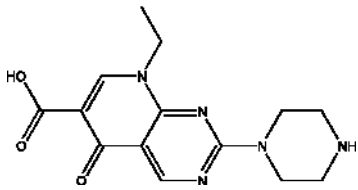
PIPEMIDIC ACID

Therapeutic Function: Antibacterial (urinary)

Chemical Name: 8-Ethyl-5,8-dihydro-5-oxo-2-(1-piperazinyl)pyrido[2,3-d]pyrimidine-6-carboxylic acid

Common Name: Piperamic acid

Structural Formula:



Chemical Abstracts Registry No.: 51940-44-4

Trade Name	Manufacturer	Country	Year Introduced
Pipram	Bellon	France	1975
Deblaston	Madaus	W. Germany	1975
Pipram	RBS Pharma	Italy	1978
Dolcol	Dainippon	Japan	1979
Pipram	Bellon	Italy	1979
Pipedac	Mediolanum	Italy	1980
Deblaston	Madaus	Switz.	1981
Filtrax	Biomedica Foscama	Italy	-
Gastrurol	Gibipharma	Italy	-
Memento	Volpino	Argentina	-
Nuril	Prodes	Spain	-
Pipedase	Scalari	Italy	-
Pipemid	Gentili	Italy	-
Pipurin	Brocchieri	Italy	-
Priper	Syncro	Argentina	-
Septidron	Ethimed	S. Africa	-
Tractur	Baldacci	Italy	-
Uropimid	C.T.	Italy	-
Urotractin	Zambeletti	Italy	-
Uroval	Firma	Italy	-

Raw Materials

Sodium hydroxide
Diethyl sulfate
Piperazine hydrate
6-Amino-2-methylthiopyrimidine
Ethoxymethylene malonic acid diethyl ester

Manufacturing Process

A mixture containing 1.33 g of 5,8-dihydro-8-ethyl-2-methylthio-5-oxopyridol[2,3-d]pyrimidine-6-carboxylic acid, 1.94 g of piperazine hexahydrate and 20 ml of dimethyl sulfoxide was heated at 110°C for 1 hour with stirring. The separated solid was collected by filtration, washed with ethanol, and then dried at such a temperature that did not rise above 50°C to give 1.57 g of the trihydrate of the product as nearly colorless needles, MP 253° to 255°C.

The starting material may be produced by reacting 6-amino-2-methylthiopyrimidine with ethoxymethylene malonic acid diethyl ester. The intermediate thus produced is converted by boiling in diphenyl ether to 6-ethoxycarbonyl-2-methylthio-5-oxo-5,8-dihydropyrido[2,3-d]pyrimidine. That is hydrolyzed by sodium hydroxide to cleave the ethoxy group and then ethylated with diethyl sulfate to give the starting material.

References

Merck Index 7332
Kleeman & Engel p. 731

DOT 11 (10, 408 (1975) & 12 (3) 99 (1976)
I.N. p. 36
Minami, S., Matsumoto, J.-I., Kawaguchi, K., Mishio, S., Shimizu, M., Takase, Y. and Nakamura, S.; US Patent 3,887,557; June 3, 1975; assigned to Dainippon Pharmaceutical Co. Ltd., Japan
Minami, S., Matsumoto, J.-I., Kawaguchi, K., Mishio, S., Shimizu, M., Takase, Y. and Nakamura, S.; US Patent 3,962,443; June 8, 1976; assigned to Dainippon Pharmaceutical Co. Ltd., Japan

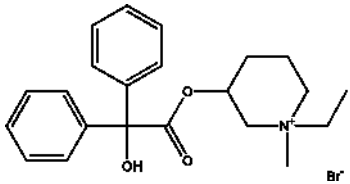
PIPENZOLATE BROMIDE

Therapeutic Function: Spasmolytic

Chemical Name: 1-Ethyl-3-[(hydroxydiphenylacetyl)oxy]-1-methylpiperidinium bromide

Common Name: N-Ethyl-3-piperidyl benzilate methobromide

Structural Formula:



Chemical Abstracts Registry No.: 125-51-9

Trade Name	Manufacturer	Country	Year Introduced
Piptal	Merrell National	US	1955
Piptal	Roger Bellon	France	1960
Piper	Panthox and Burck	Italy	-

Raw Materials

N-Ethyl-3-chloropiperidine
Benzilic acid
Methyl bromide

Manufacturing Process

N-ethyl-3-chloropiperidine was prepared according to the method of Fuson and Zirkle described in Volume 70, J. Am. Chem. Soc., p 2760. 12.0 g (0.081 mol) of N-ethyl-3-chloropiperidine was mixed with 18.6 g (0.081 mol) of benzilic acid and 80 cc of anhydrous isopropyl alcohol as a solvent. The mixture was refluxed for 72 hours. The solution was then filtered and concentrated at 30 mm of mercury. The concentrate was dissolved in water, acidified with hydrochloric acid and extracted with ether to remove the

unreacted benzilic acid.

The aqueous layer was neutralized with sodium bicarbonate and the product was extracted with ether. The ethereal solution of the product was dried with potassium carbonate, the ether was removed by distillation and the residue was distilled at 0.12 to 0.18 mm of mercury, the BP being 194° to 198°C. A yield of 16.5 g (60% of theoretical) of N-ethyl-3-piperidyl-benzilate was obtained.

34 g (0.1 mol) of the basic ester is dissolved in 75 cc of isopropyl alcohol and treated with 9.5 g (0.1 mol) of methyl bromide. The mixture is allowed to stand at room temperature until precipitation is complete. The product is removed by filtration and washed with isopropyl alcohol, yield 33 g, MP 175° to 177°C. On recrystallization from isopropyl alcohol, the MP was raised to 179° to 180°C dec.

References

Merck Index 7333
Kleeman & Engel p. 732
I.N. p 776
Biel, J.H.; US Patent 2,918,406; December 22, 1959; assigned to Lakeside Laboratories, Inc.

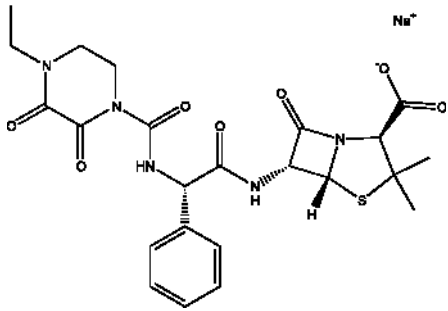
PIPERACILLIN SODIUM

Therapeutic Function: Antibiotic

Chemical Name: Sodium salt of 6-[D(-)-α-(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 59703-84-3; 61477-96-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Pentcillin	Toyama	Japan	1980
Pipril	Lederle	W. Germany	1980
Pipril	Lederle	Switz.	1980
Piperallin	Toyama	France	1981
Pipril	Lederle	UK	1982
Avocin	Cyanamid	Italy	1982
Pipracil	Lederle	US	1982
Pentocillin	Sankyo	Japan	-

Raw Materials

Diethyl oxalate
Trimethylsilyl chloride
Phosgene
N-Ethylethylenediamine
Sodium 2-ethylhexanoate
6-[D(-)-α-Aminophenylacetamido] penicillanic acid

Manufacturing Process

To a suspension of 0.9 g of 6-[D(-)-α-aminophenylacetamido]penicillanic acid in 30 ml of anhydrous ethyl acetate were added at 5°C to 10°C 0.55 g of triethylamine and 0.6 g of trimethylsilyl chloride. The resulting mixture was reacted at 15°C to 20°C for 3 hours to form trimethylsilylated 6-[D(-)-α-aminophenylacetamido]penicillanic acid.

To this acid was then added 1 g of 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride (from the reaction of N-ethylethylenediamine and diethyl oxalate to give 2,3-dioxo-4-ethyl-piperazine which is then reacted with phosgene) and the resulting mixture was reacted at 15°C to 20°C for 2 hours. After the reaction, a deposited triethylamine hydrochloride was separated by filtration, and the filtrate was incorporated with 0.4 g of n-butanol to deposit crystals. The deposited crystals were collected by filtration to obtain l.25 g of white crystals of 6-[D(-)α-(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino) phenylacetamido]penicillanic acid. Into a solution of these crystals in 30 ml of tetrahydrofuran was dropped a solution of 0.38 g of a sodium salt of 2-ethyl-hexanoic acid in 10 ml of tetrahydrofuran, upon which white crystals were deposited. The deposited crystals were collected by filtration, sufficiently washed with tetrahydrofuran and then dried to obtain 1.25 g of sodium salt of 6-[D(-)-α-(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetamido] penicillanic acid, melting point 183°C to 185°C (decomposition), yield 90%.

References

Merck Index 7335
DFU 3 (11) 829 (1978)
Kleeman & Engel p. 732
PDR p. 1026
OCDS Vol. 3 p. 207 (1984)
DOT 17 (1) 29 (1981)
I.N. p. 776
REM p. 1199

Saikawa, I,, Takano, S., Yoshida, C., Takashima, O., Momonoi, K., Kuroda, S., Komatsu, M., Yasuda, T. and Kodama, Y.; US Patents 4,087,424; May 2, 1978; 4,110,327; Aug. 29, 1978; 4,112,090; September 5, 1978; all assigned to Toyama Chemical Co., Ltd.

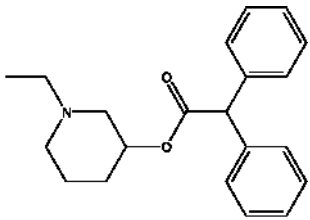
PIPERIDOLATE

Therapeutic Function: Spasmolytic

Chemical Name: α-Phenylbenzeneacetic acid 1-ethyl-3-piperidinyl ester

Common Name: N-Ethyl-3-piperidyl diphenylacetate

Structural Formula:



Chemical Abstracts Registry No.: 82-98-4; 129-77-1 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Dactil	Merrell National	US	1954
Dactil	Roger Bellon	France	1958
Cactiran	Kyorin	Japan	-
Crapinon	Sanzen	Japan	-
Dactylate	Sawai	Japan	-
Edelel	Mochida	Japan	-

Raw Materials

Furfural
Acetic acid
Hydrogen bromide
Hydrogen
Ethylamine
Diphenylacetyl chloride

Manufacturing Process

To obtain the free base, 34 g (0.256 mol) of N-ethyl-3-piperidinol and 20 g (0.22 mol) of diphenylacetyl chloride were mixed in 80 cc of isopropanol and the solution was refluxed for 2 hours. The isopropanol was evaporated in vacuo at 30 mm pressure, the residue was dissolved in 150 cc of water and the aqueous solution was extracted several times with ether. The aqueous solution was then neutralized with potassium carbonate and extracted with

ether. The ethereal solution was dried over anhydrous potassium carbonate and the ether removed by distillation. The product was then distilled at its boiling point 180° to 181°C at 0.13 mm of mercury whereby 14 g of a clear yellow, viscous liquid was obtained. The nitrogen content for $C_{21}H_{25}NO_2$ was calculated as 4.33% and the nitrogen content found was 4.21%.

The starting material was produced by the reaction of furfural with ethylamine followed by hydrogenation to give N-ethyl-N-(2-tetrahydrofurfuryl)amine. Treatment of that material with hydrogen bromide in acetic acid gives N-ethyl-3-piperidinol.

References

Merck Index 7345
Kleeman & Engel p. 733
OCDS Vol. 1 p.91 (1977)
I.N. p. 778
Biel, J.H.; US Patent 2,918,407; December 22, 1959; assigned to Lakeside Laboratories, Inc.

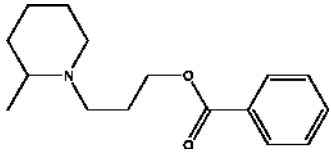
PIPEROCAINE

Therapeutic Function: Local anesthetic

Chemical Name: 1-Piperidinepropanol, 2-methyl-, benzoate (ester)

Common Name: Piperocaine

Structural Formula:



Chemical Abstracts Registry No.: 136-82-3

Trade Name	Manufacturer	Country	Year Introduced
Piperocaine	ZYF Pharm Chemical	-	-
Isocaine	Iso-Sol	-	-

Raw Materials

2-Methylpiperidine
Hydrogen chloride
Benzoyl chloride
γ-Chloropropylbenzoate
Sodium hydroxide
3-Chloropropanol

Manufacturing Process

The γ-chloropropylbenzoate was obtained by treatment of benzoyl chloride with 3-chloropropanol.

15.0 g of 2-methyl piperidine and 15.0 g of γ-chloropropylbenzoate are mixed, and heated under a reflux at a temperature of 120°-140°C for 30-40 min. The reaction mixture is then cooled, and treated with 100 ml of ether, and the precipitated secondary amine hydrochloride (i.e., some of the hydrochloride of the unchanged piperidine) filtered off. Hydrogen chloride gas is passed into the filtrate, and crude γ-(2-methylpiperidino)propylbenzoate hydrochloride thereby precipitated. The ether is decanted from the precipitate, and the latter is dissolved in 20 ml of cold water. This solution is treated with 5 ml of 40% sodium hydroxide and 5 ml of benzoyl chloride and the resulting mixture shaken vigorously until the odor of the benzoyl chloride has disappeared. In this manner any unchanged secondary amine is converted into an amide. The alkaline solution, which contains the free base, γ-(2-methylpiperidino)propylbenzoate in suspension is extracted with ether, and the ether extract is evaporated and dried.

References

McElvain S.M.; US Patent No. 1,784,903; Dec. 16, 1930
Kleemann A., Engel J.; Pharmazeutische Wirkstoffe, GeorgThieme Verlag Stuttgart, New York, 1982

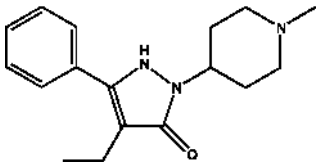
PIPERYLONE

Therapeutic Function: Analgesic

Chemical Name: 4-Ethyl-1-(1-methyl-4-piperidyl)-3-phenyl-3-pyrazolin-5-one

Common Name: Piperylone

Structural Formula:



Chemical Abstracts Registry No.: 2531-04-6

Trade Name	Manufacturer	Country	Year Introduced
Palerol	Novartis	-	-

Raw Materials

α-Ethylbenzoylacetic acid ethyl ester
N-Methyl-piperidyl-4-hydrazine

Manufacturing Process

A mixture of 8.8 parts of α-ethylbenzoylacetic acid ethyl ester and 5,3 parts of N-methyl-piperidyl-4-hydrazine is allowed to stand for 30 min at 22°C, after which the mixture is heated for 5 hours to 130°C under a pressure of 12 mm. After 4 hours 1-(N-methylpiperidyl-4)-3-phenyl-4-ethylpyrazolone-5 begins crystallize out. The reaction mixture is allowed to cool, after which the crystal mass is triturated with ether and then recrystallized from methanol-ether or from acetone. Melting point 159-161°C.

References

Merck Index, Monograph number: 7632, Twelfth edition, 1996, Editor: S. Budavari Merck and Co., Inc.
Jucker E., Erbnoether A., Lindenmann J.; US Patent No. 2,903,460, Assigned to Sandoz A.G., Basel, Switzerland

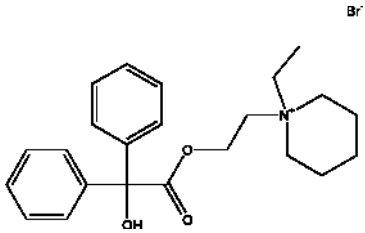
PIPETHANATE ETHOBROMIDE

Therapeutic Function: Anticholinergic, Antiulcer

Chemical Name: Benzilic acid, 2-piperidinoethyl ester ethobromide

Common Name: Piperilate ethyl bromide

Structural Formula:



Chemical Abstracts Registry No.: 4546-39-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Panpurol	Nippon Shinyaku	Japan	-

Raw Materials

Pipethanate hydrochloride
Sodium hydroxide
Ethyl bromide

Manufacturing Process

Pipethanate hydrochloride is dissolved in water and the solution is made alkaline by adding 10% sodium hydroxide solution. The crystals that are separated are filtered off and recrystallized from dilute ethanol. The monohydrate thereby obtained is dehydrated at 100°C under reduced pressure for 20 minutes. The products that are now in the form of a syrup due to loss of water of crystallization are further dehydrated for 2 days in a desiccator over phosphorus pentoxide whereupon the anhydrous pipethanate is obtained.

3.8 g of the anhydrous pipethanate prepared by the method described is dissolved in 15 cc of acetone, 18 g of purified ethyl bromide is added, and the mixture heated for 8 hours in a sealed tube at 100°C to 110°C. After cooling the crystals are separated and isolated by filtration. They are then washed with acetone to give 5.2 g (95.6%) of pipethanate ethylbromide with a decomposition point of 218°C to 220°C. The crystals are almost pure.

References

Merck Index 7346
DOT 7 (1) 23 (1971)
I.N. p. 779
Nippon Shinyaku Co., Ltd.; British Patent 1,148,858; April 16, 1969

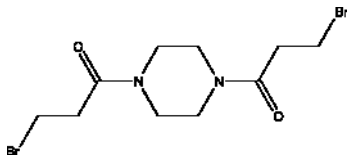
PIPOBROMAN

Therapeutic Function: Antineoplastic

Chemical Name: 1,4-Bis-(3-bromo-1-oxopropyl)piperazine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 54-91-1

Trade Name	Manufacturer	Country	Year Introduced
Vercyte	Abbott	US	1966
Vercyte	Abbott	France	1970
Vercite	Abbott	Italy	1972
Amedel	Dainippon	UK	1973

Raw Materials

Piperazine
3-Bromopropionyl chloride

Manufacturing Process

To a solution of 17.2 g (0.10 mol) of 3-bromopropionyl chloride in 100 ml of anhydrous benzene was added dropwise with stirring a solution of 8.6 g (0.10 mol) of anhydrous piperazine in 20 ml of dry chloroform over a period of 30 minutes. The temperature rose spontaneously to 45°C during the addition. After the temperature ceased to rise, stirring was continued for another hour. The reaction mixture was then filtered to remove the piperazine hydrochloride by-product. The filtrate was evaporated to dryness and the residue recrystallized from ethanol to obtain the desired N,N'-bis-(3-bromopropionyl)piperazine as a white crystalline solid melting at 103°C to 104°C. The identity of the product was further established by elemental analysis.

References

Merck Index 7355
Kleeman & Engel p. 735
OCDS Vol. 2 p. 299 (1980)
I.N. p. 779
REM p. 1156
Abbott Laboratories; British Patent 921,559; March 20, 1963

PIPOTIAZINE

Therapeutic Function: Neuroleptic

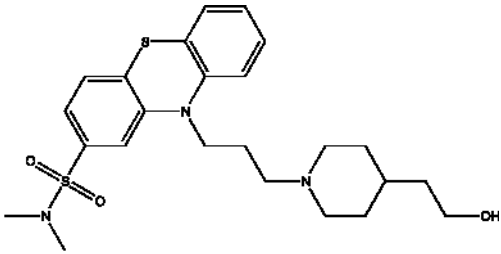
Chemical Name: 10H-Phenothiazine-2-sulfonamide, 10-(3-(4-(2-hydroxyethyl)-1-piperidinyl)propyl)-N,N-dimethyl-

Common Name: Pipothiazine; Pipotiazine

Chemical Abstracts Registry No.: 39860-99-6

Trade Name	Manufacturer	Country	Year Introduced
Piportil	Rhone-Poulenc Rorer	-	-
Piportil	Aventis	-	-

Structural Formula:



Raw Materials

Hydrochloric acid
Sodium amide
4-Hydroxyethyl piperidine
Sodium hydroxide
1-Chloro-3-tetrahydropyranyloxy propane
Methanesulfonyl chloride
Phenthiazine-2-sulfonic acid dimethylamide

Manufacturing Process

10-(3-Tetrahydropyranyloxypropyl)phenthiazine-2-sulfonic acid dimethylamide prepared by condensing 1-chloro-3-tetrahydropyranyloxy propane with phenthiazine-2-sulfonic acid dimethylamide (melting point 140°C) in xylene in the presence of sodamide.

10-(3-Hydroxypropyl)phenthiazine-2-sulfonic acid dimethylamide was prepared by the action of hydrochloric acid in ethanol on 10-(3-tetrahydropyranyloxypropyl)phenthiazine-2-sulfonic acid dimethylamide.

10-(3-Methanesulphonyloxypropyl)phenthiazine-2-sulphonic acid dimethylamide, was obtained by condensing methanesulphonyl chloride in anhydrous pyridine with 10-(3-hydroxypropyl)phenthiazine-2-sulfonic acid dimethylamide.

10-(3-Methanesulphonyloxypropyl)phenthiazine-2-sulfonic acid dimethylamide and 4-hydroxyethyl piperidine in toluene were heated under reflux with stirring. The reaction mixture was allowed to cool and water was added. The resulting toluene solution layer was decanted and washed twice with water. The toluene solution was then stirred with 5% hydrochloric acid. The hydrochloride of the desired phenthiazine base precipitated in gummy condition in the aqueous layer. This was decanted and treated with sodium hydroxide. It was then extracted three times with ethyl acetate. The extracts were dried over sodium sulfate, filtered and concentrated in vacuum. A resinous product was obtained. This product was dissolved in a mixture of benzene and cyclohexane and chromatographed on a column containing alumina. The chromatographed product was eluted successively with mixtures of benzene and cyclohexane and then with benzene and finally with a mixture of benzene and ethyl acetate. The eluates were evaporated to yield a crude product. This product was recrystallised from aqueous ethanol and yielded 10-[3-[4-(2-hydroxyethyl)piperidyl]propyl]phenthiazine-2-sulfonic acid dimethylamide.

References

Jacob R.M., Robert J.G.; US Patent No. 3,150,129; Sept. 22, 1964; Assigned: Rhone-Poulenc S.A., Paris, France a corporation of France

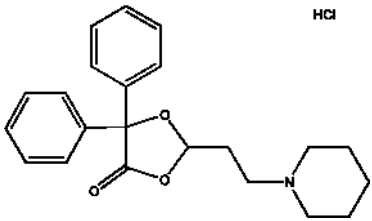
PIPOXOLAN HYDROCHLORIDE

Therapeutic Function: Spasmolytic

Chemical Name: 5,5-Diphenyl-2-[2-(1-piperidinyl)ethyl]-1,3-dioxolan-4-one hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 18174-58-8; 23744-24-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Rowapraxin	Rowa/Wagner	W. Germany	1969

Raw Materials

Benzilic acid
β-Chloropropionaldehyde diethylacetal
Piperidine
Hydrogen chloride

Manufacturing Process

33 g (0.14 mol) of benzilic acid and 22 g (0.13 mol) of β-chloropropionaldehyde diethyl acetal were dissolved in 100 ml of glacial acetic acid by heating. After cooling to 40°C, a slow stream of dry HCl gas was introduced while stirring for 2½ hours. After evaporating the glacial acetic acid in vacuo, the reforming oil was taken up in CH_2Cl_2 and treated with solid $KHCO_3$. After the evolution of CO_2 had ended, water was added and the organic phase was neutralized by means of $KHCO_3$ solution. After drying, the solvent was removed; the remaining oil distilled over under high vacuum at 0.001 mm and at 120° to 130°C to yield the compound 2-(β-chloroethyl)-4,4-

diphenyl-1,3-dioxolan-5-one hydrochloride.

This compound was boiled with 12 g of dry piperidine in 120 ml of absolute benzene for 12 hours under reflux, a total of 6 g of piperidine hydrochloride being separated out. This was filtered off and the benzene solution was concentrated by evaporation. The residue was taken up in a little chloroform and the solution was applied to a dry aluminum oxide column (according to Brockmann); it was thereafter extracted with chloroform. After concentrating the solution by evaporation, an oil was obtained, which was taken up in absolute diethylether. Introduction of dry HCl gas into the cooled solution gave a precipitate which was dissolved and allowed to crystallize from isopropanol/ether. MP 193° to 199°C.

References

Merck Index 7358
Kleeman & Engel p. 736
DOT 6 (3) 95 (1970)
I.N. p. 780
Rowa-Wagner Kommanditgesellschaft Arzneimittelfabrik, Germany; British Patent 1,109,959; April 18, 1968

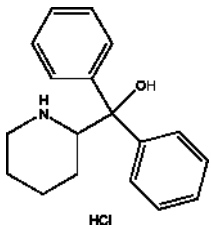
PIPRADROL HYDROCHLORIDE

Therapeutic Function: Central stimulant

Chemical Name: 2-Piperidinemethanol, α,α-diphenyl-, hydrochloride

Common Name: Pipradrol hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 71-78-3; 467-60-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Alertonic	Adcock Ingram Ltd.	-	-

Raw Materials

Hydrogen	α,α-Diphenyl-2-pyridinemethanol hydrochloride

Formaldehyde	Adams' platinum catalyst
Formic acid	Hydrochloric acid

Manufacturing Process

A mixture of 48 g (0.167 mole) of α,α-diphenyl-2-pyridinemethanol hydrochloride (Emraert et al., Ber. 72B, 1188 (1939); 74B, 714 (1940), 160 ml of ethanol, and 3 0.5 g of Adams' platinum catalyst was shaken under an initial hydrogen pressure of 60 pounds. The theoretical amount of hydrogen was absorbed in 5 hours. The reaction mixture was refluxed, diluted with enough water to dissolve all the white solid, and filtered hot from the catalyst. The filtrate was cooled and filtered; yield of 38 g of α,α-diphenyl-alpha-(2-piperidyl)methanol white product melting at 308-309°C with decomposition.

A mixture of 3.5 grams (0.013 mole) of the above α,α-diphenyl-alpha-(2-piperidyl)methanol, 4 g (0.05 mole) of formaldehyde (37%), and 6 grams (0.1 mole) of formic acid was refluxed for 2 days. The reaction mixture was treated with 1.3 g (0.013 mole) of conc. hydrochloric acid and vacuum distilled on the steam bath. The residue was recrystallized from butanone to give the α,α-diphenyl-alpha-(2-piperidyl)methanol hydrochloride which melted at 228-229°C (dec.).

References

Merck Index, Monograph number: 7638, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Werner H.W., Tilford Ch.H.; US Patent No. 2,624,739; Jan. 6, 1953; Assigned to The Wm. Merrel Company, Ohio, a corporation of Delavere

PIPRINHYDRINATE

Therapeutic Function: Antihistaminic, Antiemetic

Chemical Name: 4-Diphenylmethoxy-1-methylpiperidine-, compd. with 8-chlorotheophylline (1:1)

Common Name: Diphenylpyraline teoclate; Piprinhydrinate

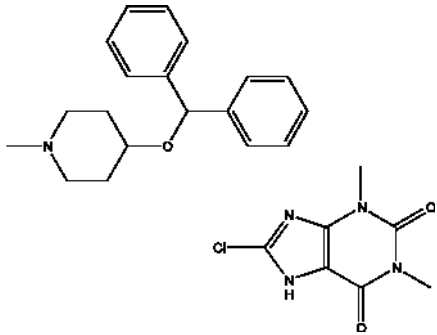
Chemical Abstracts Registry No.: 606-90-6

Trade Name	Manufacturer	Country	Year Introduced
Piprinhydrinate	Kraeber and Co. GmbH	-	-
Piprinhydrinate	Transo-Pharm	-	-

Raw Materials

1-Methyl-4-piperidinol
Benzhydryl bromide
8-Chlorotheophylline

Structural Formula:



Manufacturing Process

A mixture of 46 g of 1-methyl-4-piperidinol (0.4 mol), 49.4 g of benzhydryl bromide (0.2 mol) and 100 ml of xylene was refluxed for approximately 24 hours. The reaction mixture separated into two phases with the upper phase containing the desired ether compound dissolved in xylene. The lower phase consisted of the hydro bromide salt of the excess 1-methyl-4-piperidinol. The upper phase was separated from the lower phase and the desired benzhydryl ether recovered in the crude state by distilling off the xylene under reduced pressure. The crude benzhydryl ether was a clear reddish oil. It was dissolved in 75 ml of 20% hydrochloric acid and the aqueous acid solution then washed three times with 50 ml portions each of ethyl ether. The aqueous acid solution was then decolorized with activated carbon and thereafter slowly admixed with 75 ml of 28% aqueous ammonia. The benzhydryl ether separated as an oily material and was removed from the aqueous mixture by extraction with three 50 ml portions of ethylether. On evaporation of the ethyl ether from the ethyl ether solution, the benzhydryl ether was recovered as a pale yellow oil. The benzhydryl ether was dissolved in 60 ml of isopropanol and the isopropanol solution acidified to a PH of 3 with dry hydrogen chloride-methanol solution. The acidic propanol solution was then diluted with ethyl ether until a faint turbidity was observed. In a short time, the crystalline hydrochloride salt of the benzhydryl ether separated from the propanol solution. The crystallized salt was recrystallized once from 75 ml of isopropanol with the aid of ethyl ether in order to further purify the material. A yield 24.5 g of the pure hydrochloride salt 1-methylpiperldyl-4-benzhydryl ether (diphenylpyraline) was obtained. This was 39% of the theoretical yield. The pure material had a melting point of 206°C.

107 g (0.5 mole) 8-chlorotheophylline was dissolved in the diluted solution of ammonia contained 0.5 moles NH_3. 1 equivalent of this ammonim salt was mixed with 1 equivalent hydrochloride of 1-methylpiperldyl-4-benzhydryl ether in 150 ml of water. 4-Diphenylmethoxy-1-methylpiperidine compound of 8-chlorotheophylline precipitated, filtered off, washed, dried. Yield was quantitative. MP: 151-152°C.

References

Howland L. et al.; US Patent No. 2,479,843; August 23, 1949; Assigned to Nopco Chemical Company, Harrison,N.J., a corporation of New Jersey

Schuler W.A.; D.B. Patent No. 934,890; July 8, 1949; Chemische Fabrik Promonta Gesellschaft mit beschrunkter Haftung, Hamburg

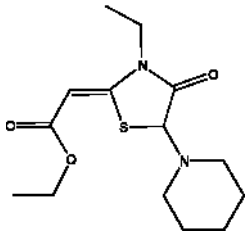
PIPROZOLIN

Therapeutic Function: Choleretic

Chemical Name: [3-Ethyl-4-oxo-5-(1-piperidinyl)-2-thiazolidinylidene]acetic acid ethyl ester

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 17243-64-0

Trade Name	Manufacturer	Country	Year Introduced
Probilin	Goedecke	W. Germany	1977
Probilin	Parke Davis	Italy	1979
Coleflux	Finadiet	Argentina	-
Epsyl	Exa	Argentina	-
Secrebil	Isnardi	Italy	-

Raw Materials

Ethyl thioglycolate
Piperidine
Diethyl sulfate
Sodium ethylate
Ethyl cyanoacetate

Manufacturing Process

Ethyl thioglycolate and ethyl cyanoacetate are first reacted in the presence of sodium ethylate to give 4-oxo-thiazolidin-2-ylideneacetic acid ethyl ester. That is reacted with diethyl sulfate and then with piperidine to give piprozolin.

References

Merck Index 7361
DFU 2 (10) 681 (1977)

Kleeman & Engel p. 737
OCDS Vol. 2 p. 270 (1980)
DOT 14 (1) 26 (1976)
I.N. p. 781
Satzinger, G., Herrmann, M. and Vollmer, K.O.; US Patent 3,971,794; July 27, 1976; assigned to Warner-Lambert Co.

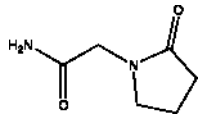
PIRACETAM

Therapeutic Function: Psychotropic

Chemical Name: 2-Oxo-1-pyrrolidineacetamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 7491-74-9

Trade Name	Manufacturer	Country	Year Introduced
Nootropyl	UCB	France	1972
Nootropil	UCB-Smit	Italy	1974
Nootrop	UCB Chemie	W. Germany	1974
Normabrain	Cassella-Riedel	W. Germany	1974
Gabacet	Carrion	France	1980
Ciclocetam	Callol	Spain	-
Ciclofalina	Almirall	Spain	-
Encefalux	Bama-Geve	Spain	-
Eumental	Wassermann	Spain	-
Genogris	Vita	Spain	-
Gericetam	Level	Spain	-
Huberdasen	Hubber	Spain	-
Ideaxan	Millot	France	-
Merapiran	Finadiet	Argentina	-
Nootron	Biosintetica	Brazil	-
Nootropicon	Sidus	Argentina	-
Norotrop	Drifen	Turkey	-
Norzetam	Albert Pharma	Spain	-
Oikamid	Pliva	Yugoslavia	-
Pirroxil	S.I.T.	Italy	-
Pyramen	Pharmachim	Bulgaria	-
Stimubral	Lusofarmaco	Portugal	-
Stimucortex	Kalifarma	Spain	-

Raw Materials

2-Pyrrolidone	Ethyl chloroacetate
Sodium hydride	Ammonia

Manufacturing Process

2-Pyrrolidone is first reacted with sodium hydride, then with ethyl chloroacetate to give ethyl 2-oxo-1-pyrrolidine acetate.

A solution of 0.3 mol of ethyl 2-oxo-1-pyrrolidine acetate in 300 ml of methanol, saturated with ammonia at 20° to 30°C, is heated at 40° to 50°C for 5 hours, while continuously introducing ammonia. The reaction mixture is evaporated to dryness and the residue recrystallized from isopropanol. 2-Oxo-1-pyrrolidineacetamide is obtained in a yield of 86%. MP 151.5° to 152.5°C.

References

Merck Index 7363
Kleeman & Engel p. 737
DOT 9 (6) 215 (1973) & (8) 327 (1973)
I.N. p. 781
Morren, H.; US Patent 3,459,738; August 5, 1969; assigned to UCB (Union Chimique-Chemische Bedrijven), Belgium

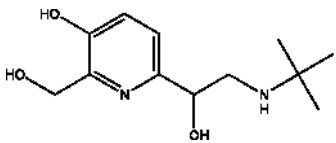
PIRBUTEROL

Therapeutic Function: Bronchodilator

Chemical Name: 2-Hydroxymethyl-3-hydroxy-(1-hydroxy-2-tert-butylaminoethyl)pyridine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 38677-81-5

Trade Name	Manufacturer	Country	Year Introduced
Exirel	Pfizer Taito	Japan	1982
Exirel	Pfizer	UK	1983
Exirel	Pfizer	Switz.	1983

Raw Materials

N-tert-Butyl-2-(5-benzyloxy-6-hydroxymethyl-2-pyridyl)-2-hydroxyacetamide
Diborane
Hydrogen

Manufacturing Process

To 78 ml of a 1 M solution of diborane in tetrahydrofuran under nitrogen and cooled to 0°C is added dropwise over a period of 40 minutes 13.5 g of N-tert-butyl-2-(5-benzyloxy-6-hydroxymethyl-2-pyridyl)-2-hydroxyacetamide in 250 ml of the same solvent. The reaction mixture is allowed to stir at room temperature for 3.5 hours, and is then heated to reflux for 30 minutes and cooled to room temperature. Hydrogen chloride (70 ml, 1.34 N) in ethanol is added dropwise, followed by the addition of 300 ml of ether. The mixture is allowed to stir for 1 hour and is then filtered, yielding 11.0 g, melting point 202°C (dec.). The hydrochloride dissolved in water is treated with a sodium hydroxide solution to pH 11 and is extracted into chloroform (2 x 250 ml). The chloroform layer is dried over sodium sulfate, concentrated to dryness in vacuo, and the residue recrystallized from isopropyl ether, 3.78 g, melting point 81°C to 83.5°C.

A solution of 1.7 g of 2-hydroxymethyl-3-benzyloxy-(1-hydroxy-2-tert-butyl-aminoethyl)pyridine in 30 ml of methanol containing 1.2 ml of water is shaken with 700 mg of 5% palladiumon-charcoal in an atmosphere of hydrogen at atmospheric pressure. In 17 minutes the theoretical amount of hydrogen has been consumed and the catalyst is filtered. Concentration of the filtrate under reduced pressure provides 1.4 g of the crude product as an oil. Ethanol (5 ml) is added to the residual oil followed by 6 ml of 1.75 N ethanolic hydrogen chloride solution and, finally, by 5 ml of isopropyl ether. The precipitated product is filtered and washed with isopropyl ether containing 20% ethanol, 1.35 g, melting point 182°C (dec.).

References

Merck Index 7364
DFU 2 (1) 60 (1977)
OCDS Vol. 2 p. 280 (1980)
DOT 19 (2) 113 (1983) & (7) 384 (1983)
I.N. p. 782
Barth, W.E.; US Patents 3,700,681; October 24, 1972; 3,763,173; October 2, 1973; 3,772,314; November 13, 1973; all assigned to Pfizer, Inc.

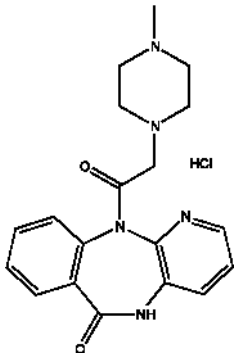
PIRENZEPINE HYDROCHLORIDE

Therapeutic Function: Antiulcer, Antiemetic

Chemical Name: 6H-Pyrido(2,3-b)(1,4)benzodiazepin-6-one, 5,11-dihydro-11-((4-methyl-1-piperazinyl)acetyl)-, dihydrochloride

Common Name: Pirenzepine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 29868-97-1; 28797-61-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Droxol	Microsules Bernabo	-	-
Gasteril	Ripari-Gero	-	-
Gastril	Torrent	-	-
Gastropin	Boehringer-Ingelheim	-	-
Gastrosed	Amsa	-	-
Ulcosan	Dompe	-	-

Raw Materials

Triethylamine
5,11-Dihydro-6H-pyrido[2,3-b][1,4]benzo-diazepin-6-one
N-Methylpiperazine
Chloroacetyl chloride

Manufacturing Process

48.4 g of 5,11-dihydro-6H-pyrido[2,3-b][1,4]benzo-diazepin-6-one were refluxed in 900 ml of absolute dioxane for 15 minutes. Thereafter, over a period of 45 minutes, 28 ml of chloroacetyl chloride and 52 ml of triethylamine were simultaneously added dropwise to the mixture. The mixture was refluxed for eight hours and then vacuum-filtered after having cooled. The filtrate was evaporated in vacuum. The crystalline residue was recrystallized from acetonitrile in the presence of activated charcoal. MP: 212°-213°C (with decomposition). Yield: 85% of theory.

A mixture of 67.5 g of 11-chloroacetyl-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one, 183 ml of N-methylpiperazine and 1.37 liters of absolute benzene was refluxed for 18 hours. Thereafter, the crystalline precipitate was vacuum filtered off, dissolved in aqueous 20% hydrochloric acid, the solution was evaporated in vacuum, the crystalline residue was

dissolved in 250 ml of water while heating, the solution was admixed with 150 ml of isopropanol and active charcoal, filtered, and 2.5 liters of isopropanol were added to the filtrate. After cooling, the precipitate was vacuum filtered off, yielding 70% of theory of the 5,11-dihydro-11-[(4'-methyl-1'-piperazinyl)-acetyl]-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one dihydrochloride, M.P. 257-259°C (decomp.).

The free base of pirenzepine, obtained from the dihydrochloride by making an aqueous solution thereof alkaline with dilute sodium hydroxide and extracting it with chloroform, had MP: 226°-228°C after recrystallization from methanol/ether.

References

Schmidt G. et al.; US Patent No. 3,743,734; July 3, 1973; Assigned to Boehringer Ingelheim G.m.b.H., am Rhein, Germany

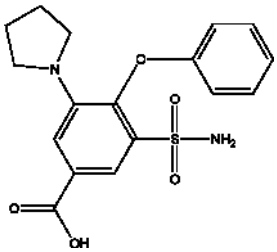
PIRETANIDE

Therapeutic Function: Diuretic

Chemical Name: 3-N-Pyrrolidino-4-phenoxy-5-sulfamylbenzoic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 55837-27-9

Trade Name	Manufacturer	Country	Year Introduced
Arelix	Hoechst	Italy	1980
Arelix	Cassella-Riedel	W. Germany	1982
Tauliz	Hoechst	W. Germany	-

Raw Materials

3-N-Succinimido-4-phenoxy-5-sulfamylbenzoic acid methyl ester
Sodium borohydride
Sodium hydroxide

Manufacturing Process

12.3 g (0.03 mol) of 3-N-succinimido-4-phenoxy-5-sulfamylbenzoic acid methyl ester are dissolved or suspended in 100 ml of absolute diglyme. 9 g of boron trifluoride etherate are added direct to this mixture and a solution of 2.4 g (~0.063 mol) of $NaBH_4$ in 80 ml of diglyme is then added dropwise at room temperature with stirring. As the reaction proceeds exothermically, it is necessary to cool with ice water. The reaction is normally complete after the dropwise addition and a short period of stirring thereafter.

The excess reducing agent is then decomposed by means of a little water (foaming), the solution is filtered and about 300 ml of water are added while stirring. The 3-N-pyrrolidino-4phenoxy-5-sulfamylbenzoic acid methyl ester which has crystallized out is recrystallized from methanol in the form of colorless crystals, melting point 191°C to 192°C.

61 g of 3-N-pyrrolidino-4-phenoxy-5-sulfamylbenzoic acid methyl ester are suspended in 350 ml of 1 N NaOH and the suspension is heated for one hour on the waterbath. 3-N-pyrrolidino4-phenoxy-5-sulfamylbenzoic acid is precipitated from the clear solution by means of 2 N HCl while stirring well. The almost pure crude product can be recrystallized from methanol/water in the form of light yellow platelets, melting point 225°C to 227°C, with decomposition.

References

Merck Index 7366
DFU 2 (6) 393 (1977)
OCDS Vol. 3 p. 58 (1984)
DOT 18 (6) 274 (1982) & (10) 555 (1982)
I.N. p. 782
Bormann, D., Merkel, W. and Muschaweck, R.; US Patents 4,010,273; March 1, 1977; 4,093,735; June 6, 1978; 4,111,953; September 5, 1978; 4,118,397; October 3, 1978; and 4,161,531; July 17, 1979; all assigned to Hoechst AG

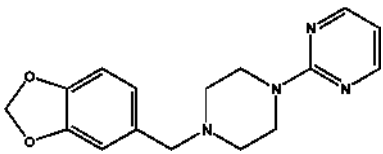
PIRIBEDIL

Therapeutic Function: Vasodilator

Chemical Name: 2-[4-(1,3-Benzodioxol-5-ylmethyl)-1-piperazinyl]pyrimidine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 3605-01-4

Trade Name	Manufacturer	Country	Year Introduced
Trivastal	Eutherapie	France	1969
Trivastan	Servier	Italy	1975
Trivastal	Pharmacodex	W. Germany	1975
Circularina	Searle	-	-

Raw Materials

2-Chloropyrimidine
1-(3':4'-Methylenedioxybenzyl)-piperazine

Manufacturing Process

To a solution of 21 g of 1-(3':4'-methylenedioxybenzyl)-piperazine in solution in 300 cc of anhydrous xylene there were added 28 g of anhydrous potassium carbonate and then 11.3 g of 2-chloropyrimidine. The suspension was then heated for 9 hours at boiling point (130°C). After this time, the mixture was cooled and extracted several times with 10% hydrochloric acid. The acid solution obtained was washed with ether and then rendered alkaline with potassium carbonate; the oily product which was separated was extracted with chloroform and this, after drying with potassium carbonate and evaporation, gave an oily residue weighing 20 g. By dissolution in boiling ethanol and crystallization, 15 g of crystals melting at 96°C were recovered.

References

Merck Index 7368
Kleeman & Engel p. 739
DOT (As ET-495) 6 (1) 29 (1970) & 10 (9) 324, 340 (1974)
I.N. p. 783
Regnier, G., Canevari, R. and Laubie, M.; US Patent 3,299,067; January 17, 1967; assigned to Science Union Et Cie, Societe Francaise De Recherche Medicale (France)

PIRITRAMIDE

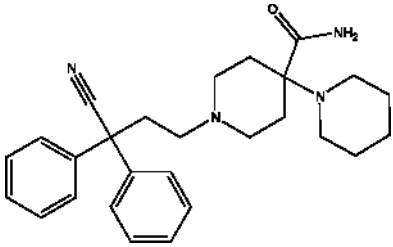
Therapeutic Function: Analgesic

Chemical Name: 1-(3,3-Diphenyl-3-cyanopropyl)-4-piperidino-4-piperidinecarboxamide

Common Name: Pirinitramide

Chemical Abstracts Registry No.: 302-41-0

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Dipidolor	Janssen	W. Germany	1969
Dipidolor	Janssen	UK	1972
Piridolan	Leo	Sweden	-

Raw Materials

3,3-Diphenyl-3-cyanopropyl bromide
4-Piperidino-4-piperidinecarboxamide

Manufacturing Process

A mixture of 84 parts of 3,3-diphenyl-3-cyanopropyl bromide, 41 parts of 4-piperidino-4-piperidinecarboxamide, 64 parts of sodium carbonate, a small amount of potassium iodide and 1,200 parts of anhydrous toluene was stirred, and heated under reflux for 48 hours. At the end of this time the reaction mixture was allowed to cool to room temperature, and 500 parts of water were added. The resultant precipitate was removed by filtration, and triturated with diisopropyl ether. The crystalline material thus obtained was removed by filtration, and recrystallized from 320 parts of acetone, to give 1-(3,3-diphenyl-3-cyanopropyl)-4-piperidino-4-piperidinecarboxamide, melting at about 149°C to 150°C.

References

Merck Index 7373
Kleeman & Engel p. 739
OCDS Vol. 1 p. 308 (1977)
DOT 5 (3) 107 (1969)
I.N. p. 783
N.V. Research Laboratorium Dr. C. Janssen; British Patent 915,835; January 16, 1963
Janssen, P.A.J.; US Patent 3,080,360; March 5, 1963; assigned to Research Laboratorium Dr. C. Janssen N.V.

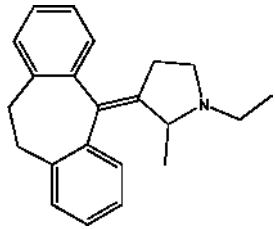
PIROHEPTINE

Therapeutic Function: Antiparkinsonian

Chemical Name: 3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-ethyl-2-methylpyrrolidine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 16378-21-5

Trade Name	Manufacturer	Country	Year Introduced
Trimol	Fujisawa	Japan	1974

Raw Materials

2-Methyl-3-(10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-ylidene)-1-pyrroline
Ethyl iodide
Sodium borohydride

Manufacturing Process

(1) To 3.8 g of 2-methyl-3-(10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-ylidene)-1-pyrroline, there were added 8 g of ethyl iodide. This mixture was placed into a closed vessel and heated at 80°C in a water-bath for one hour. After completing the reaction, the reaction mixture was cooled and the unreacted ethyl iodide was distilled off to yield 5.5 g of 1-ethyl-2methyl-3-(10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-ylidene)-1-pyrrolinium iodide in the form of yellow crystals. These crystals were recrystallized from a mixture of acetone and ether to yield yellow needles of the melting point 223°C.

(2)1-Ethyl-2-methyl-3-(10,11)-dihydro-5H-dibenzo[a,d]cycloheptene-5-ylidene)-1-pyrroliniumiodide (4.7 g) was dissolved in 7 cc of methanol. To this solution there were added 1.4 g of sodium boron hydride within about 80 minutes with stirring and stirring of the solution was continued for two hours to complete the reaction. The reaction mixture was acidified with 10% aqueous hydrochloric acid solution and then the methanol was distilled off. The residual solution was alkalized with 20% aqueous sodium hydroxide solution and extracted with ether. The ether layer was dried over magnesium sulfate and the ether was distilled off. The resulting residue was further distilled under reduced pressure to yield 2.0 g of 1-ethyl-2-methyl-3-(10,11)-dihydro-5H-dibenzo[a,d]cycloheptene-5-ylidene)pyrrolidine (boiling point 167°C/4 mm Hg.).

References

Merck Index 7375
DOT 9 (6) 247 (1973) & 10 (9) 325 (1974)
I.N. p. 784
Deguchi, Y., Nojima, H. and Kato, N.; US Patent 3,454,495; July 8, 1969; assigned to Fujisawa Pharmaceutical Co., Ltd. (Japan)

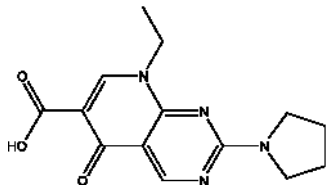
PIROMIDIC ACID

Therapeutic Function: Antibacterial (urinary)

Chemical Name: 8-Ethyl-5,8-dihydro-5-oxo-2-(1-pyrrolidinyl)pyrido[2,3-d]pyrimidine-6-carboxylic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 19562-30-2

Trade Name	Manufacturer	Country	Year Introduced
Panacid	Dainippon	Japan	1972
Pirodal	I.S.F.	Italy	1977
Bactramyl	Carrion	France	1978
Septural	Gruenenthal	W. Germany	1978
Adelir	Teikoku	Japan	-
Coltix	Gerardo Ramon	Argentina	-
Panerco	Erco	Denmark	-
Purim	Mayoly-Spindler	France	-
Reelon	Sanken	Japan	-
Uriclor	Almirall	Spain	-
Urisept	Srbolek	Yugoslavia	-
Zaomeal	Isei	Japan	-

Raw Materials

Pyrrolidine
Sodium hydroxide
Diethyl sulfate
6-Amino-2-methylthiopyrimidine
Ethoxymethylene malonic acid diethyl ester

Manufacturing Process

150 mg of 6-carboxy-5,8-dihydro-8-ethyl-2-methylthio-5-oxopyrido[2,3-d]pyrimidine was added to 30 ml of absolute ethanol containing 1.1 g of dissolved pyrrolidine, and the mixture was reacted for 5 hours at 95°C in a sealed tube. The solvent was removed by distillation, and the residue was recrystallized from methanol-chloroform. There were obtained 111 mg of 6-carboxy-5,8-dihydro-8-ethyl-5-oxo-2-pyrrolidino-pyrido[2,3-d]pyrimidine having a MP of 314° to 316°C.

The starting material is produced by reacting 6-amino-2-methylthiopyrimidine with ethoxymethylene malonic acid diethyl ester. That intermediate is thermally treated in diphenyl ether to give 6-ethoxycarbonyl-2-methylthio-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine. The ethoxy group is hydrolyzed off with sodium hydroxide and one nitrogen is ethylated with diethyl sulfate to give the starting material. These are the same initial steps as used in the pipemidic acid syntheses earlier in this volume.

References

Merck Index 7377
Kleeman and Engel p. 739
OCDS Vol. 2 p. 470 (1980)
DOT 7 (5) 188 (1971)
I.N. p. 36
Dainippon Pharmaceutical Co. Ltd., Japan; British Patent 1,129,358; October 2, 1968
Minami, S., Shono, T., Shmmizu, M. and Takase, Y.; US Patent 3,673,184; June 27, 1972; assigned to Dainippon Pharmaceutical Co. Ltd.
Pesson, M.E. and Geiger, S.W.; US Patent 4,125,720; November 14, 1978; assigned to Laboratoire Roger Bellon

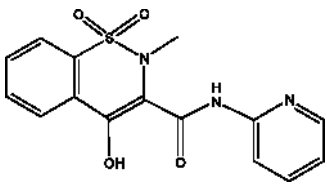
PIROXICAM

Therapeutic Function: Antiinflammatory, Analgesic

Chemical Name: 2H-1,2-Benzothiazine-3-carboxamide, 4-hydroxy-2-methyl-N-2-pyridinyl-, 1,1-dioxide

Common Name: Piroksikam; Pyroxycam

Structural Formula:



Chemical Abstracts Registry No.: 36322-90-4

Trade Name	Manufacturer	Country	Year Introduced
Amida	Euphoric Pharmaceuticals Pvt. Ltd.	-	-
Anartrir	Qif	-	-
Apo-Piroxicam	Apotex Inc.	Canada	-
Artril	Pharmaetica	-	-
Dacam	Star	-	-
Desinflam	Sintyal	-	-
Erazon	Krka	Slovenia	-
Feldene gel	Pfizer	USA	-
Feldoral Sedico	Sedico	Egypt	-
Flogostop	Szabo	-	-
Foldox	Recalcine	-	-
Hotemin	Egis	Hungary	-
Oxa	Beta	-	-
Piroflam	Intas	-	-
Piroflam	Lichtenstein	-	-
Piroflam	Opus	-	-
Pirox	Cipla Limited	India	-
Piroxan	Diba	-	-
Piroxicam	Glaxo Wellcome Poznan S.A.	Poland	-
Piroxicam	Norton Healthcare Ltd.	UK	-
Piroxicam	IPCA laboratories Ltd.	India	-
Piroxicam	Pharmachim Holding EAD, Sopharma AD	Bulgaria	-
Piroxicam	Chemo Iberica	Spain	-
Piroxicam	Nantong General Pharmaceutical Factory	China	-
Piroxicam	Pharmaline	Livan	-
Piroxicam	Jelfa S.A.	Poland	-
Piroxicam	LaborMed Pharma	Rumania	-
Piroxicam	Zdravle	Yugoslavia	-
Piroxicam	Darou Paksh Pharmaceutical Company	Iran	-
Piroxicam	Leciva	Czech Republic	-
Piroxicam Jenapharm	Jenapharm	Germany	-
Piroxicam-Ratiopharm	Ratiopharm	Germany	-
Piroxicam Stada	Stada Arzneimittel AG	Germany	-
Piroxicam-Teva	Teva	Israel	-
Proxigel	Procaps	-	-
Reumador	Slovakofarma	-	-
Reumaplus	Medichrom	-	-
Roxicam	Zdravle	Yugoslavia	-
Roxikam	Rolab	-	-

Trade Name	Manufacturer	Country	Year Introduced
Roxikam	Zdravje	-	-
Sinalgico	Finadiet	-	-
Tetram	Nycomed	-	-

Raw Materials

Methyl iodide
Methyl 3-oxo-1,2-benzoisothyazolin-2-acetate 1,1-dioxide
Sodium hydroxide
Sodium methoxide
Hydrochloric acid

Manufacturing Process

189.6 g (3.51 mol) of sodium methoxide in 1.4 L of dry dimethylsulfoxide was stirred at room temperature (~ 25°C), while under a dry nitrogen atmosphere. To the stirred slurry, there were then added in one complete portion 300 g (1.17 moles) of methyl 3-oxo-1,2-benzoisothyazolin-2-acetate 1,1-dioxide (Chemische Berichte, vol. 30, p. 1267 (1897)) and flask containing the system was then immediately immersed in an ice-methanol bath. The resulting deep red solution was cooled to 30°C and the ice bath removed. The solution was then stirred under dry nitrogen at 30°C for 4 min, cooled quickly to 18°C and then immediately poured into 4.8 L of 3 N hydrochloric acid solution admixed with ice. The resulting slurry was stirred for 15 min, filtered, then washed with water to give 250 g of crude product. Recrystallization from a chloroform-ethanol mixture (1:1) in the presence of charcoal, then afforded a 61% yield of methyl 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide, melting point 173-174°C after two recrystallizations from isopropanol.

A 22 L round-bottomed flask charged with 800 g (3.13 moles) of methyl 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide, 3.2 l of water, 9.6 l of 95% ethanol, 673 ml of methyl iodide (1.53 kg, 10.87 moles) and 3.14 L of 1 N aqueous sodium hydroxide. The reaction mixture was then stirred for 30 min at room temperature, under nitrogen atmosphere and then solution was stored for 23 h. The slurry was then chilled at 0°C and filtered. After washing the filter cake twice with water, ethanol and then diethyl ether there were obtained 537 g of methyl 3,4-dihydro-2-methyl-4-oxo-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide, melting point 165°-168°C after recrystallization from 1.25 L of acetonitrile.

In 3 L round-bottomed flask there were placed methyl 3,4-dihydro-2-methyl-4-oxo-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide, 2-aminopyridin and dry xylene. Nitrogen gas was then bubbled into the suspension for 5 min, then the reaction mixture was heated to begin a period of slow distillation, with complete solution effected during the first 10 min of heating. After 5.5 h, the period of slow distillation was discontinued and reaction mixture was allowed to heat at reflux for approximately 16 h. After that the reaction mixture was cooled to room temperature and filtered. The solid material was crystallized from chloroform with methanol and againe from methanol and then there were obtained piroxicam, melting point 197°-200°C, dec.

References

Lombardino J.G.; US Patent No. 3,591,584; July 6, 1971; Assigned: Pfizer Inc., New York, N.Y.

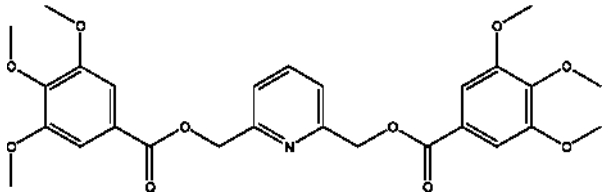
PIROZADIL

Therapeutic Function: Antihyperlipidemic, Platelet aggregation inhibitor

Chemical Name: 2,6-Pyridinemethanol-bis(3,4,5-trimethoxybenzoate)

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 54110-25-7

Trade Name	Manufacturer	Country	Year Introduced
Pemix	Prodes	Spain	1982

Raw Materials

3,4,5-Trimethoxybenzoic acid
Thionyl chloride
Pyridine-2,6-dimethanol

Manufacturing Process

15 kg (70.7 mols) of 3,4,5-trimethoxybenzoic acid and 65 liters of benzene were introduced into a reactor, to which mixture was added 27.4 liters of thionyl chloride. The mass was heated to 56°C to 70°C during a period of 5 hours. The excess of benzene and thionyl chloride was distilled under vacuum. The residue was kept under vacuum at 120°C to 123°C for 1 hour, to obtain a hard crystalline solid.

A solution comprising 3.24 kg (23.3 mols) of pyridine-2,6-dimethanol in 35 liters of pure pyridine was added to the residue and the mass was heated to 80°C for 2½ hours. The reaction mass became brown in color. The chlorhydrate of pyridine so formed was cooled and crystallized. The resulting reaction mass was then poured into water. The precipitate obtained was

filtered, repeatedly rinsed with water, and dissolved in 400 liters of methanol. The resulting solution was filtered with activated charcoal. From this filtration 50 liters of methanol were distilled at normal pressure and then crystallized. 8.35 kg (15.8 mols) of pyridine-2,6dimethanol trimethoxybenzoate were obtained, which represented a yield of 68%.

The product was a white crystalline solid which melted at 119°C to 126°C. Recrystallization in methanolone gave a product which melted at 126°C to 127°C.

References

Merck Index 7379
DFU 6 (5) 290 (1981)
DOT 18, Suppl. 1
Instituto International Terapeutico; British Patent 1,401,608; July 30, 1975

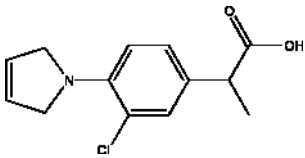
PIRPROFEN

Therapeutic Function: Antiinflammatory

Chemical Name: α-(3-Chloro-4-pyrrolinophenyl)-propionic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 31793-07-4

Trade Name	Manufacturer	Country	Year Introduced
Rengasil	Ciba Geigy	France	1981
Rengasil	Ciba Geigy	Switz.	1981

Raw Materials

Ethyl α-(3-chloro-4-aminophenyl)-propionate hydrochloride
1,4-Dibromo-2-butene

Manufacturing Process

To the mixture of 85.5 g ethyl α-(3-chloro-4-aminophenyl)-propionate hydrochloride, 142 g sodium carbonate and 600 ml dimethyl formamide, 107

g 1,4-dibromo-2-butene are added dropwise while stirring and the whole is refluxed for 5 hours and allowed to stand overnight at room temperature. The mixture is filtered, the filtrate evaporated in vacuo, the residue is triturated with hexane, the mixture filtered, the residue washed with petroleum ether and the filtrate evaporated. The residue is combined with 280 ml 25% aqueous sodium hydroxide and the mixture refluxed for 8 hours. After cooling, it is diluted with water, washed with diethyl ether, the pH adjusted to 5 to 5.2 with hydrochloric acid and extracted with diethyl ether. The extract is dried, filtered, evaporated and the residue crystallized from benzene-hexane, to yield the α-(3-chloro-4-pyrrolinophenyl)-propionic acid melting at 94°C to 96°C.

References

Merck Index 7380
DFU 1 (1) 23 (1976)
OCDS Vol. 2 p. 69 (1980)
DOT 11 (3) 103 (1975)
I.N. p. 784
Carney, R.W.J. and De Stevens, G.; US Patent 3,641,040; February 8, 1972; assigned to Ciba Geigy Corp.

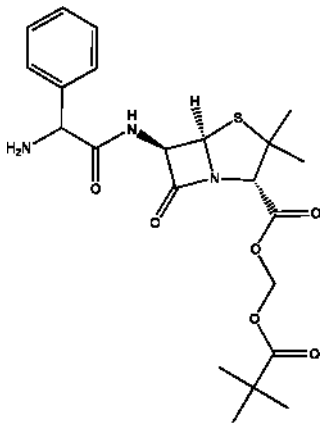
PIVAMPICILLIN

Therapeutic Function: Antibacterial

Chemical Name: 6-[(Aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (2,2-dimethyl-1-oxopropoxy)methyl ester

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 33817-20-8; 26309-95-5 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Maxifen	Sharp and Dohme	W. Germany	1972
Berocillin	Boehringer Ingelheim	W. Germany	1972
Pondocillina	Sigma Tau	Italy	1972
Pivatil	MSD	Italy	1972
Pivatil	Chibret	France	1973
Pondocillin	Burgess	UK	1980
Acerum	Jeba	Spain	-
Bensamin	Turro	Spain	-
Brotacilina	Escaned	Spain	-
Co-Pivam	Sanchez-Covisa	Spain	-
Crisbiotic	Crisol	Spain	-
Dancilin	Hemofarm	Yugoslavia	-
Devonian	Perga	Spain	-
Diancina	Septa	Spain	-
Inacilin	Inibsa	Spain	-
Isvitrol	Therapia	Spain	-
Kesmicina	Kessler	Spain	-
Lancabiotic	Lanzas	Spain	-
Novopivam	Osiris	Argentina	-
Oxidina	Sanitas	Argentina	-
Penimenal	Alalan	Spain	-
Pibena	Jebena	Spain	-
Piva	Efesal	Spain	-
Pivabiot	Galepharma Iberica	Spain	-
Pivadilon	De La Cruz	Spain	-
Pivambol	B.O.I.	Spain	-
Pivamkey	Pereira	Spain	-
Pivapen	Juste	Spain	-
Pivastol	Graino	Spain	-
Piviotic	Miquel	Spain	-
Sanguicillin	Zdravlje	Yugoslavia	-
Tam-Cilin	Quimia	Spain	-
Tryco	Durban	Spain	-
Vampi-Framan	Oftalmiso	Spain	-

Raw Materials

Hydrogen
Potassium D(-)-α-azidobenzylpenicillinate
Chloromethyl pivalate

Manufacturing Process

(A) Pivaloyloxymethyl D(-)-α-azidobenzylpenicillinate: To a suspension of potassium D(-)α-azidobenzylpenicillinate (4.14 g) and potassium dicarbonate

(1.5 g) in acetone (100 ml) and 10% aqueous sodium iodide (2 ml), chloromethyl pivalate (2.7 ml) was added and the mixture refluxed for 2 hours. After cooling, the suspension was filtered and the filtrate evaporated to dryness in vacuo. The remaining residue was washed repeatedly by decantation with petroleum ether to remove unreacted chloromethyl pivalate. The oily residue was taken up in ethyl acetate (100 ml), and the resulting solution washed with aqueous sodium bicarbonate and water, dried and evaporated in vacuo to yield the desired compound as a yellowish gum, which crystallized from ether, melting point 114°C to 115°C.

(B) Pivaloyloxymethyl D(-)-α-aminobenzylpenicillinate, hydrochloride: To a solution of pivaloyloxymethyl D(-)-α-azidobenzylpenicillinate (prepared as described above) in ethyl acetate (75 ml) a 0.2 M phosphate buffer (pH 2.2) (75 ml) and 10% palladium on carbon catalyst (4 g) were added, and the mixture was shaken in a hydrogen atmosphere for 2 hours at room temperature. The catalyst was filtered off, washed with ethyl acetate (25 ml) and phosphate buffer (25 ml), and the phases of the filtrate were separated. The aqueous phase was washed with ether, neutralized (pH 6.5 to 7.0) with aqueous sodium bicarbonate, and extracted with ethyl acetate (2 x 75 ml). To the combined extracts, water (75 ml) was added, and the pH adjusted to 2.5 with 1 N hydrochloric acid. The aqueous layer was separated, the organic phase extracted with water (25 ml), and the combined extracts were washed with ether, and freeze-dried. The desired compound was obtained as a colorless, amorphous powder.

The purity of the compound was determined iodometrically to be 91%. A crystalline hydrochloride was obtained from isopropanol with a melting point of 155°C to 156°C (dec.).

References

Merck Index 7387
Kleeman & Engel p. 741
OCDS Vol. 1 p. 414 (1977)
DOT 8 (4) 148 (1972) & 19 (6) 331 (1983)
I.N. p. 785
REM p. 1201
Frederiksen, E.K. and Godtfredsen, W.O.; US Patent 3,660,575; May 2, 1972; assigned to Lovens Kemiske Fabrik Produktionsaktieselskab (Denmark)
Binderup, E.T., Petersen, H.J, and Liisberg, S.; US Patent 3,956,279; May 11, 1976; assigned to Leo Pharmaceutical Products Ltd. (Denmark)

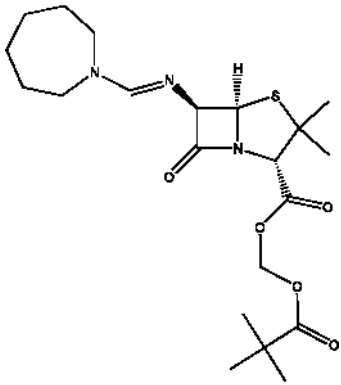
PIVMECILLINAM

Therapeutic Function: Antibacterial

Chemical Name: 6-[[(Hexahydro-1H-azepin-1-yl)methylene]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (2,2-dimethyl-1-oxopropoxy)methyl ester

Common Name: Amdinocillin pivoxil

Structural Formula:



Chemical Abstracts Registry No.: 32886-97-8

Trade Name	Manufacturer	Country	Year Introduced
Selexid	Leo	UK	1977
Melysin	Takeda	Japan	1979
Selexid	Leo	Switz.	1980
Negaxid	Sigma Tau	Italy	1980

Raw Materials

N-Formylhexamethyleneimine
Oxalyl chloride
Pivaloyloxymethyl 6-aminopenicillinate tosylate
Sodium bicarbonate

Manufacturing Process

The starting material N-formylhexamethyleneimine was prepared from hexamethyleneimine and chloral.

12.7 g of N-formylhexamethyleneimine were dissolved in 250 ml of dry ether. While stirring and cooling, 8.5 ml of oxalyl chloride in 50 ml of dry ether were added dropwise, whereafter the mixture was stirred overnight at room temperature. The precipitated amide chloride was filtered off and washed with dry ether, and was placed in an exsiccator.

27.5 g of pivaloyloxymethyl 6-aminopenicillinate tosylate was suspended in 1,500 ml of ethyl acetate with continuous stirring and cooling in an ice bath and 950 ml of ice-cold aqueous sodium bicarbonate (2%) were added. The ethyl acetate layer was separated and was shaken with 750 ml of ice-water containing 25 ml of aqueous sodium bicarbonate (2%), whereafter it was dried over magnesium sulfate at 0°C. After filtration, the solution was evaporated to dryness in vacuo. The residue was dissolved in a solution of 15.5 ml of dry triethylamine in 75 ml of dry alcohol-free chloroform. To this solution, 10 g of the above prepared amide chloride dissolved in 75 ml of dry

alcohol-free chloroform were added dropwise at a temperature of about -20°C. After standing for half an hour at -20°C, the temperature was raised to 0°C within 15 minutes and the solution was evaporated to dryness in vacuo. The residue was stirred with 750 ml of ether. Undissolved triethylamine hydrochloride was filtered off, and the filtrate was again evaporated to dryness in vacuo. The residue was reprecipitated from acetone (200 ml) - water (150 ml). After recrystallization from cyclohexane an analytically pure product was obtained with a melting point of 118.5°C to 119.5°C.

References

Merck Index 391
Kleeman & Engel p. 741
DOT 19 (6) 331 (1983)
I.N. p. 786
REM p. 1201
Lund, F.J.; US Patent 3,957,764; May 18, 1976; assigned to Lovens Kemiske Fabrik Produktionsartieselskab (Denmark)

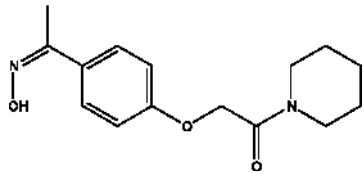
PIXIFENIDE

Therapeutic Function: Antiinflammatory

Chemical Name: 1-[[4-[1-(Hydroxyimino)ethyl]phenoxy]acetyl]piperidine

Common Name: N-(p-1-Nitrosoethyl)phenoxyacetylpiperidine; Pifoxime

Structural Formula:



Chemical Abstracts Registry No.: 31224-92-7

Trade Name	Manufacturer	Country	Year Introduced
Flamanil	Salvoxyl-Wander	France	1975

Raw Materials

p-Hydroxyacetophenone
Methanol
Hydroxylamine
Chloroacetic acid
Piperidine

Manufacturing Process

(A) Preparation of p-Acetylphenoxyacetic Acid: p-Hydroxy-acetophenone is treated with chloroacetic acid in aqueous solution in the presence of sodium hydroxide. The desired acid is then isolated from its sodium salt in a total yield of 80 to 82%, excess of p-hydroxy-acetophenone having been extracted with methylene chloride.

(B) Preparation of Methyl p-Acetylphenoxy-Acetate: A mixture of 80 g of the acid obtained in (A) and 200 ml of methyl alcohol in 600 ml of dichloromethane is refluxed in the presence of sulfuric acid. The desired ester is isolated in accordance with a method known per se, and recrystallized. When the refluxing period is 12 hours, the ester is obtained with a yield of 70%. When the refluxing period is 18 hours, the yield for this ester is 85%.

(C) Preparation of N-(p-Acetylphenoxy-Acetyl)-Piperidine: The ester from (B) is refluxed for 8 hours with 2.5 mols of thoroughly dried piperidine. Then 1 volume of water is added and the product is left to crystallize in the cold. The desired amide is obtained in an 80% yield.

(D) Preparation of N-(p-[1-Isonitrosoethyl]-Phenoxy-Acetyl)-Piperidine: The amide from (C) is refluxed for 5 hours with technical (98%) hydroxylamine and alcohol denatured with methanol. The desired product is obtained in a 75% yield.

In semiindustrial synthesis, to achieve better yields, it is possible to omit (A), by directly preparing the ester (B) by reaction of p-hydroxy acetophenone on ethyl 2-bromoacetate in the presence of potassium carbonate in butanone. The yield of ester is 90%, and elimination of excess of p-hydroxyacetophenone is effected by washing with sodium hydroxide.

References

Merck Index 7300
Kleeman & Engel p. 725
DOT 12 (2) 50 (1976)
Mieville, A.; US Patent 3,907,792; September 23, 1975

PIZOTYLINE HYDROCHLORIDE

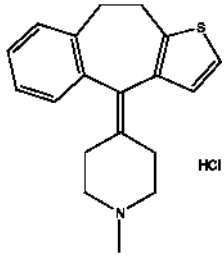
Therapeutic Function: Migraine therapy

Chemical Name: 4-(9,10-Dihydro-4H-benzo[4,5]cyclohepta[1,2-b]thien-4-ylidene-1-methylpiperidine hydrochloride

Common Name: Pizotifen

Chemical Abstracts Registry No.: 15574-96-6 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Sandomigran	Sandoz	Italy	1972
Sandomigran	Sandoz	W. Germany	1974
Sanomigran	Wander	UK	1975
Mosegor	Wander	W. Germany	1976
Sanmigran	Salvoxyl-Wander	France	1976
Polomigran	Polfa	Poland	-

Raw Materials

Phosphorus
Hydrogen chloride
Phthalic anhydride
Magnesium
Thienyl-(2)-acetic acid
1-Methyl-4-chloropiperidine
Phosphorus pentoxide

Manufacturing Process

(A) Preparation of Thenylidene-(2)-Phthalide: 24.2 g of thienyl-(2)-acetic acid, 52.0 g of phthalic acid anhydride, 4.0 g of anhydrous sodium acetate and 125 ml of 1-methylpyrrolidone-(2) are heated while stirring in an open flask for 3 hours to 205° to 208°C, while nitrogen is passed through. It is then cooled and the viscous reaction mixture poured into 1 liter of water. The precipitated substance is filtered off, washed with water and then dissolved in 200 ml of chloroform. After filtering off some undissolved substance, shaking is effected twice with 100 ml of 2 N sodium carbonate solution and then with water, drying is then carried out over sodium sulfate and the volume is reduced by evaporation. The crude phthalide is repeatedly recrystallized from ethanol, while treating with animal charcoal. It melts at 114° to 115°C.

(B) Preparation of o-[2-Thienyl-(2')-Ethyl]Benzoic Acid: 24.0 g of thenylidene-(2)-phthalide, 8.8 g of red pulverized phosphorus, 240 ml of hydrochloric acid (d = 1.7) and 240 ml of glacial acetic acid are heated to boiling under nitrogen and while stirring vigorously. 70 ml toluene are then added and 6.0 g of red phosphorus added in small portions over a period of 1 hour. It is then poured into 3 liters of ice water, stirred with 300 ml of chloroform and the phosphorus removed by filtration.

The chloroform phase is then removed, the aqueous phase extracted twice more with 200 ml of chloroform and the united extracts shaken out 4 times,

each time with 200 ml of 2 N sodium hydroxide solution. The alkaline solution is then rendered acid to Congo red reagent, using hydrochloric acid and extracted 3 times with chloroform. After drying over sodium sulfate and evaporating the solvent, the residue is chromatographed on aluminum oxide (Activity Stage V). The substance eluted with benzene and benzene/chloroform (1:1) is recrystallized from chloroform/hexane (1:1); MP 107° to 109°C.

(C) Preparation of 9,10-Dihydro-4H-Benzo[4,5]Cyclohepta[1,2-b]Thiophen-(4)-One: 200 ml of 85% phosphoric acid and 112 g of phosphorus pentoxide are heated to 135°C. 7.0 g of o-[2-thienyl-(2')-ethyl]benzoic acid are then introduced while stirring thoroughly over a period of 30 min. Stirring is then continued for another hour at 135°C and the reaction mixture is then stirred into 1 liter of ice water. Extraction is then effected 3 times, using 250 ml ether portions, the ethereal extract is washed with 2 N sodium carbonate solution, dried over sodium sulfate and reduced in volume by evaporation. The residue is boiled up with 55 ml of ethanol, the solution freed of resin by decanting and then stirred at room temperature for 6 hours with animal charcoal. It is then filtered off, reduced in volume in a vacuum and the residue distilled. BP 120° to 124°C/0.005 mm, $n_D^{24.5}$ = 1.6559.

(D) Preparation of 4-[1'-Methyl-Piperidyl-(4')]-9,10-Dihydro-4H-Benzo[4,5]Cyclohepta[1,2b]Thiophen-(4)-ol: 0.94 g of magnesium filings which have been activated with iodine are covered with a layer of absolute tetrahydrofuran and etched with a few drops of ethylene bromide. A solution of 5.0 g of 1-methyl-4-chloropiperidine in 5 ml of tetrahydrofuran is then added dropwise and boiling then effected for a further hour under reflux. After cooling to room temperature, the solution of 4.5 g of 9,10-dihydro-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-(4)-one in 5 ml of tetrahydrofuran is added dropwise.

Stirring is carried out first for 3 hours at room temperature and then for 2 hours at boiling temperature, it is then cooled and poured into 300 ml of ice-cold 20% ammonium chloride solution. It is then shaken out with methylene chloride, the methylene chloride solution washed with water and shaken 3 times with 30 ml portions of aqueous 2 N tartaric acid solution. The tartaric acid extract is rendered alkaline while cooling thoroughly and then extracted twice with methylene chloride. After washing with water, drying over potassium carbonate and reducing in volume by evaporation, the residue is recrystallized from ethanol. MP 197° to 199°C.

(E) Preparation of 4-[1'-Methyl-Piperidylidene-(4')]-9,10-Dihydro-4H-Benzo[4,5]Cyclohepta[1,2-b]Thiophene Hydrochloride: 2 g of 4-[1'-methyl-piperidyl-(4')]-9,10-dihydro4H-benzo[4,5]cyclohepta[1,2-b]thiophen-(4)-ol, 60 ml of glacial acetic acid and 20 ml of concentrated hydrochloric acid are boiled for 30 minutes under reflux. After evaporating in a vacuum, the residue is triturated with 3 ml of acetone, the precipitated hydrochloride is then filtered off and it is recrystallized from isopropanol/ether. MP 261° to 263°C (decomposition).

References

Merck Index 7389
Kleeman & Engel p. 742

DOT 9 (6) 221 (1973)
I.N. p. 786
Jucker, E., Ebnother, A., Stoll, A., Bastian, J.-M. and Rissi, E.; US Patent 3,272,826; September 13, 1966; assigned to Sandoz Ltd., Switzerland

POLOXALKOL

Therapeutic Function: Pharmaceutic aid (surfactant)

Chemical Name: Poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene)

Common Name: Poloxalene

Structural Formula: $HO(CH_2CH_2O)_a[CH(CH_3)CH_2O]_b(CH_2CH_2O)_cH$
Average values for a, b, c are a= 12, b = 34, c = 12

Chemical Abstracts Registry No.: 9003-11-6

Trade Name	Manufacturer	Country	Year Introduced
Polykol	Upjohn	US	1958
Therabloat	Norden	US	-

Raw Materials

Propylene glycol
Ethylene oxide

Manufacturing Process

(A) In a 1-liter 3-necked round bottom flask equipped with a mechanical stirrer, reflux condenser, thermometer and propylene oxide feed inlet, there were placed 57 g (0.75 mol) of propylene glycol and 7.5 g of anhydrous sodium hydroxide. The flask was purged with nitrogen to remove air and heated to 120°C with stirring and until the sodium hydroxide was dissolved. Then sufficient propylene oxide was introduced into the mixture as fast as it would react until the product possessed a calculated molecular weight of 2,380. The product was cooled under nitrogen, the NaOH catalyst neutralized with sulfuric acid and the product filtered. The final product was a water-insoluble polyoxypropylene glycol having an average molecular weight of 1,620 as determined by hydroxyl number or acetylation analytical test procedures.

(B) The foregoing polyoxypropylene glycol having an average 1,620 molecular weight was placed in the same apparatus as described in procedure (A), in the amount of 500 g (0.308 mol), to which there was added 5 g of anhydrous sodium hydroxide. 105 g of ethylene oxide was added at an average temperature of 120°C, using the same technique as employed in (A). The amount of added ethylene oxide corresponded to 17.4% of the total weight of the polyoxypropylene glycol base plus the weight of added ethylene oxide.

References

Merck Index 7431
I.N. p. 789
REM p. 1320
Lundsted, L.G.; US Patent 2,674,619; April 6, 1954; assigned to Wyandotte Chemicals Corporation

POLYESTRADIOL PHOSPHATE

Therapeutic Function: Estrogen

Chemical Name: Estra-1,3,5(10)-triene-3,17 diol (17-beta)-, polymer with phosporic acid

Common Name: Polymeric ester of phosphoric acid and estradiol

Structural Formula: Estradiol phosphate polymer

Chemical Abstracts Registry No.: 28014-46-2

Trade Name	Manufacturer	Country	Year Introduced
Estradurin	Ayerst	US	1957
Estradurin	Abello	Spain	-
Estradurin	Leo	Sweden	-

Raw Materials

Estradiol
Phosphorus oxychloride

Manufacturing Process

3 g of estradiol was dissolved in 75 ml of anhydrous pyridine. The solution was cooled to -10°C, whereupon a solution of 1.1 ml of phosphorus oxychloride in 10 ml of anhydrous pyridine was added with agitation. After the addition, which required 7 minutes, the reaction mixture was kept at -10°C for a further period of 3 hours, and then it was left standing at room temperature for 15 hours. A clear solution thus resulted, to which finely crushed ice was then added. The resulting solution was evaporated in vacuum to dryness. After drying in a vacuum desiccator, 3.8 g of a white powder was obtained. This powder was suspended in 2 ml of pyridine, and 25 ml of 0.5 N sodium hydroxide was added, whereupon a solution was obtained which was then diluted with water to 100 ml.

The solution was then dialyzed through a cellophane membrane against 4 liters of water for 10 hours, with stirring. The dialysis was repeated 2 additional times, with fresh amounts of water. To the dialyzed solution there was added 2 ml of 1 N hydrochloric acid, whereupon polyestradiol phosphate

was precipitated as a white bulky precipitate. This was centrifuged off and washed repeatedly with 0.1 N hydrochloric acid. Thereafter it was dried in a vacuum desiccator. The yield was 3 g of polyestradiol phosphate. The analysis shows 0.65% of water, 1.35% of pyridine and 9.3% of phosphorus (calculated on a dry sample).

References

Merck Index 7439
PDR p. 618
I.N. p. 790
REM p. 987
Diczfalusy, E.R., Ferno, O.B., Fex, H.J., Hogberg, K.B. and Linderot, T.O.E.; US Patent 2,928,849; March 15, 1960; assigned to Leo AB, Sweden

POLYETHYLENE GLYCOL 3350

Therapeutic Function: Laxative

Chemical Name: Synthetic polyglycol having an average molecular weight of 3350

Common Name: -

Structural Formula:

Chemical Abstracts Registry No.: 25322-68-3

Trade Name	Manufacturer	Country	Year Introduced
MiraLax	Braintree Laboratories	-	-
Polyethylene Glycol 3350	Schwarz Pharma	-	-

Raw Materials

Ethylene oxide
Polyethylene glycol 400
Potassium hydroxide

Manufacturing Process

Polyethylene glycol 3350 was obtained by polymerization of ethylene oxide in an autoclave at 80-100°C using as a catalyst dipotassium alcogolate of polyethylene glycol 400.

Dipotassium alcogolate of polyethylene glycol 400 was synthesized by a

heating of the dry mixture of polyethylene glycol 400 and potassium hydroxide. The molecular weight of polymer was regulated by the ratio of monomer:catalyst.

References

Bailey F.E. and Koleske J.// Poly(ethylene oxide). N.Y., Acad. Press, 1976

POLYMYXIN

Therapeutic Function: Antibacterial

Chemical Name: See structure

Common Name: -

Structural Formula: Complex antibiotic

Chemical Abstracts Registry No.: 1406-11-7

Trade Name	Manufacturer	Country	Year Introduced
Aerosporin	Burroughs-Wellcome	US	1951
Cortisporin	Burroughs-Wellcome	US	-
Mastimyxin	Chassot	Switz.	-
Neo-Polycin	Merrell Dow	US	-
Neosporin	Burroughs-Wellcome	US	-
Octicair	Pharmafair	US	-
Ophthocort	Parke Davis	US	-
Otobiotic	Schering	US	-
Otocort	Lemmon	US	-
Polyfax	Pitman-Moore	US	-
Polysporin	Burroughs-Wellcome	US	-
Pyocidin	Berlex	US	-
Topisporin	Pharmafair	US	-
Tri-Thalmic	Schein	US	-

Raw Materials

Bacterium Bacillus polymyxa
Nutrient medium
Corn meal

Manufacturing Process

As described in US Patent 2,595,605, in a pilot plant tank 225 liters of a medium containing the following ingredients was prepared: 2% ammonium sulfate, 0.2% potassium dihydrogen phosphate, 0.05% magnesium sulfate

heptahydrate, 0.005% sodium chloride, 0.001% ferrous sulfate heptahydrate, 0.5% yeast extract, 1% dextrose, 1% calcium carbonate and 3% corn meal. The fermentation medium was adjusted to pH 7.3 to 7.4. It was then sterilized for 30 minutes at 110°C. After sterilization the pH was about 7. To the medium was added 225 ml of mineral oil.

The fermentation medium was inoculated with Bacillus polymyxa prepared as follows: A culture of Bacillus polymyxa in a tube with Trypticase soybean broth was incubated overnight at 25°C. 5 ml of this culture was transferred to 100 ml of the tank medium in a 500 ml Erlenmeyer flask which was incubated for 48 hours at room temperature. This 100 ml culture served as inoculum for one tank. During the course of fermentation the medium was aerated at the rate of 0.3 volume of air per volume of mash per minute. The temperature was maintained at about 27°C. Samples of mash were taken every 8 hours in order to determine pH and the presence of contaminants and spores. After 88 hours of fermentation the pH was about 6.3 and an assay using Escherichia coli showed the presence of 1,200 units of polymyxin per cubic centimeter. The polymyxin was extracted and purified by removing the mycelia, adsorbing the active principle on charcoal and eluting with acidic methanol.

Polymyxin is usually used as the sulfate.

References

Merck Index 7445
Kleeman & Engel p. 743
PDR pp.671, 732, 738, 757, 888, 1034, 1232, 1380, 1415, 1429, 1606, 1645
DOT 8 (1) 21 (1972)
I.N. p. 790
REM p. 1202
Ainsworth, G.C. and Pope, C.G.; US Patent 2,565,057; August 21, 1951; assigned to Burroughs Wellcome & Co. (U.S.A.) Incorporated
Petty, M.A.; US Patent 2,595,605; May 6, 1952; assigned to American Cyanamid Company
Benedict, R.G. and Stodola, F.H.; US Patent 2,771,397; November 20, 1956; assigned to the US Secretary of Agriculture

POLYTHIAZIDE

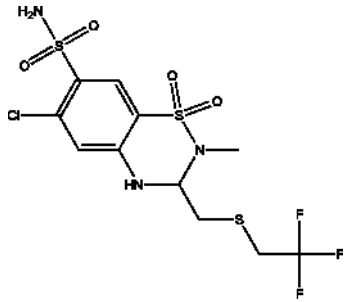
Therapeutic Function: Diuretic

Chemical Name: 6-Chloro-3,4-dihydro-2-methyl-3-[[(2,2,2-trifluoroethyl) thio]methyl]-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide

Common Name: -

Chemical Abstracts Registry No.: 346-18-9

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Renese	Pfizer	US	1961
Drenusil	Pfizer	W. Germany	1962
Renese	Pfizer	Italy	1962
Renese	Pfizer	France	1965
Envarese	Pfizer	France	-
Minizide	Pfizer	US	-
Nephril	Pfizer	UK	-
Polyregulon	Yamanouchi	Japan	-
Toleran	Medica	Finland	-

Raw Materials

4-Amino-2-chloro-5-(methylsulfamyl)benzenesulfonamide
Sodium
Mercaptoacetaldehyde dimethylacetal
Trifluoroethyl iodide

Manufacturing Process

(A) Preparation of trifluoroethylthioacetaldehyde dimethylacetal: To 4.6 g (0.2 mol) of metallic sodium dissolved in 75 ml of absolute methanol is rapidly added 24.4 g (0.2 mol) of mercaptoacetaldehyde dimethylacetal followed by dropwise addition of 42.0 g (0.2 mol) of trifluoroethyl iodide.

The resulting reddish mixture is refluxed on a steam bath for one hour. One half of the alcohol is removed by concentration and the remainder diluted with several volumes of water and extracted with ether. The combined ether extracts are dried over sodium sulfate, the ether then removed at reduced pressure and the residue distilled to about 30 g (BP 82°C/25 mm).

(B) Preparation of 4-Amino-2-Chloro-5-(Methylsulfamyl)Benzenesulfonamide: The 5-substituted-2,4-disulfamyl anilines may be prepared by procedures described in the literature, for example, the general procedures in Monatsch. Chem. vol. 48, p 87 (1927), which involves the treatment of a m-substituted aniline with from 10 to 20 parts by weight of chlorosulfonic acid followed by the gradual addition of from about 90 to 170 parts by weight of sodium chloride. The resultant mixture is heated at approximately 150°C for about 2

hours after which the reaction mixture is poured into water and the resultant 5substituted aniline-2,4-disulfonyl chloride is filtered and is then treated with concentrated ammonium hydroxide or suitable amine by standard procedures to obtain the corresponding disulfonamide.

(C) Preparation of 2-Methyl-3-(2,2,2-Trifluoroethyl)Thiomethyl-6-Chloro-7-Sulfamyl-3,4-Dihydro-1,2,4-Benzothiadiazine-1,1-Dioxide: To 4.6 g (0.015 mol) of 4-amino-2-chloro5-(methylsulfamyl)benzenesulfonamide in 30 ml of the dimethyl ether of ethylene glycol is added 4.08 g (0.02 mol) of 2,2,2-trifluoroethylmercaptoacetaldehyde dimethylacetal followed by 1 ml of ethyl acetate saturated with hydrogen chloride gas. The resulting solution is refluxed for 1.5 hours, cooled and then slowly added to cold water dropwise with stirring. The crude product is filtered, dried and recrystallized from isopropanol (3.2 g), MP 202° to 202.5°C. A second recrystallization from isopropanol raised the MP to 202° to 203°C.

References

Merck Index 7457
Kleeman & Engel p. 743
PDR pp. 1409, 1421
OCDS Vol. 1 p. 360 (1977)
I.N. p. 791
REM p. 940
McManus, J.M.; US Patent 3,009,911; November 21, 1961; assigned to Chas. Pfizer & Co., Inc.

PORFIMER SODIUM

Therapeutic Function: Antineoplastic, Photosensitizer

Chemical Name: Photofrin porfimer sodium (porfimer sodium disigned also as polyporphin oligomer containing ester and ether linkage)

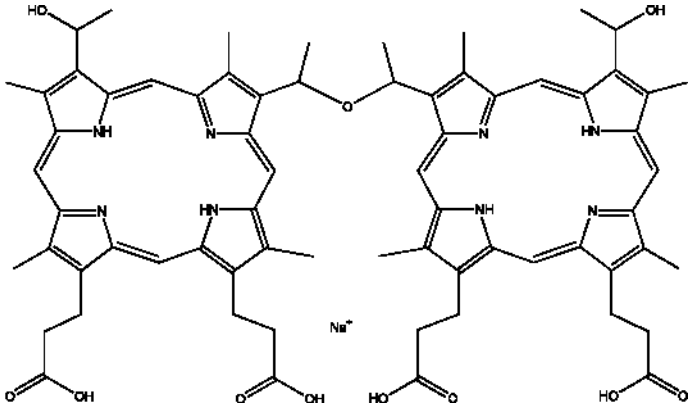
Common Name: Porfimer Sodium; Photofrin II

Trade Name	Manufacturer	Country	Year Introduced
PhotoBarr	Axcan Pharma Inc.	Canada	-
Photofrin II	Lederle Parenterals, Inc.	USA	-
Photofrin II	QLT Phototherapeutics Inc.	-	-
Photofrin II	Wyeth-Ayerst Lederle Parenterals, Inc.	-	-
Photofrin II	Axcan Scandipharm Inc.	USA	-

Raw Materials

Acetic acid
Sodium hydroxide
Sodium acetate
Hematoporphyrin hydrochloride
Sulfuric acid

Structural Formula:



Chemical Abstracts Registry No.: 87806-31-3

Manufacturing Process

285 ml of acetic acid was added to a 1000 ml Erlenmeyer flask containing Teflon-coated magnetic stirring bar. Stirring the acetic acid, slowly 15 ml of concentrated sulfuric acid was added; weighing out 15.0 g of hematoporphyrin hydrochloride (preferably obtained from Roussel Corporation, Paris, France); adding to the acid solution; the reaction acetic mixture was stirred for 1 h. To the reaction acetic mixture 3 L of 5% sodium acetate was added.

The 5% sodium acetate solution now contains a dark red precipitate which is preferably allowed to stand for 1 h with occasional stirring; the dark red precipitate is then again filtered, preferably using the above-identified filter mechanism; the filter cake from the filtering process is then washed with glass-distilled water until the filtrate is at pH of 5.5-6.0 (1500-2500 ml of wash water may be required); and the filter cake is then preferably allowed to dry in air at room temperature. The air-dried precipitate is ground, using for instance, a mortar and pestle until a fine powder is obtained. The powder may then be transferred to a 250 ml round bottom flask. The flask is then attached to a rotating evaporator and rotation under vacuum is maintained at room temperature for preferably 24 h and hemoporphyrin acetate was obtained.

Acetylated hematoporphyrin (1 part by weight) is dissolved in 0.1 N sodium hydroxide (50 parts by volume) and stirred for 1 h at room temperature. After the stir period the solution is adjusted to pH 9.4 to 9.6 with 1 N hydrochloric acid. It is filtered through a 5 μm filter and then concentrated to (12.5 parts) of its original volume in an ultrafilter with 10,000 molecular weight cut off membranes. The solution is then purified via diafiltration maintaining constant volume with 120 volumes of water and keeping the pH at 9.4 to 9.6 with 0.1 N sodium hydroxide. This is also done at room temperature. After the purification, the solution is removed from the ultrafilter, diluted to 3/8 (18.8 parts) of its original volume and pH adjusted to 7.5 to 7.7 with 1 N hydrochloric acid. The solution is then stored at 4°C for 14 to 21 days. After

storage, the solution is pH adjusted to 9.4 to 9.6 with 0.1 N sodium hydroxide and concentrated to 1/4 (12.5 parts) of its original volume. The solution is then repurified as above. The solution is diluted to 3/8 (18.8 parts) of its original volume and pH adjusted to 7.5 to 7.7 with 1 N hydrochloric acid. The solution is then analyzed and, if necessary, it is adjusted to between 13 to 18 mg/ml by the addition of water. The solution is then filtered through a 0.22 μm filter into bottles for storage at 1°C to 4°C to await further processing.

References

Dougherty T.J. et al.; US Patent No. 4,649,151; March 10, 1987; Assigned: Health Research, Inc., Buffalo, N.Y.
Zawadzki R.K., Clauss S.L.; US Patent No. 5,244,914; Sep. 14, 1993; Assigned: American Cyanamid Company, Stamford, Conn.

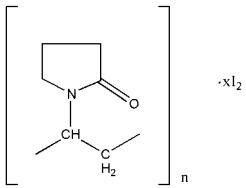
POVIDONE-IODINE

Therapeutic Function: Topical antiinfective

Chemical Name: 1-Ethenyl-2-pyrrolidinone homopolymer compound with iodine

Common Name: PVP-I

Structural Formula:



Chemical Abstracts Registry No.: 25655-41-8

Trade Name	Manufacturer	Country	Year Introduced
Betadine	Purdue Frederick	US	1957
Betadine	Sarget	France	1970
Efodine	Fougera	US	1978
Vagidine	Beecham	US	1981
Clinidine	Clinipad	US	1982
Mallisol	Mallard	US	1983
ACU-Dyne	Acme Laboratories Ltd.	US	-
Batticon	Trommsdorff	W. Germany	-
Betadine Ginecologico	Chinoin	Italy	-
Betaisodona	Mundipharma	Austria	-

Trade Name	Manufacturer	Country	Year Introduced
Braunol	Braun	W. Germany	-
Chem-O-Dine	Remedia	S. Africa	-
Difexon	Bago	Argentina	-
Disadine	Stuart	UK	-
Isodine	Purdue Frederick	US	-
Jodobac	Bode	W. Germany	-
Jodocur	Farm. Milanese	Italy	-
Neojodin	Iwaki	Japan	-
Nutradine	Restan	S. Africa	-
Pevidine	Berk	UK	-
Polydine	Fischer	Israel	-
Povadyne	Chaston	US	-
Proviodine	Rougier	Canada	-
Summer's Eve	Fleet	US	-
Topionic	Rius	Spain	-

Raw Materials

Polyvinylpyrrolidone
Iodine

Manufacturing Process

12 g of dry polyvinylpyrrolidone having a K value of 90 (water content about 2 to 3%) was added to 6 g of solid iodine crystals in a glass bottle containing a few pebbles and beads. This was rolled for 3 days on a roller mill with occasional manual stirring to loosen the material caked on the sides of the bottle. Analysis showed that the thus-obtained product contained 35.4% total iodine and 31.91% available iodine. The material was heat-treated at 95°C for 64 hours in a closed glass bottle with occasional stirring. On completion of this treatment, analysis showed that the material contained 35.3% total iodine, 25.7% available iodine, according to US Patent 2,706,701.

References

Merck Index 7595
PDR pp. 880, 888, 1432
DOT 7 (4) 149 (1971)
I.N. p. 793
REM p. 1164
Beller, H. and Hosmer, W.A.; US Patent 2,706,701; April 19, 1955; assigned to General Aniline & Film Corporation
Hosmer, W.A.; US Patent 2,826,532; March 11, 1958; assigned to General Aniline & Film Corporation
Siggia, S.; US Patent 2,900,305; August 18, 1959; assigned to General Aniline & Film Corporation

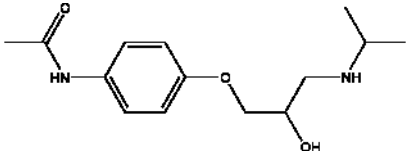
PRACTOLOL

Therapeutic Function: Antiarrhythmic

Chemical Name: N-[4-[2-Hydroxy-3-[(1-methylethyl)amino]propoxy]phenyl] acetamide

Common Name: 1-(4-Acetamidophenoxy)-3-isopropylamino-2-propanol

Structural Formula:



Chemical Abstracts Registry No.: 6673-35-4

Trade Name	Manufacturer	Country	Year Introduced
Eraldin	I.C.I.	UK	1970
Eraldin	I.C. Pharma	Italy	1972
Dalzic	Rhein Pharma	W. Germany	1973
Eraldine	I.C.I. Pharma	France	1973
Cardiol	Orion	Finland	-
Pralon	Farmos	Finland	-

Raw Materials

4-Acetamidophenol
Epichlorohydrin
Isopropylamine

Manufacturing Process

The 1-(4-acetamidophenoxy)-2,3-epoxypropane used as starting material may be obtained as follows. To a solution of 4.5 parts of 4-acetamidophenol and 1.5 parts of sodium hydroxide in 50 parts of water at 15°C, there is added 3.5 parts of epichlorohydrin. The mixture is stirred for 16 hours at ambient temperature, filtered and the solid residue is washed with water. There is thus obtained 1-(4-acetamidophenoxy)-2,3-epoxypropane, MP 110°C.

A mixture of 2 parts of 1-(4-acetamidophenoxy)-2,3-epoxypropane and 10 parts of isopropylamine is stirred at ambient temperature for 16 hours. The resulting solution is evaporated to dryness under reduced pressure and the residue is crystallized from butyl acetate. There is thus obtained 1-(4-acetamidophenoxy)-3-isopropylamino-2-propanol, MP 134° to 136°C.

References

Merck Index 7597
OCDS Vol. 2 pp. 106, 108 (1980)
DOT 6 (5) 188 (1970)
I.N. p. 794
Howe, R. and Smith, L.H.; US Patent 3,408,387; October 29, 1968; assigned to Imperial Chemical Industries Limited, England

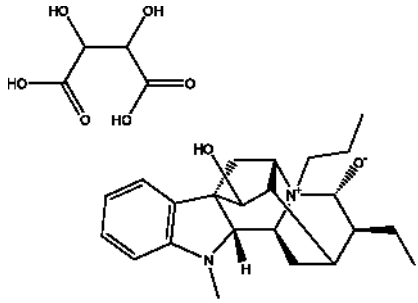
PRAJMALINE BITARTRATE

Therapeutic Function: Antiarrhythmic

Chemical Name: 17R,21α-Dihydroxy-4-propylajmalanium bitartrate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 2589-47-1; 35080-11-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Neo-Gilurtymal	Giulini	W. Germany	1973
Neo-Aritmina	Byk Gulden	Italy	1979

Raw Materials

Ajmaline
Sodium bicarbonate
Allyl bromide
Tartaric acid

Manufacturing Process

1 g of ajmaline was dissolved in 4 cc of chloroform, and 1 cc of allyl bromide

was added to the resulting solution. The reaction mixture thus obtained was allowed to stand for 24 hours at room temperature. Thereafter, the clear reaction solution was briefly cooled to a temperature below 0°C, whereby crystallization set in. The crystals were filtered off and were then recrystallized from a mixture of absolute methanol and absolute ether. The purified colorless crystalline product was identified to be N-(b)-allyl-ajmalinium-bromide having a melting point of 252°C to 254°C.

75 g of N-(b)-n-propyl-ajmalinium-bromide were suspended in 3 liters of an aqueous saturated solution of sodium bicarbonate, and the suspension was admixed with 3 liters of chloroform. The resulting mixture was vigorously stirred for six to eight hours. Thereafter, the chloroform phase was separated and evaporated to dryness. 68 g of a yellow syrup remained as a residue. The aldehyde base was dissolved in about 150 cc of acetone and, while stirring and cooling on an ice bath, the solution was slowly admixed with a solution of 25 g of tartaric acid in 2 liters of acetone. The fine white precipitate formed thereby was separated by vacuum filtration, washed with ether and dried. The raw product, weighing 80 g, was recrystallized once from a mixture of ethanol and ether, yielding 50 g of N-(b)-n-propyl-ajmalinium hydrogen tartrate having a melting point of 149°C to 152°C (decomposition).

References

Merck Index 7598
Kleeman & Engel p. 744
I.N. p. 794
Keck, J.; US Patent 3,414,577; December 3, 1968; assigned to Boehringer Ingelheim G.m.b.H. (Germany)

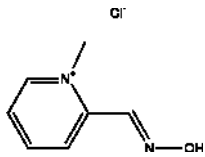
PRALIDOXIME CHLORIDE

Therapeutic Function: Antidote (nerve gas)

Chemical Name: 2-[(Hydroxyimino)methyl]-1-methylpyridinium chloride

Common Name: 2-PAM chloride

Structural Formula:



Chemical Abstracts Registry No.: 51-15-0; 495-94-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Contrathion	Specia	France	1961
Protopam	Ayerst	US	1964
Combo Pen	Rodana Res. Corp.	US	-

Raw Materials

2-Pyridinealdoxime	α-Picoline
Nitrosyl chloride	Dimethyl sulfate
Methyl chloride	Sodium hydroxide

Manufacturing Process

As described in US Patent 3,123,613, the preparation of the intermediate product, 2-pyridinealdoxime methomethylsulfate, is as follows. 1 kg of 2-pyridinealdoxime is dissolved in 6 liters of acetone and filtered until clear. 2 kg (2 equivalents) of freshly distilled dimethyl sulfate are added and the solution mixed. In about 30 minutes crystals start to appear, after which a cooling bath is used to keep the temperature at about 30° to 35°C until the reaction is nearly complete (about 2 hours).

The mixture is allowed to stand at room temperature overnight, the crystals filtered off and washed on a filter with acetone. The product is obtained as colorless needles, which melt at 111° to 112.5°C. The methylsulfate is not stable indefinitely. For preparation of pure chloride salt it is desirable to use methylsulfate which gives no titratable acidity with sodium hydroxide using bromophenol blue as indicator.

10 g of 2-pyridinealdoxime methomethylsulfate are then dissolved in 6 cc of concentrated hydrochloric acid, and 60 cc of isopropanol is added with stirring. Crystals appear almost instantly. After 2 hours standing at room temperature, the crystals are separated by filtration and washed with acetone. The product had a melting point of 227° to 228°C and the yield was 85%.

An alternative route is described in US Patent 3,155,674.

(A) Preparation of 1-Methyl-2-Picolinium Chloride: 98 ml of α-picoline is dissolved in 200 ml of methanol, cooled and 85 ml (at -68°C) of methyl chloride is added. The solution is charged to an autoclave, sealed and the nitrogen pressure of 300 psig is established. The mixture is heated at 120° to 130°C for 2 hours, cooled and opened. The resulting solution is then evaporated to dryness in vacuo, yielding a residue of 110 g. This residue is then dissolved in 50 ml of water and extracted with two 50 ml portions of ether. The aqueous phase is then diluted to 150 ml with water and an assay for ionic chloride is performed which indicates the presence of chloride ion equivalent to 721 mg/ml of l-methyl-2picolinium chloride.

(B) Preparation of 2-(Hydroxyiminomethyl)-1-Methyl Pyridinium Chloride: An aqueous solution of 15 ml of 1-methyl-2-picolinium chloride having a concentration of 477 mg/ml is covered with 50 ml of benzene in an atmosphere of nitrogen and cooled to below 10°C. An aqueous solution of sodium hydroxide is added dropwise and the mixture is stirred for 5 minutes and allowed to stratify. The aqueous phase is then drawn off and the benzene

solution is added slowly to a solution of 3 ml of nitrosyl chloride in 175 ml of benzene containing 0.5 ml of dimethyl formamide at about 10°C in an atmosphere of nitrogen with good agitation. The mixture is then stirred for 1.5 hours and then extracted with four 5 ml of portions of water. The aqueous extracts are then concentrated in vacuo, 30 ml of isopropanol is added and the concentration is repeated. 20 ml of isopropanol is then added to the concentrated mixture, and the mixture is cooled to room temperature and filtered, yielding 3.04 g of crude 2-(hydroxyiminomethyl)-1-methylpyridinium chloride, melting at 202° to 214°C with decomposition. The filtrate is then further concentrated to a 7 g residue which is crystallized from absolute alcohol and yields 0.9 g of 2-(hydroxyiminomethyl)-1-methyl pyridinium chloride melting at 221° to 225°C with decomposition.

References

Merck Index 7599
Kleeman & Engel p. 744
PDR p. 648
I.N. p. 794
REM p. 901
Bloch, L.P.; US Patent 3,123,613; March 3, 1964; assigned to Campbell Pharmaceuticals, Inc.
Ellin, R.I., Easterday, D.E. and Kondritzer, A.A.; US Patent 3,140,289; July 7, 1964; assigned to the US Secretary of the Army
McDowell, W.B.; US Patent 3,155,674; November 3, 1964; assigned to Olin Mathieson Chemical Corporation

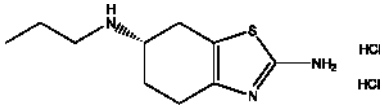
PRAMIPEXOLE DIHYDROCHLORIDE

Therapeutic Function: Antiparkinsonian, Antipsychotic

Chemical Name: 2,6-Benzothiazolediamine-4,5,6,7-tetrahydro-N6-propyl, dihydrochloride, (6S)-

Common Name: Pramipexole dihydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 104632-25-9; 104632-26-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Mirapex	Pharmacia and Upjohn	USA	-

Raw Materials

Phthalic anhydride	4-Aminocyclohexanol hydrochloride
Ethyldiisopropyl amine	Potassium dichromate
Acetic acid	Bromine
Thiourea	Hydrazine hydrate
n-Propanal	Hydrochloric acid
Hydrobromic acid	Sodium borohydride

Manufacturing Process

75.5 g (0.5 mol) of 4-aminocyclohexanol hydrochloride and 74.0 g (0.5 mol) of phthalic acid anhydride are mixed with 65 g (0.5 mol) of ethyldiisopropyl amine and 1000 ml of toluene and boiled for 36 hours with a water separator. Then water is added, the toluene phase is separated off and the aqueous phase is extracted several times with chloroform. The organic phases are combined, dried and concentrated. The concentrated residue is recrystallised from isopropanol and 4-(phthalimido)-cyclohexanol was obtained. Yield: 95 g (77.8%). Melting point 175°-176°C.

95 g (0.388 mol) of 4-(phthalimido)-cyclohexanol are dissolved in 600 ml of chloroform and, after the addition of 450 ml of water and 120 ml of sulfuric acid, 90 g (0.3 mol) of potassium dichromate are added in batches. The internal temperature of the mixture is maintained at between 25° and 30°C by slight cooling. The mixture is stirred for a further 3 hours, then the chloroform phase is separated off and the mixture extracted twice more with chloroform. After drying and concentration of the extracts 82 g (86.9%) of 4-(phthalimido)-cyclohexanone was obtained.

48.6 g (0.2 mol) of 4-(phthalimido)cyclohexanone are dissolved in glacial acetic acid, mixed with 36% of hydrobromic acid in glacial acetic acid and then 32 g (0.2 mol) of bromine in glacial acetic acid is added dropwise with cooling. The mixture is then concentrated by evaporation in vacuo and the residue is triturated several times with diethylether. The ether extracts are discarded and the residue is dissolved in of ethanol. After thiourea have been added the mixture is refluxed for 5 hours. It is then concentrated by evaporation, made alkaline with sodium hydroxide solution and extracted with chloroform. After drying and concentration of the extracts, the residue is purified by column chromatography on silica gel (eluant: chloroform/methanol = 1/1). The 2-amino-6-phthalimido-4,5,6,7-tetrahydro-benzthiazol was obtained. Melting point 244-246°C, dec. Yield: 30 g (50%).

9.5 g (31.7 mmol) of 2-amino-6-phthalimido-4,5,6,7-tetrahydro-benzthiazole are suspended in 100 ml of ethanol and, after the addition of 1.8 g (36 mmol) of hydrazine hydrate, refluxed for 2 hours. The mixture is then concentrated and purified by column chromatography on silica gel using methanol as eluant. The 2,6-diamino- 4,5,6,7-tetrahydro-benzthiazole was obtained.

To a solution of 2,6-diamino- 4,5,6,7-tetrahydro-benzthiazole in dimethylformamide are added n-propanal and the mixture is heated to 50°C for 1 hour. After cooling, the reaction solution is mixed with sodium borohydride and heated to 50°C for 30 min. The solvent is largely eliminated in vacuo. Whilst cooling with ice, the residue is mixed with water and 2 N hydrochloric acid until a pH of 1 is obtained. The aqueous solution is extracted

with ethylacetate and the organic phase discarded. The aqueous phase is mixed with potassium carbonate until an alkaline reaction is obtained and then extracted with ethyl acetate. The organic phase is dried and concentrated. The 2-amino-6-n-propylamino-4,5,6,7-tetrahydro-benzthiazole dihydrochloride crystallizes out when ethereal hydrochloric acid is added. Yield: 42%. Melting point: 286°-288°C.

References

Griss G. et al.; US Patent No. 4,886,812; Dec. 12, 1989; Assigned: Dr. Karl Thomae GmbH, Biberach an der Riss, Fed. Rep. of Germany

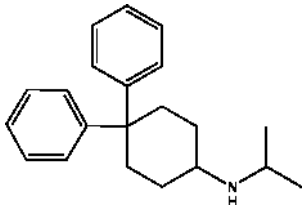
PRAMIVERIN

Therapeutic Function: Spasmolytic

Chemical Name: N-(1-Methylethyl)-4,4-diphenylcyclohexanamine

Common Name: Primaverine; Propaminodiphen

Structural Formula:



Chemical Abstracts Registry No.: 14334-40-8; 14334-41-9 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Sistalgin	Bracco	Italy	1974
Sistalgin	Cascan	W. Germany	1976

Raw Materials

Isopropylamine
4,4-Diphenyl-cyclohexen-(2)-one
Hydrogen

Manufacturing Process

20 g 4,4-diphenyl-cyclohexen-(2)-one, 10 g isopropylamine, and 50 ml tetrahydrofuran are agitated for 10 hours in a bomb tube at 200°C. Subsequently, the reaction mixture is cooled, and the tetrahydrofuran and the

excess isopropylamine are distilled off. The remaining Schiff base is dissolved in methanol and after the addition of 2 g platinum oxide, the base is hydrogenated at normal pressure and room temperature until a quantity of hydrogen corresponding to 2 mols has been absorbed.

The mixture is filtered off from the catalyst, made acidic with dilute hydrochloric acid, and the methanol is removed under vacuum. The remaining aqueous solution is made alkaline with solution of sodium hydroxide and extracted with ether. After drying and concentrating the ether extract, there is obtained 17 g 1-isopropylamino-4,4-diphenyl-cyclohexane, boiling point 164°C to 165°C/0.05 mm. The hydrochloride melts at 230°C.

References

Merck Index 7602
Kleeman & Engel p. 745
DOT 11 (8) 320 (1975)
I.N. p. 795
Unger, R., Sommer, S., Schorscher, E. and Encakel, H.J.; US Patent 3,376,312; April 2, 1968; assigned to E. Merck A.G. (Germany)

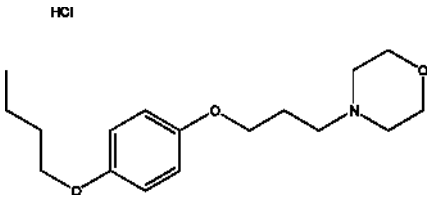
PRAMOXINE HYDROCHLORIDE

Therapeutic Function: Local anesthetic

Chemical Name: 4-[3-(4-Butoxyphenoxy)propyl]morpholine hydrochloride

Common Name: Pramocaine hydrochloride; Proxazocain hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 637-58-1; 140-65-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Tronothane	Abbott	US	1954
Tronothane	Abbott	France	1956
Proctofoam	Reed Carnrick	US	1975
Prax	Ferndale	US	1980
Analpram	Ferndale	US	-
Anusol	Parke Davis	US	-

Trade Name	Manufacturer	Country	Year Introduced
F.E.P.	Boots	US	-
Fleet Relief	Fleet	US	-
Otic-HC	Hauck	US	-
Pramosone	Ferndale	US	-
Tronolane	Ross	US	-
Zone-A	U.A.D. Labs	US	-

Raw Materials

Hydroquinone monobutyl ether
Potassium hydroxide
γ-Morpholinopropyl chloride
Hydrogen chloride

Manufacturing Process

About 5.6 g of potassium hydroxide is dissolved in about 150 cc of refluxing ethanol, and then about 16.6 g of hydroquinone monobutyl ether is added to the alcoholic solution. When the hydroquinone is dissolved, about 16.3 g of γ-morpholinopropyl chloride (dissolved in a small amount of ethanol) is added to the refluxing solution. The solution is refluxed for about 24 hours and then cooled. The product is recovered by filtering the reaction mixture and then removing the solvent by vacuum distillation. The oily residue is acidified and shaken with ether. The acidic phase is made strongly alkaline with 40% sodium hydroxide, and the oil which separates is extracted into ether. The ethereal phase is dried, and the solvent removed by vacuum distillation. The product distills at 183° to 184°C at a pressure of 2.8 mm. The hydrochloride salt of the foregoing base is prepared by dissolving the base in ether and acidifying with hydrochloric acid and is found to have a MP of 181° to 183°C.

References

Merck Index 7603
Kleeman & Engel p. 745
PDR pp. 684, 875, 880, 928, 1316, 1565, 1808
OCDS Vol. 1 p. 18 (1977)
I.N. p. 795
REM p. 1057
Wright, H.B. and Moore, M.B.; US Patent 2,870,151; January 20, 1959; assigned to Abbott Laboratories

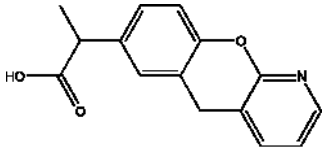
PRANOPROFEN

Therapeutic Function: Analgesic, Antiinflammatory

Chemical Name: 2-(5H-[1]Benzopyrano[2,3-b]-pyridin-7-yl)propionic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 52549-17-4

Trade Name	Manufacturer	Country	Year Introduced
Niflan	Yoshitomi	Japan	1981

Raw Materials

Ethyl 2-cyano-2-(5H-[1]benzopyrano[2,3-b]-pyridin-7-yl)propionate
Hydrogen chloride

Manufacturing Process

A mixture of 100 g of ethyl 2-cyano-2-(5H-[1]benzopyrano[2,3-b]-pyridin-7-yl)propionate, 500 ml of glacial acetic acid and 200 g of concentrated hydrochloric acid is refluxed for 48 hours. The reaction mixture is concentrated, and the residue is dissolved in hot water. The solution is adjusted to pH 2 to 3 by addition of 10% sodium hydroxide. The resulting crystalline precipitate is washed thoroughly with water, and recrystallized from aqueous dioxane to give 74 g of 2-(5H-[1]benzopyrano[2,3-b]-pyridin-7-yl)propionic acid as white crystals melting at 183°C to 183.5°C.

References

Merck Index 7604
DFU 2 (3) 217 (1977) (As Y-8004) & 2 (12) 829 (1977)
Nakanishi, M., Oe, T. and Tsuruda, M.; US Patent 3,931,205; January 6, 1976; assigned to Yoshitomi Pharmaceutical Industries, Ltd.

PRASTERONE

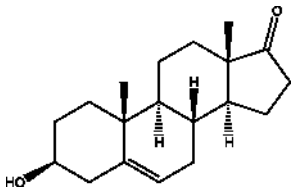
Therapeutic Function: Glucocorticoid

Chemical Name: Androst-5-en-17-one, 3-hydroxy-, (3β)-

Common Name: Dehydroandrosterone; Dehydroepiandrosterone; Dehydroisoandrosterone; Prasterone

Chemical Abstracts Registry No.: 53-43-0

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Aslera	Genelabs Technologies, Inc.	-	-
Prasterone	Proquina SA	-	-
Deandros	Schering AG	-	-

Raw Materials

16-Dehydropregnenolon-3β-acetate
Hydroxylamine hydrochloride
Phosphorus pentachloride

Manufacturing Process

To a solution of 1 gram of 16-dehydropregnenolon-3β-acetate in 10 ml pyridine is added 0.22 gram of hydroxylamine hydrochloride, and the mixture is allowed to stand at room temperature for four days. One gram of 16-dehydropregnenolon-3β-acetate oxime is dissolved in 30 ml of hot dioxane, and then the solution is cooled in an ice bath until about one-half of the dioxane has solidified. Then 1 gram of phosphorus pentachloride is added and the mixture is shaken until all the dioxane has melted. The mixture is maintained at 35°C, for seventy-five minutes, then an excess of ice is added and the solution is again allowed to stand at 35°C. After about thirty minutes, a solution of 5 ml of concentrated hydrochloric acid in 10 ml of water is added, and the mixture is diluted with water, extracted with ether and the ethereal extract washed with dilute sodium hydroxide solution. The ether is removed on a steam bath and the residue is worked up to yield dehydro-isoandrosterone.

References

Tendick F.H., Lawson E.J.; US Patent No. 2,335,616; Nov. 30, 1943; Assigned to Parke Davis and Company, Detroit, Mich., a corporation of Michigan

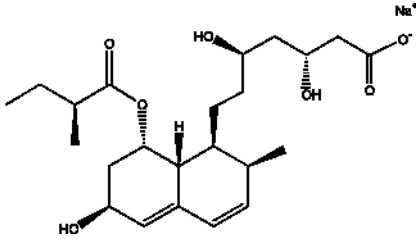
PRAVASTATIN SODIUM

Therapeutic Function: Antihyperlipidemic

Chemical Name: (1S-(1-α(β-S*,δ-S*),2α,6α,8β(R*),8a-α))-1-Naphthaleneheptanoic acid 1,2,6,7,8,8a-hexahydro-2-methyl-8-(2-methyl-1-oxobutoxy)-β,δ,6-trihydroxy-, monosodium salt

Common Name: Eptastation sodium; Pravastatin sodium

Structural Formula:



Chemical Abstracts Registry No.: 81131-70-6; 81093-37-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Apo-Pravastatin	Apotex Inc.	Canada	-
Apo-Pravastatin	Cobalt Pharmaceuticals Inc.	-	-
Lipostat	Bristol-Myers Squibb	France	-
Prastatin	Emcure Pharmaceuticals Ltd.	India	-
Prava	B.-M. Sq./South Africa	S. Africa	-
Pravachol	Bristol-Meyers Squibb	France	-
Pravachol	Silanes	-	-
Pravachol	Generic	-	-
Pravator	Solus	-	-

Raw Materials

Nocardia autotrophica subsp. amethystina FERM P-6183
2-Methyl-8-(2-methyl-1-oxobutoxy)-β,δ-dihydroxy(1S-(1-α(β-S*,δ-S*),2-α,6-α,8-β(R*),8a-α))-1-1,2,6,7,8,8a-hexahydronaphthaleneheptanoate sodium
Sodium hydrogen carbonate
Mortierella maculata nov. spec. E-97 [NCAIM(P)F 001266]

Manufacturing Process

Pravastatin was isolated as products of enzymatic hydroxylation by some kinds of microorganisms of [1S-[1-α(R*),7β,8β(2S*,4S*)8αβ]]-2-methylbutanoic acid 1,2,3,7,8,8a-hexahydro-7-methyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2))-pyran-2-yl)ethyl]-1-naphthalenic lactone (campactin) or their carboxylic acid or their salts (products of animal metabolism of microorganisms from the genera Nocardia, Streptomyces et cetera).

Pravastatin may be preparated by using the microorganisms of genera Nocardia (method 1) and Mortierella (method 2).

Method 1

Cultivation of Nocardia autotrophica subsp. amethystine

Cells of Nocardia autotrophica subsp. amethystina FERM P-6183 was inoculated from a slant culture by means of a platinum loop into each of twenty 500 ml Erlenmeyer flasks, each containing 100 ml of a culture medium having the following composition: glucose - 1.0%, peptone - 0.2%, meat extract - 0.1%, yeast extract - 0.1%, corn steep liquor 0.3%, tap water balance..

Shaking was then carried out at 26°C and 220 r.p.m. for 2 days, at which time sodium 2-methyl-8-(2-methyl-1-oxobutoxy)-β,δ-dihydroxy(1S-(1-α(β-S*,δ-S*),2-α,6-α,8-β(R*),8a-α))-1-1,2,6,7,8,8a-hexahydronaphthaleneheptanoate was added to a final concentration of 0.05% w/v. Incubation was continued at 26°C and 220 r.p.m. for a further 5 days.

Preparation of pravastatin

After completion of the cultivation, the reaction mixture was filtered and the pH of the filtrate was adjusted to a value of 3 by the addition of trifluoroacetic acid. The acidified filtrate was then extracted three times, each with 1 liter of ethyl acetate, to give extracts containing a mixture (6-α and 6-β) of (1S-(1-α,β- S*,δ-S*),2-α,8-βR*),8a-α))-1-naphthaleneheptanoic acid 1,2,6,7,8,8a-hexahydro-2-methyl-8-(2-methyl-1-oxobutoxy)-β,δ,6-trihydroxy.

This extract was then immediately transferred into a 5% w/v aqueous solution of sodium hydrogen carbonate, and the pH of the mixture was adjusted to a value of 7.0 by the addition of 2 N hydrochloric acid. The mixture was then adsorbed on a Diaion HP-20 column. The column was washed with water and then eluted with 50% v/v aqueous acetone to give a fraction containing (1S-(1-α,β- S*,δ-S*),2-α,6-α,8-βR*),8a-α))-1-naphthaleneheptanoic acid 1,2,6,7,8,8a-hexahydro-2-methyl-8-(2-methyl-1-oxobutoxy)-β,δ,6-trihydroxy-, monosodium salt (pravastatin). This was freeze-dried, to give 200 mg of pravastatine.

Method 2

Cultivation of Mortierella maculata nov. spec. E-97 [NCAIM(P)F 001266]

A spore suspension was prepared with 5 ml of a 0.9% sodium chloride solution obtained from a 7-10 day old, malt extract-yeast extract agar slant culture of Mortierella maculata nov. spec. E-97 [NCAIM(P)F 001266] strain able to 6-β-hydroxylate compactin and the suspension was used to inoculate 100 ml inoculum medium PI (glucose-50 g, soybean meal-20 g, in 1000 ml tap water) sterilized in a 500 ml Erlenmeyer flask.

5 liters working volume a bioconversion culture medium is prepared (glucose-20 g, glycerine-20 g, soybean meal-20 g, peptone-5 g, potassium dihydrogen phosphate-0.5 g, polypropylene glycol 2000-1 g, in 1000 ml tap water); the components of the culture medium are added corresponding to 5 liters. Then it was sterilized for 45 min at 121°C and seeded with 500 ml of the inoculum culture.

Before sterilization the pH of the medium was adjusted to 7.0 value.

The fermentation was carried out at 28°C, with a stirring rate of 400 rpm and

with an aeration rate from bottom direction 60 liters/hour for 4 days. At the 2nd day after the transfer the culture started to foam heavily, which can be decreased by the addition of further polypropylene glycol 2000. The pH reached 6.3-7.5 by the 4th day. The feeding of the sodium 2-methyl-8-(2-methyl-1-oxobutoxy)-β,δ-dihydroxy(1S-(1-α(β- S*,δ-S*),2-α,6-α,8-β(R*),8a-α))-1-1,2,6,7,8,8a-hexahydronaphthaleneheptanoate substrate is allowed to be started if the pH of the broth is above 6.3.

Preparation of pravastatin

At the 4th day of the fermentation 2.5 g compactin substrate is added in sterile filtered aqueous solution. Calculated for the volume of the broth 0.5-1.0% glucose was added into the culture depending on the pH in the form of 50% solution sterilized at 121°C for 25 min in parallel with the substrate feeding. After 24 hours the compactin substrate is consumed from the culture (is detected by HPLC) and was converted to pravastatin. By lyophilization of the aqueous residue 1.3 g pravastatin was obtained. The chromatographically pure product was crystallized from a mixture of ethanol and ethyl acetate. Melting point: 170-173°C (decomp.).

References

Terahara A., Tanaka M.; US Patent No. 4,537,859; Aug. 27, 1985; Assigned: Sankyo Company, Limited, Tokyo, Japan
Jekkel A., et al.; US Patent No. 6,682,913 B1; Jan. 27, 2004; Assigned: Institute for Drug Research Ltd.

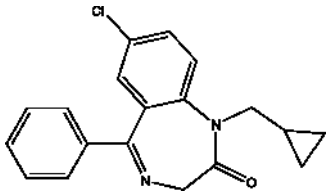
PRAZEPAM

Therapeutic Function: Tranquilizer

Chemical Name: 7-Chloro-1-(cyclopropylmethyl)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 2955-38-6

Trade Name	Manufacturer	Country	Year Introduced
Demetrin	Goedecke	W. Germany	1973
Centrax	Parke Davis	US	1977
Demetrin	Cosmopharma	Switz.	1978
Lysanxia	Substantia	France	1979
Prazene	Parke Davis	Italy	1980
Trepidan	Sigma Tau	Italy	1980
Centrax	Warner William	UK	1981
Demetrin	Parke Davis	France	1982
Reapam	Goedecke	W. Germany	-
Verstran	Warner-Chilcott	US	-

Raw Materials

Phthalimidoacetyl chloride
Manganese dioxide
Hydrazine hydrate
Lithium aluminum hydride
2-Amino-5-chlorobenzophenone
Cyclopropane carboxylic acid chloride

Manufacturing Process

Preparation of 2-Cyclopropylcarbonylamido-5-Chlorobenzophenone: To 400.5 g (1.73 mols) of 2-amino-5-chlorobenzophenone dissolved in 220 g (2.18 mols) of triethylamine and 3.5 liters of tetrahydrofuran is added cautiously 181 g (1.73 mols) of cyclopropanecarboxylic acid chloride. The reaction is refluxed 2½ hours and allowed to cool to room temperature. The solvent is then removed under vacuum to obtain 2-cyclopropylcarbonylamido-5-chlorobenzophenone as a residue which is dissolved in 1 liter of methylene chloride, washed twice with 5% hydrochloric acid, and then twice with 10% potassium hydroxide. The methylene chloride solution is then dried over anhydrous magnesium sulfate, filtered and the solvent removed under vacuum. The residue is recrystallized from 1,500 ml of methanol, charcoal-treating the hot solution to give 356 g of 2-cyclopropylcarbonylamido-5-chlorobenzophenone, MP 105° to 105.5°C (69% yield).

Preparation of 2-Cyclopropylmethylamino-5-Chlorobenzhydrol: To a slurry of 94.8 g (2.47 mols) of lithium aluminum hydride in 1.2 liters of tetrahydrofuran is added with stirring a solution of 356 g (1.18 mols) of 2-cyclopropylcarbonylamido-5-chlorobenzophenone in 1.8 liters of tetrahydrofuran. The addition takes 80 minutes while maintaining gentle refluxing, and the reaction mixture is then refluxed overnight and allowed to cool to room temperature over a period of 3 days. The complex formed in the reaction mixture is then hydrolyzed with water.

During the hydrolysis, 500 ml of tetrahydrofuran is added to facilitate stirring. At a point where the flocculant white precipitate settles quickly when stirring is interrupted, the mixture is filtered, the filter cake washed with solvent, the combined filtrates dried over magnesium sulfate, filtered and the solvent removed under vacuum to obtain 2-cyclopropylmethylamino-5-chlorobenzhydrol as a residue. The residue is recrystallized from 1,300 ml of Skelly B, giving 315 g of 2-cyclopropylmethylamino-5-chlorobenzhydrol, MP 85° to 85.5°C (93% yield).

Preparation of 2-Cyclopropylmethylamino-5-Chlorobenzophenone: To a solution of 315 g (1.09 mols) of 2-cyclopropylmethylamino-5-chlorobenzhydrol in 4 liters of benzene is added 453.6 g (5.22 mols) of manganese dioxide, freshly prepared according to the method of Attenburrow et al, J.C.S. 1952, 1104. The mixture is then refluxed for 1¼ hours, filtered, and the filtrate evaporated under vacuum. The reddish residue is recrystallized from 510 ml of 90% acetone-10% water, giving 181 g of pure 2-cyclopropylmethylamino-5-chlorobenzophenone, MP 79° to 80°C (58% yield). Upon concentration of the mother liquor a second crop of 2-cyclopropylmethylamino-5-chlorobenzophenone weighing 34.1 g and melting at 76.5°-78°C are obtained.

Preparation of 2-(N-Phthalimidoacetyl-N-Cyclopropylmethyl) -Amino-5-Chlorobenzophenone: To a solution of 36.0 g (0.126 mol) of 2-cyclopropylmethylamino-5-chlorobenzophenone in 500 ml of tetrahydrofuran is added 50.7 g (0.252 mol) of phthalimidoacetyl chloride. The resulting solution is refluxed for 16 to 24 hours, the solvent removed under vacuum, the residual oil crystallized from 200 ml of ethanol and recrystallized from 500 ml of 80% ethanol-20% tetrahydrofuran giving 44.7 g of 2-(N-phthalimidoacetyl-N-cyclopropylmethyl)-amino-5-chlorobenzophenone, MP 163° to 164°C (75% yield).

Preparation of 1-Cyclopropylmethyl-5-Phenyl-7-Chloro-1H-1,4-Benzodiazepine-2(3H)-one: To a solution of 39.5 g (0.0845 mol) of 2-(N-phthalimidoacetyl-N-cyclopropylmethyl)amino5-chlorobenzophenone in a mixture of 423 ml of chloroform and 423 ml of ethanol is added 9.52 g (0.1903 mol) of hydrazine hydrate and 9.52 ml of water. This solution is allowed to stand at room temperature. In 3 hours a precipitate begins to form in the solution. After standing 16 to 24 hours a voluminous pulpy white precipitate forms. The solvents are removed under vacuum while keeping the temperature under 40°C and the residue is partitioned between dilute ammonia water and ether.

The aqueous layer is separated and washed with ether, the ether extracted with 5% hydrochloric acid, the acidic solution is made basic with 10% sodium hydroxide and again extracted with ether. Since some spontaneous crystallization occurs in the ether, the solvent is removed without drying under vacuum and the residue is recrystallized from 35 ml of ethanol giving 18.0 g of 1-cyclopropylmethyl-5-phenyl-7-chloro-1H-1,4-benzodiazepine-2(3H)-one, MP 145° to 146°C (65% yield), according to US Patent 3,192,199.

References

Merck Index 7608
Kleeman & Engel p. 747
PDR p. 1320
OCDS Vol. 2 p. 405 (1980)
DOT 2 (3) 119 (1966); 9 (6) 237 (1973); & 10 (5) 179 (1974)
I.N. p. 796
REM p. 1063
McMillan, F.H. and Pattison, I.; US Patent 3,192,199; June 29, 1965
Wuest, H.M.; US Patent 3,192,200; June 29, 1965

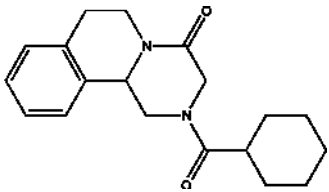
PRAZIQUANTEL

Therapeutic Function: Anthelmintic

Chemical Name: 2-(Cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 55268-74-1

Trade Name	Manufacturer	Country	Year Introduced
Cesol	Merck	W. Germany	1980
Biltricide	Bayer	W. Germany	1980
Cenaride	Merck Clevenot	France	1981
Biltricide	Bayer	France	1983
Biltricide	Miles	US	1983
Droncit	Bayvet	US	-

Raw Materials

2-Cyclohexylcarbonyl-4-oxo-2,3,6,7-tetrahydro-4H-pyrazino[2,1-a] isoquinoline
Hydrogen

Manufacturing Process

15 g of a nickel-aluminum alloy (1:1) is introduced in incremental portions and under agitation into 200 ml of 20% sodium hydroxide solution within 5 minutes; the mixture is maintained at 80°C for 45 minutes, then allowed to settle, decanted off, washed with water, and 1,000 ml of 1% (-)-tartaric acid solution is added thereto, adjusted to pH 5 with 1 N sodium hydroxide solution. The mixture is heated under agitation for 90 minutes to 80°C, decanted, and washed with water and methanol. The thus-obtained (-)-tartaric acid-Raney nickel catalyst is added to a solution of 2-cyclohexylcarbonyl-4-oxo-2,3,6,7-tetrahydro-4H-pyrazino[2,1-a]isoquinoline. The reaction mixture is hydrogenated under normal pressure and at room temperature. After the catalyst has been filtered off and the solvent evaporated, 2-cyclohexylcarbonyl-4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline, melting point 136°C to 138°C, is produced.

References

Merck Index 7609
Kleeman & Engel p. 748
PDR p. 1249
DOT 13 (3) 121 (1977) & 17 (10) 429 (1981)
I.N. p. 796
REM p. 1237
Seubert, J., Thomas, H. and Andrews, P.; US Patent 4,001,411; January 4, 1977; assigned to Merck Patent G.m.b.H. (Germany)

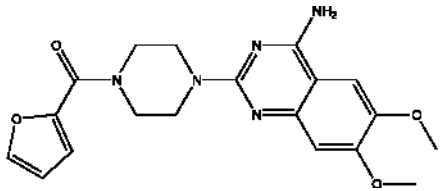
PRAZOSIN

Therapeutic Function: Antihypertensive

Chemical Name: 1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)piperazine

Common Name: Furazosin

Structural Formula:



Chemical Abstracts Registry No.: 19216-56-9; 19237-84-4 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Hypovase	Pfizer	UK	1974
Minipress	Pfizer	US	1976
Minipress	Pfizer	W. Germany	1977
Minipress	Pfizer	Italy	1978
Minipress	Pfizer	France	1979
Minipress	Pfizer Taito	Japan	1981
Adversuten	Arzneimittelwerk Dresden	E. Germany	-
Orbisan	Mack	W. Germany	-
Pratsiol	Orion	Finland	-
Prazac	Erco	Denmark	-
Sinetens	Carlo Erba	UK	-
Vasoflex	Alkaloid	Yugoslavia	-

Raw Materials

Piperazine
2,4-Dichloro-6,7-dimethoxyquinazoline
Ammonia
2-Furoyl chloride

Manufacturing Process

Preparation of 2-Chloro-4-Amino-6,7-Dimethoxyquinazoline: To 800 ml of a solution of anhydrous ammonia in tetrahydrofuran at room temperature is added 30 g of 2,4-dichloro-6,7-dimethoxyquinazoline [F.H.S. Curd et al., J. Chem. Soc., p 1759 (1948)]. The mixture is stirred for 44 hours. The precipitate (29 g, MP 267° to 268°C) is filtered and recrystallized from methanol to yield 19 g of 2-chloro-4-amino-6,7-dimethoxyquinazoline, MP 302°C (dec.).

Preparation of 2-(1-Piperazinyl)-4-Amino-6,7-Dimethoxyquinazoline: To 5 g of 2-chloro-4-amino-6,7-dimethoxyquinazoline, is added 20 g of a 25% solution of piperazine in ethanol. The mixture is heated at 160°C for 16 hours in a pressure bottle. The solvent is then evaporated and the residue is recrystallized from methanol/water.

Preparation of 2[4-(2-Furoyl)-Piperazinyl]-4-Amino-6,7-Dimethoxyquinazoline: To 0.10 mol 2-(1-piperazinyl)-4-amino-6,7-dimethoxyquinazoline in 300 ml methanol is added with vigorous stirring, 0.10 mol 2-furoyl chloride. After addition is complete, the mixture is stirred for 3 hours at room temperature. The solids are filtered to give the desired product, MP 278° to 280°C.

References

Merck Index 7610
Kleeman & Engel p. 748
PDR pp. 1420, 1421
OCDS Vol. 2 p. 382 (1980) & 3, 194 (1984)
DOT 11 (2) 67, 80 (1975)
I.N. p. 796
REM p. 844
Hess, H.-J.E.; US Patent 3,511,836; May 12, 1970; assigned to Chas. Pfizer & Co., Inc.

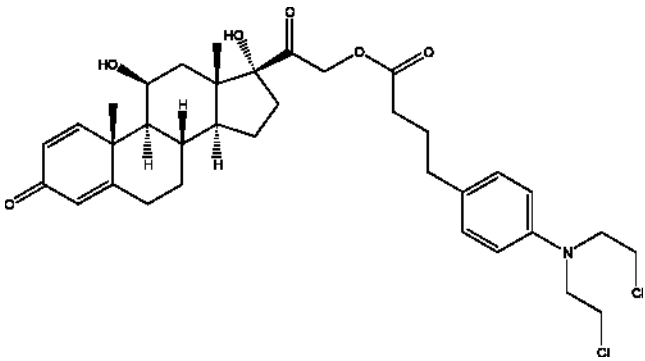
PREDNIMUSTINE

Therapeutic Function: Cancer chemotherapy

Chemical Name: Prednisolone 21-[4'-[p-bis(2-chloroethyl)amino]phenyl] butyrate

Common Name: Prednisolone chlorambucil ester

Structural Formula:



Chemical Abstracts Registry No.: 29069-24-7

Trade Name	Manufacturer	Country	Year Introduced
Stereocyt	Bellon	France	1978
Sterecyt	Leo	Switz.	1981
Mostarina	Abello	Spain	-

Raw Materials

Prednisolone
p-[N-Bis(β-chloroethyl)amino]phenyl butyric acid
Thionyl chloride

Manufacturing Process

p-[N-bis(β-chloroethyl)amino] phenyl butyric acid was dissolved in a mixture of 150 ml dry benzene and 8.04 ml dry pyridine. The solution was cooled in an ice bath, and a solution of thionyl chloride in 30 ml dry benzene was slowly added with stirring under anhydrous conditions.

The reaction mixture was then kept at room temperature for 1 hour and thereafter poured into a mixture of 5.0 N HCl and crushed ice. The benzene solution was immediately washed with water, with cold 1.0 N $NaHCO_3$ and finally with cold water. After drying over anhydrous sodium sulfate, the benzene was removed in vacuo. The residue is the p-[N-bis(β-chloroethyl)amino]phenyl butyric anhydride which could be used without any further purification.

To a solution of 42.0 g of p-[N-bis(β-chloroethyl)amino]phenyl butyric anhydride in 500 ml dry pyridine was added 24.4 g of prednisolone. The reaction mixture was kept at room temperature for 24 hours under anhydrous condition. It was then poured into a mixture of concentrated HCl and crushed ice and extracted with ether-ethyl acetate (1:1).

The organic phase was washed several times with cold 1.0 N K_2CO_3 and finally

water. After drying over $CaCl_2$ the solvent was removed in vacuo.

The residue is prednisolone 21-[4'-[p-bis(β-chloroethyl)amino]phenyl]butyrate which after crystallization from methanol/water had a melting point of 163°C to 164°C.

References

Merck Index 7612
DFU 1 (3) 137 (1976)
Kleeman & Engel p. 749
OCDS Vol. 3 p. 93 (1984)
DOT 16 (3) 84 (1980)
I.N. p. 797
Fox, H.J., Hogberg, K.B. and Konyves, I.; US Patent 3,732,260; May 8, 1973; assigned to A.B. Leo

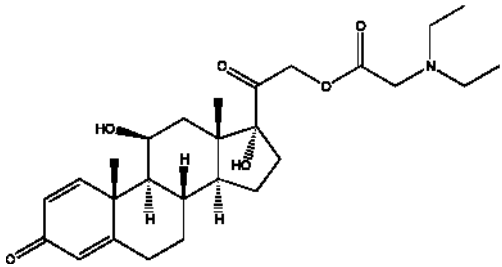
PREDNISOLAMATE

Therapeutic Function: Glucocorticoid

Chemical Name: 11β,17,21-Trihydroxypregna-1,4-diene-3,20-dione 21-N,N-diethylglycine ester

Common Name: Prednisolamate; Prednisolone diethylaminoacetate

Structural Formula:



Chemical Abstracts Registry No.: 5626-34-6

Trade Name	Manufacturer	Country	Year Introduced
Prednisolamate	Pfizer and Co.	-	-

Raw Materials

Prednisolone
Chloroacetyl chloride
Diethylamine

Manufacturing Process

To a solution of 30 g prednisolone and 10.2 ml pyridine in 99 ml dimethylformamide, cooled to 0°C in an ice bath and protected from atmospheric moisture, was added dropwise with stirring 9.6 ml chloroacetyl chloride. Stirring was continued for 1 hour at 0°C, then stopped and the reaction allowed to come to room temperature and stand overnight. The following morning the reaction mixture was poured with vigorous stirring into a vessel containing 360 ml 1 N sulfuric acid, and the product washed with fresh portions of water to neutral wash was obtained. The product was thoroughly dried in a vacuum desiccator and recrystallized from isopropyl alcohol, using 200 ml solvent. The yield was better than 80%, and the compound had MP: 240.6°-242.8°C and $[\alpha]^D$ = +114.6° (Dioxane).

Two grams of this prednisolone chloracetate and 40 ml of colorless, freshly distilled diethylamine were refluxed, with stirring, under nitrogen for one hour. The excess diethylamine was removed in vacuum at room temperature. The residue was taken up in 100 ml $CHCl_3$, and a small amount of water; the $CHCl_3$, was washed with one 50 ml portion of 5% aqueous sodium bicarbonate and two 50 ml portions of water, and dried over sodium sulfate. The chloroform was then concentrated to dryness in vacuum. The residue was recrystallized from acetone-hexane yielded prednisolone 21-diethylaminoacetate 1.67 g; MP: 175.0°-197.2°C. This product (1 g) was suspended in a mixture of 15 ml acetone and 1.5 ml chloroform. The suspension was cooled to 0°C in an ice bath, and with vigorous stirring the ethereal HCl solution was slowly added until the resulting mixture gave an acid reaction to the congo red paper. The product was removed by filtration and recrystallized from ethanol. The yield was approximately 80%; MP: 239.4°-239.8°C; $[\alpha]^D$ = +120.7° (water). The product was the hydrochloride salt of the prednisolone-N,N-diethylaminoacetate, very active therapeutically and excellently water-soluble.

References

Ch.Pfizer and Co., Inc., a corporation of the State Delaware, USA; G.B. Patent No. 862,370; Aug. 31, 1956

PREDNISOLONE

Therapeutic Function: Glucocorticoid

Chemical Name: 11β,17,21-Trihydroxypregna-1,4-diene-3,20-dione

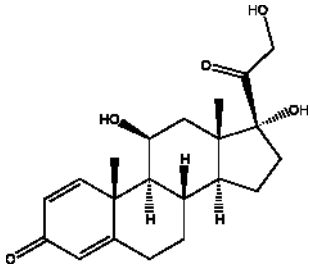
Common Name: Metacortandralone; Δ^1-Hydrocortisone

Chemical Abstracts Registry No.: 50-24-8

Raw Materials

Hydrocortisone	Bacterium Corynebacterium simplex

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Sterane	Pfizer	US	1955
Meticortelone	Schering	US	1955
Delta-Cortef	Upjohn	US	1955
Hydeltra	MSD	US	1955
Paracortol	Parke Davis	US	1957
Sterolone	Rowell	US	1957
Prednis	U.S.V. Pharm.	US	1957
Ulacort	Fellows-Testagar	US	1960
Cosilone	Person Covey	US	1963
Adnisolone	Adams	Australia	-
Aprednislon	Arcana	Austria	-
Caberdelta	Caber	Italy	-
Cordrol	Vita Elixir	US	-
Cortalone	Halsey	US	-
Cortisolone	S.I.T.	Italy	-
Cotolone	Truxton	US	-
Dacortin	Igoda	Spain	-
Decaprednil	Dorsch	W. Germany	-
Decortasmyl	Larec	Ecuador	-
Delta-Hycortol	Medica	Finland	-
Delta-Larma	Larma	Spain	-
Deltalone	D.D.S.A.	UK	-
Deltasolone	Knoll	Australia	-
Deltidrosol	Poli	Italy	-
Deltisolon	Ferring	Sweden	-
Domucortone	Medici Domus	Italy	-
Encortolone	Polfa	Poland	-
Fernisolon	Ferndale	US	-
Ibisterolon	I.B.I.	Italy	-
Keteocort -H	Desitin	W. Germany	-
Neodelta	Amelix	Italy	-
Normosona	Normon	Spain	-
Novoprednisolone	Novopharm	Canada	-
Panafcortelone	Glebe	Australia	-
Predartrina	Farmochimica	Italy	-
Prednicen	Central	US	-

Trade Name	Manufacturer	Country	Year Introduced
Predni-Coelin	Pfleger	W. Germany	-
Prednicort	Cortec	Denmark	-
Predni-Helvacort	Helvepharm	Switz.	-
Predni-H-Tablinen	Sanorania	W. Germany	-
Predniretard	Boots-Dacour	France	-
Prelone	Langley	Australia	-
Ropredlone	Robinson	US	-
Scherisolon	Schering	W. Germany	-
Serilone	Serpero	Italy	-
Stermin	Schlicksup	US	-
Vitacort	Vitarine	US	-

Manufacturing Process

The following procedure is described in US Patent 2,837,464: from a solution of 3 grams of yeast extract (Difco) in 3.0 liters of tap water containing 13.2 grams of potassium dihydrogen phosphate and 26.4 grams disodium hydrogen phosphate (pH of the solution, 6.9) 27 portions of 100 ml each are withdrawn, placed in 300 ml Erlenmeyer flasks and sterilized by autoclaving for 15 minutes at 15 pounds steam pressure (120°C). After autoclaving and cooling of the broth, one ml of suspension of Corynebacterium simplex (ATCC 6946) is placed in each flask. The flasks are then shaken on a shake table at 220 rpm and 28°C for 24 hours.

Into each of 27 Erlenmeyer flasks are placed 150 mg of Kendall's Compound F (hydrocortisone). The flasks and contents are then sterilized for 15 minutes at 15 pounds steam pressure (120°C). To each flask are then added 5.0 ml of ethanol. The 24-hour bacterial culture is then transferred aseptically and the resulting suspensions are shaken on a shake table at 220 rpm and 28°C for 48 hours. The pH at the end of the shake period is 7.0.

The contents of all the flasks are combined and extracted with a total of 9.0 liters of chloroform in 3 equal portions. The combined extracts are then concentrated to a residue which weighs 3.75 grams. The MP of the residue is 227°-232°C. From 2.75 grams of this crude material on sludging with 50 ml of acetone and cooling, there is recovered on filtration 1.35 grams of $\Delta^{1,4}$-pregnadiene-11β,17α,21-triol-3,20-dione,MP 237°-239°C (dec.). Additional product can be recovered from the mother liquor. Recrystallization from acetone raised the MP to 239°-241°C (dec.).

References

Merck Index 7613
Kleeman & Engel p. 750
PDR pp. 830, 1569, 1606
OCDS Vol. 1 p. 192 (1977) & 2, 178 (1980)
I.N. p. 797
REM p. 969
Nobile, A.; US Patent 2,837,464; June 3, 1958; assigned to Schering Corporation

Oliveto, E.P. and Gould, D.H.; US Patent 2,897,216; July 28, 1959; assigned to Schering Corporation

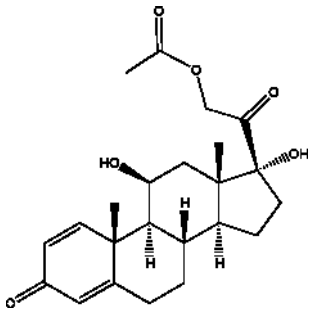
PREDNISOLONE ACETATE

Therapeutic Function: Glucocorticoid

Chemical Name: 11β,17,21-Trihydroxypregna-1,4-diene-3,20-dione 21-acetate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 52-21-1

Trade Name	Manufacturer	Country	Year Introduced
Sterane	Phipharmex	US	1955
Nisolone	Ascher	US	1962
Savacort	Savage	US	1969
Econapred	Alcon	US	1973
Pred Mild	Allergan	US	1974
Pred Cor 100	Hauck	US	1977
Alto-Pred	Alto	US	-
Cortipred	Italsuisse	Italy	-
Deltacortilen	S.I.F.I.	Italy	-
Dermo-Nydol	Brichard	France	-
Durapred	Federal	US	-
Hexacorton	Spirig	Switz.	-
Ibisterolon-Pommada	I.B.I.	Italy	-
Inflanefran	Allergan	W. Germany	-
Key-Pred	Hyrex	US	-
Metimyd	Schering	US	-
Meticortelone	Essex	Italy	-

Trade Name	Manufacturer	Country	Year Introduced
Predate	Legere	US	-
Predicort	Dunhall	US	-
Prednifor	Vifor	Switz.	-
Prenema	Nortech	US	-
Pricortin	Premedics	US	-
Sigpred	Sig	US	-
Ulacort	Fellows-Testagar	US	-
Ultracortenol	Dispersa	Switz.	-

Raw Materials

Prednisolone
Acetic anhydride

Manufacturing Process

To a solution of 0.85 gram of 1,4-pregnadiene-11β,17α,21-triol-3,20-dione (prednisolone) in 5 ml of pyridine are added 3 ml of acetic anhydride. The reaction mixture is allowed to stand at room temperature overnight and is then diluted with ice water. The resulting precipitate is filtered from the mixture and recrystallized from acetone-hexane. There is recovered 0.45 gram of 1,4-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate, MP 235°239°C. On recrystallization, the MP rose to 237°-239°C.

References

Merck Index 7613
Kleeman & Engel p. 750
PDR pp. 1033, 1633
OCDS Vol. 1 p. 192 (1977)
I.N. p. 798
REM p. 969
Nobile, A.; US Patent 3,134,718; May 26, 1964; assigned to Schering Corporation

PREDNISOLONE PHOSPHATE SODIUM

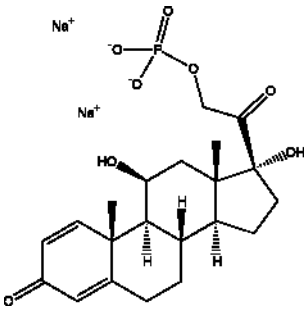
Therapeutic Function: Glucocorticoid

Chemical Name: 11β,17,21-Trihydroxypregna-1,4-diene-3,20-dione 21-(dihydrogen phosphate) disodium salt

Common Name: -

Chemical Abstracts Registry No.: 125-02-0

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Hydeltrasol	MSD	US	1957
Inflamase	Cooper Vision	US	1969
Optival	White	US	1969
PSP-IV	Tutag	US	1972
Alto-Pred	Alto	US	-
Caberdelta	Caber	Italy	-
Codelsol	MSD	UK	-
Hydrosol	Rocky Mtn.	US	-
Key-Pred S.P.	Hyrex	US	-
Metreton	Schering	US	-
Nor-Preds	North Amer. Pharm.	US	-
Parisolon	Riker	US	-
Predate S	Legere	US	-
Prednesol	Glaxo	US	-
Savacort	Savage	US	-
Sodasone	Fellows-Testagar	US	-
Solucort	Chibret	France	-
Solu-Pred	Myers-Carter	US	-

Raw Materials

Prednisolone
Sodium hydroxide
Phosphoric acid
Sodium iodide
Methanesulfonyl chloride

Manufacturing Process

Preparation of Prednisolone 21-Methanesulfonate: Seventy liters of dry pyridine and 7.5 kg of prednisolone are charged to a 30-gallon jacketed glass-lined still. The mixture is agitated until complete solution is obtained. About 40 liters of pyridine are distilled at high vacuum while maintaining the batch temperature below 40°C. The solution is cooled to 0°C, and 2.2 liters of methanesulfonyl chloride are charged. The batch temperature is maintained between 0°C and +3°C during charging of the methanesulfonyl chloride. An atmosphere of flowing nitrogen is maintained in the still, and the mixture is

agitated during the last stages of the addition. The mixture is then aged for one hour, and 15 gallons of ice water are added cautiously to the still while maintaining the temperature between 0° and 5°C.

The still contents are then transferred to a jacketed kettle equipped with an agitator, and 62 kg of cracked ice in 15 gallons of deionized water are added. The batch is aged one hour and a solution of 2 liters of concentrated (37%) hydrochloric acid in 4 gallons of deionized water is added. The batch is centrifuged and the centrifuge cake washed free of pyridine with deionized water. The centrifuge cake is then vacuum-dried at 50°C to a moisture content of about 1%, which requires about 3 days of drying. Yield about 7.77 kg (92%), according to US Patent 2,932,657.

Preparation of Prednisolone 21-Iodide: To a 30-gallon jacketed glass-lined still 64.5 lb (31.0 liters) of dimethylformamide are charged by vacuum. The still contents are agitated as 7.74 kg of dry (less than 1% moisture) prednisolone 21-methanesulfonate are charged. Then 4.02 kg of sodium iodide are charged. The still contents are heated to 57° to 60°C by means of a steam jacket and held at this temperature for 30 minutes. The batch is cooled to 35°C and 12 gallons of deionized water are added at the rate of about 1 gallon per minute. In the event the solution becomes cloudy, addition of water is interrupted and the mixture agitated for five minutes before resumption of water addition. After all of the water is added, the batch is transferred to a 50 gallon kettle equipped with agitator and an additional 16.7 gallons of deionized water are added. The batch is cooled to 0° to 5°C and aged for one hour. The batch is filtered and the filter cake washed and vacuum dried at 30° to 35°C to a moisture content of less than 1%. Yield about 7.95 kg (96%), according to US Patent 2,932,657.

Preparation of Prednisolone 21-Disodium Phosphate: Acetonitrile (50.0 ml) containing phosphoric acid (90%; 1.0 ml) was treated with triethylamine (3.0 ml) and the solution added to 11β,17α-dihydroxy-21-iodopregna-1,4-diene-3,20-dione (1.0 gram; powdered). The mixture was refluxed for 2.75 hours and the solvent was then evaporated under reduced pressure to give a yellow oil. The oil was taken up in methanol (25 ml) and titrated to pH 10.9 with sodium hydroxide in methanol (N) using a pH meter. The precipitate was filtered off and the filtrate evaporated to a gum under reduced pressure. The gum was taken up in methanol (5 ml), filtered through filter paper and acetone (100 ml) was added to the filtrate. The precipitate was filtered off, washed with acetone and dried at 100°C/1 mm for 0.75 hour giving a pale yellow solid, prednisolone disodium phosphate (0.74 gram), which was completely soluble in water, according to US Patent 2,936,313.

References

Merck Index 7615
Kleeman & Engel p. 752
PDR pp. 1033, 1633
I.N. p. 798
REM p. 970
Sarett, L.H.; US Patent 2,789,117; April 16, 1957; assigned to Merck & Co., Inc.
Christensen, B.G., Hirschmann, R.F. and Putter, I.; US Patent 2,932,657; April 12, 1960; assigned to Merck & Co., Inc.

Elks, J. and Phillipps, G.H.; US Patent 2,936,313; May 10, 1960; assigned to Glaxo Laboratories Limited, England

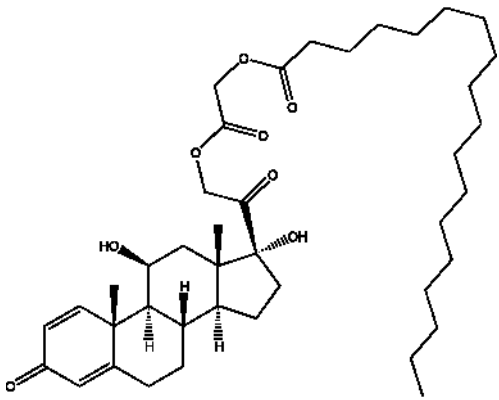
PREDNISOLONE STEAROYLGLYCOLATE

Therapeutic Function: Glucocorticoid

Chemical Name: 11β,17-Dihydroxy-21-[[[(1-oxoctadecyl)oxy]acetyl]oxy] pregna-1,4-diene-3,20-dione

Common Name: Prednisolone steaglate

Structural Formula:



Chemical Abstracts Registry No.: 5060-55-9

Trade Name	Manufacturer	Country	Year Introduced
Deturgylone	Dausse	France	1970
Erbacort	Erba	Italy	-
Estilsona	Erba	Italy	-
Glistelone	Erba	Italy	-
Glitisone	Vis	Italy	-
Prenisol	Cifa	Italy	-
Rollsone	Bellon	France	-
Sintisone	Erba	Italy	-
Verisone	Tiber	Italy	-

Raw Materials

Prednisolone
Potassium stearate
Prednisolone-21-chloroacetate
Stearoyl-glycolyl chloride

Manufacturing Process

This material can be prepared, e.g., by reaction of prednisolone-21-chloroacetate in solvent with the sodium or potassium salt of the corresponding aliphatic or aromatic acid, or by reaction of prednisolone with the chloride of the corresponding acyl-glycolic acid, in the presence of a hydrochloric acid acceptor.

Alternative (A): 3 grams (0.0068 mol) prednisolone chloroacetate dissolved in 200 ml tetrahydrofuran and 10 ml H_2O are added with 2.7 grams (0.0084 mol) K stearate and 0.06 g NaI and heated to boiling, under stirring, for 36 hours, then evaporated in vacuum to dryness.

The residue is washed with H_2O to disappearance of the Cl-ion from the filtrate. Crystallization from diluted alcohol results in prednisolone-21-stearoyl-glycolate (MP 104°-105°C).

Alternative (B): 3.6 grams (0.01 mol) prednisolone and 4.32 grams (0.012 mol) stearoylglycolyl-chloride, separately dissolved in dry dioxane, are added with 0.89 ml (0.011 mol) dry pyridine. The mixture is kept at 60°C for 20 hours, then poured into water-ice and filtered. Crystallization from diluted ethanol results in prednisolone-21-stearoyl-glycolate (MP 104°-105°C).

References

Merck Index 7618
Kleeman & Engel p. 753
DOT 3 (1) 18 (1967)
I.N. p. 799
Giraldi, P.N. and Nannini, G.; US Patent 3,171,846; March 2, 1965; assigned to Carlo Erba SpA, Italy

PREDNISOLONE TEBUTATE

Therapeutic Function: Glucocorticoid

Chemical Name: 21-(3,3-Dimethyl-1-oxobutoxy)-11β,17-dihydroxypregna-1,4-diene-3,20-dione

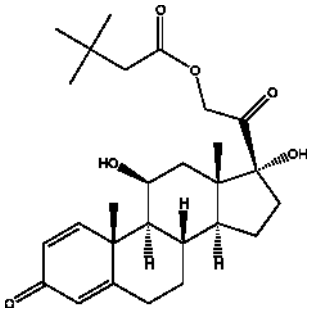
Common Name: Prednisolone-21-tert-butyl acetate

Chemical Abstracts Registry No.: 7681-14-3

Raw Materials

tert-Butyl acetyl chloride
Prednisolone

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Hydeltra TBA	MSD	US	1956
Codelcortone TBA	MSD	US	-
Predate TBA	Legere	US	-
Prednisol TBA	Pasadena	US	-
Rodelta TBA	Rocky Mtn.	US	-

Manufacturing Process

A solution of about 10 parts of tertiary-butyl acetyl chloride in 45 parts of dry chloroform is added portionwise to a cold solution of 25 parts of $\Delta^{1,4}$-3,20-diketo-11β,17α,21-trihydroxy-pregnadiene(prednisolone) in 125 parts of anhydrous pyridine. The resulting solution is allowed to stand for about 15 hours at 0° to 5°C, and the reaction solution is poured into 750 parts of water. The resulting aqueous mixture is extracted four times with 250 parts of chloroform each extraction. The combined chloroform layers are washed with water, dilute aqueous hydrochloric acid solution, water, 5% aqueous sodium bicarbonate solution, and finally with water. The chloroform extract is dried over magnesium sulfate, and the chloroform is evaporated in vacuo to give a residual oil. This oil is triturated with alcohol until it crystallizes, and is then recrystallized from ethanol to give substantially pure $\Delta^{1,4}$3,20-diketo-11β,17α,21-trihydroxy-pregnadiene21-tertiary-butyl acetate.

References

Merck Index 7619
Kleeman & Engel p. 754
PDR pp. 1033, 1183
I.N. p. 798
REM p. 970
Sarett, L.H.; US Patent 2,736,734; February 28, 1956; assigned to Merck & Co., Inc.

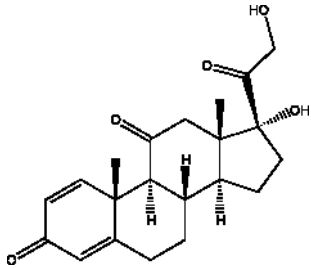
PREDNISONE

Therapeutic Function: Glucocorticoid

Chemical Name: 17α,21-Dihydroxy-pregna-1,4-diene-3,11,20-trione

Common Name: Deltacortisone

Structural Formula:



Chemical Abstracts Registry No.: 53-03-2

Trade Name	Manufacturer	Country	Year Introduced
Meticorten	Schering	US	1955
Deltasone	Upjohn	US	1955
Deltra	MSD	US	1955
Paracort	Parke Davis	US	1960
Lisacort	Fellows-Testagar	US	1960
Servisone	Lederle	US	1970
Orasone	Rowell	US	1972
Wojtab	Philips Roxane	US	1981
Adasone	Adams	Australia	-
Alto-Pred	Alto	US	-
Colisone	Merck-Frosst	Canada	-
Cortan	Halsey	US	-
Cortancyl	Roussel	France	-
Cortialper	Santos	Spain	-
Dacortin	Igoda	Spain	-
Decortin	Merck	W. Germany	-
Decortisyl	Roussel	UK	-
Decorton	Salfa	Italy	-
Deidrocortisone	Stip	Italy	-
Deltacortene	Lepetit	Italy	-
Delta Dome	Dome	US	-
Delta Prenovis	Vister	Italy	-
Deltison	Ferring	Sweden	-
Erftopred	Erfto	W. Germany	-
Fernisone	Ferndale	US	-

Trade Name	Manufacturer	Country	Year Introduced
Hostacortin	Hoechst	W. Germany	-
Inocortyl	Liposeptine	France	-
Keteocort	Desitin	W. Germany	-
Keysone	Key	US	-
Liquid Pred	Muro	US	-
Marnisonal	Juan Martin	Spain	-
Marvidiene	Panther-Osfa	Italy	-
Me-Korti	Farmos	Finland	-
Nisone	Llorente	Spain	-
Nizon	Bosnalijek	Yugoslavia	-
Novoprednisone	Novopharm	Canada	-
Nurison	Noury Pharma	Netherlands	-
Panafcort	Protea	Australia	-
Parmenison	Kwizda	Austria	-
Predniartrit	Maipe	Spain	-
Prednicen-M	Seymour	US	-
Prednifor	Vifor	Switz.	-
Prednilonga	Dorsch	W. Germany	-
Predni-Tablinen	Sanorania	W. Germany	-
Predni-Wolner	Wolner	Spain	-
Prednovister	Substancia	Spain	-
Predsol	Morgan	Italy	-
Predsone	Century	US	-
Presone	Langley	Australia	-
Pronison	Galenika	Yugoslavia	-
Propred	Medac	Australia	-
Rectodelt	Trommsdorff	W. Germany	-
Ropred	Robinson	US	-
Sarogesic	Saron	US	-
Sone	Fawns and McAllan	Australia	-
Sterapred	Mayrand	US	-
Supopred	Europa	Spain	-
Urtilone	Recherche Therap.	France	-
Wescopred	Saunders	Canada	-
Winpred	I.C.N.	Canada	-

Raw Materials

Bacterium Corynebacterium simplex
Cortisone

Manufacturing Process

From a solution of 30 grams of yeast extract (Difco) in 3.0 liters of tap water containing 13.2 grams of potassium dihydrogen phosphate and 26.4 grams of disodium hydrogen phosphate (pH of the solution 6.9) 27 portions of 100 ml each are withdrawn, placed in 300 ml Erlenmeyer flasks and sterilized by autoclaving for 15 minutes at 15 pounds steam pressure (120°C). After autoclaving and cooling of the broth one ml of a suspension of

Corynebacterium simplex (ATCC 6946) is placed in each flask. The flasks are then shaken on a shake table at 220 rpm and 28°C for 24 hours.

Into each of 27 Erlenmeyer flasks are placed 150 mg of Kendall's Compound E (cortisone). The flasks and contents are then sterilized for 15 minutes at 15 pounds steam pressure (120°C). To each flask are then added 5.0 ml of ethanol. The 24-hour bacterial culture is then transferred aseptically and the resulting suspensions are shaken on a shake table at 220 rpm and 28°C for 48 hours. The final pH is 7.2.

The contents of all the flasks are combined and extracted with a total of 9.0 liters of chloroform in three equal portions. The combined extracts are then concentrated to a residue which is crystallized from acetone-hexane. There results 1.1 grams of $\Delta^{1,4}$-pregnadiene-17α,21-diol-3,11,20-trione,MP 210°-215°C (dec.). Several additional recrystallizations raised the MP to 230°-232°C (dec.).

References

Merck Index 7621
Kleeman & Engel p. 755
PDR pp.830, 993, 1268, 1573, 1606, 1723, 1837
OCDS Vol. 1 p. 192 (1977)
I.N. p. 799
REM p. 970
Djerassi, C., Rosenkranz, G. and Berlin, J.; US Patent 2,579,479; December 25, 1951; assigned to Syntex SA, Mexico
Nobile, A.; US Patent 2,837,464; June 3, 1958; assigned to Schering Corporation
Oliveto, E.P. and Gould, D.H.; US Patent 2,897,216; July 28, 1959; assigned to Schering Corporation

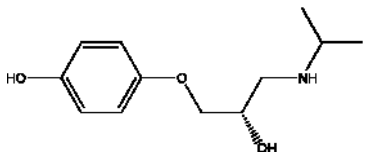
PRENALTEROL

Therapeutic Function: Adrenergic

Chemical Name: 4-[2-Hydroxy-3-[(1-methylethyl)amino]propoxy]phenol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 57526-81-5

Trade Name	Manufacturer	Country	Year Introduced
Coleb	Astra	W. Germany	1981
Hyprenan	Astra	UK	1981
Varbian	Ciba	UK	1981

Raw Materials

4-Hydroxyphenoxypropylene oxide
Isopropylamine

Manufacturing Process

A solution of 100 g (1.7 mols) of isopropylamine in 60 cc of water was stirred into a solution of 4-hydroxyphenoxypropylene oxide. After the exothermic reaction has subsided, the reaction mixture was heated for two hours at 60°C. Thereafter, the aqueous ethanol was distilled off, and the solid residue was dissolved in aqueous hydrochloric acid comprising more than the theoretical stoichiometric molar equivalent of hydrochloric acid. The aqueous acid solution was extracted with ether and was then made alkaline with sodium hydroxide, whereby a solid crystalline precipitate was formed which was filtered off and dried over phosphorus pentoxide. The product was 1,1-(4'-hydroxyphenoxy)-2-hydroxy-3-isopropylamino-propane. Its hydrochloride had a melting point of 166°C to 169°C.

References

Merck Index 7639
DFU 4 (1) 46 (1979)
OCDS Vol. 3 p. 30 (1984)
DOT 17 (5) 199 (1981) & 18 (4) 190 (1982)
I.N. p. 801
Koppe, H., Engelhardt, A., Ludwig, G. and Zeile, K.; US Patent 3,637,852; January 25, 1972; assigned to Boehringer Ingelheim G.m.b.H. (Germany)

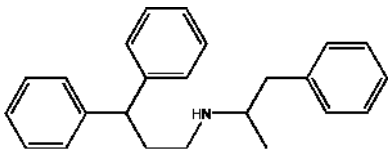
PRENYLAMINE

Therapeutic Function: Coronary vasodilator

Chemical Name: N-(1-Methyl-2-phenylethyl)-γ-phenylbenzenepropanamine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 390-64-7

Trade Name	Manufacturer	Country	Year Introduced
Synadrin	Hoechst	UK	1961
Segontin	Hoechst	Italy	1962
Segontin	Hoechst	W. Germany	1964
Segontine	Hoechst	France	-
Agozol	Tableta	Rumania	-
Angiovigor	Violani-Farmavigor	Italy	-
Angorsan	Isola-Ibi	Italy	-
Cardional	Unipharm	Israel	-
Corditin-Same	Savoma	Italy	-
Coredamin	Meiji	Japan	-
Crepasin	Hoei	Japan	-
Daxauten	Woelm Pharma	W. Germany	-
Epocol	Teisan-Nagase	Japan	-
Eucardion	Vita	Italy	-
Falicor	Fahlberg-List	E. Germany	-
Herzcon	Sana	Japan	-
Incoran	I.T.A.	Italy	-
Irrorin	Alfa Farm.	Italy	-
Lactamine	Daisan	Japan	-
Newsantin	Sawai	Japan	-
NP 30	Sanken	Japan	-
Nyuple	Ohta	Japan	-
Onlemin	Ono	Japan	-
Plactamin	Morishita	Japan	-
Prectolact	Showa Yakuhin	Japan	-
Rausetin	Tanabe	Japan	-
Reocorin	Farmochimica	Italy	-
Roinin	Mohan	Japan	-
Seccidin	Nippon Kayaku, Co.	Japan	-
Wasangor	Wassermann	Italy	-

Raw Materials

Phenyl acetone
1,1-Diphenyl-propylamine-(3)
Palladium
Hydrogen

Manufacturing Process

10.6 g of 1,1-diphenylpropylamine-(3) are hydrogenated by means of palladium with 6.7 g of phenyl acetone in 200 cc of methanol at 50°C. The calculated amount of hydrogen is taken up. The separated oily base is dissolved by heating with alcohol. After filtration water is added until turbidity sets in. 24.5 g of 2-(1',1'-diphenylpropyl-3'-amino)-3-phenyl-propane are obtained with a boiling point at 195°C to 198°C under a pressure of 0.5 mm of mercury, which after prolonged standing crystallizes out. Melting point

about 38°C to 40°C. Hydrochloride (prepared in usual manner): melting point 188°C to 190°C.

References

Merck Index 7641
Kleeman & Engel p. 759
OCDS Vol. 1 p. 76 (1977)
I.N. p. 801
Ehrhart, G., Ott, H. and Lindner, E.; US Patent 3,152,173; October 6, 1964; assigned to Farbwerke Hoechst A.G. (Germany)

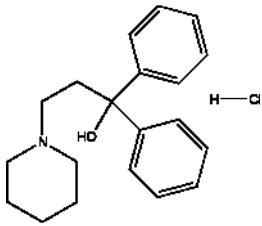
PRIDINOL HYDROCHLORIDE

Therapeutic Function: Antiparkinsonian, Anticholinergic

Chemical Name: 1,1-Diphenyl-3-piperidino-1-propanol hydrochloride

Common Name: Pridinol; Ridinol

Structural Formula:



Chemical Abstracts Registry No.: 968-58-1

Trade Name	Manufacturer	Country	Year Introduced
Hikiceton	Tatsumi	-	-
Konlax	Nippon Shinyaku	-	-
Loxeen	Hommel	-	-
Myoson	Strathmann	-	-

Raw Materials

Bromobenzene
1-Piperidinopropionic acid n-butyl ester
Magnesium

Manufacturing Process

24 parts by weight of 1-piperidinopropionic acid n-butyl ester (BP: 137-

138°C) was added dropwise to solution of phenyl magnesium bromide from 157 parts by weight of bromobenzene and 24 parts of magnesium.

There was a spontaneous heating and the ether boiled. The mixture refluxed for 2 hours after the completion adding. Then it was poured into mixture of 200 parts of 37% hydrochloric acid and 800 parts (by weight) of ice with stirring. Hydrochloride of α,α-diphenyl-1-piperidinepropanol precipitated. It was filtered off, washed with ether, diluted hydrochloric acid and dried over sodium hydroxide in vacuum dessicator. The colorless crystals were light dissolved in hot water and had MP: 216°C. The base is the colorless powder with MP: 119-120°C.

References

Eisleb O.; D.B. Patent No. 875,660; May 4 1953; Fabwerke Hoechst, vormals Meister Lucius and Bruning, Frankfurt/M/-Hoechst

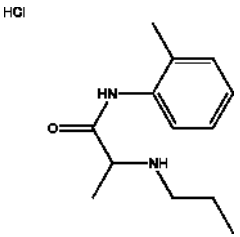
PRILOCAINE HYDROCHLORIDE

Therapeutic Function: Local anesthetic

Chemical Name: N-(2-Methylphenyl)-2-(propylamino)-propanamide hydrochloride

Common Name: Propitocaine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 1786-81-8; 721-50-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Xylonest	Astra	W. Germany	1963
Citanest	Astra	UK	1974
Citanest	Astra	US	1966
Citanest	Pierrel	Italy	1968
Citanest	Bellon	France	1973

Raw Materials

o-Toluidine
α-Bromopropionyl bromide
n-Propylamine

Manufacturing Process

One mol of ortho-toluidine is dissolved in 800 ml of glacial acetic acid. The mixture is cooled to 10°C whereupon 1.1 mols of α-bromopropionylbromide is added. The mixture is vigorously stirred for about a minute and a solution of sodium acetate (330 grams of $CH_3COONa \cdot 3H_2O$ in 1,380 ml of water) or another buffering or alkalizing substance or solution is added in one portion. The reaction mixture is then shaken for half an hour. The precipitate formed is filtered off, washed with water and dried. The product is sufficiently pure for further processing. Yield: 70-80% of theory. MP 133°-134°C.

One mol of α-bromopropio-ortho-toluidine is mixed with a solution of 3 mols of n-propylamine in 500 ml of water-free benzene and the reaction mixture is heated in an autoclave to 80°C for 8 hours. After cooling the reaction mixture is treated as described above. The base is obtained as a colorless oil. BP 159°-162°C/0.1 mm. Yield 55%. The base is then converted to the hydrochloride by reaction with HCl.

References

Merck Index 7646
DFU 8 (12) 1021 (1983)
Kleeman & Engel p. 760
OCDS Vol. 1 p. 17 (1977)
I.N. p. 802
REM p. 1053
Aktiebolaget Astra: Apotekarnes Kemiska Fabriker, Sweden; British Patent 839,943; June 29, 1960

PRIMIDONE

Therapeutic Function: Anticonvulsant

Chemical Name: 5-Ethyldihydro-5-phenyl-4,6(1H,5H)-pyrimidinedione

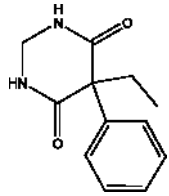
Common Name: 2-Desoxyphenobarbital; Primaclone

Chemical Abstracts Registry No.: 125-33-7

Raw Materials

α,α-Phenylethylmalonic acid diamide
Formamide

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Mysoline	I.C.I.	France	1953
Mysoline	Ayerst	US	1954
Cyral	Gerot	Austria	-
Liskantin	Desitin	W. Germany	-
Majsolin	Pliva	Yugoslavia	-
Midone	Protea	Australia	-
Mylepsinum	ICI Pharma	W. Germany	-
Mysedon	Medica	Finland	-
Primidone	Schein	US	-
Primoline	Darby	US	-
Primron	Fujinaga	Japan	-
Prysoline	Abic	Israel	-
Resimatil	Labaz	W. Germany	-
Sertan	Chinoin	Hungary	-

Manufacturing Process

50 parts of α,α-phenylethylmalondiamide and 150 parts of formamide are boiled together under reflux for 2 hours. The mixture is then cooled to 0°C and filtered. The solid residue is washed with 50 parts of ethanol and then crystallized from 660 parts of an 80% ethanol water mixture. There is obtained 5-phenyl-5-ethylhexahydropyrimidine-4,6-dione, MP 281°C-282°C.

References

Merck Index 7649
Kleeman & Engel p. 761
PDR pp. 631, 830, 1606
OCDS Vol. 1 p. 276 (1977)
I.N. p. 803
REM p. 1081
Boon, W.R., Carrington, H.C. and Vasey, C.H.; US Patent 2,578,847; December 18, 1951; assigned to Imperial Chemical Industries Limited, England

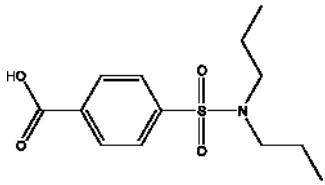
PROBENECID

Therapeutic Function: Antiarthritic

Chemical Name: 4-[(Dipropylamino)sulfonyl]benzoic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 57-66-9

Trade Name	Manufacturer	Country	Year Introduced
Benemid	MSD	US	1952
Benemide	Theraplix	France	1954
Benecid	Kaken	Japan	-
Benuryl	I.C.N.	Canada	-
Colbenemid	MSD	UK	-
Panuric	Propan-Lipworth	S. Africa	-
Perdurine	Pharma-Union	Belgium	-
Probemid	Lefa	Spain	-
Probenicid	Lederle	US	-
Probenemid	Merck-Banyu	Japan	-
Procid	Protea	Australia	-
Solpurin	Salfa	Italy	-
Urecid	Frosst	Australia	-
Uroben	Mitim	Italy	-

Raw Materials

p-Carboxybenzene sulfonyl chloride
Di-n-propylamine

Manufacturing Process

24.0 grams (0.11 mol) of p-carboxybenzenesulfonyl chloride was added in small portions to a suspension of 20.0 grams (0.146 mol) of di-n-propylamine in 100 milliliters of 10% sodium hydroxide with vigorous stirring at a temperature of 15°-25°C. Stirring was continued for 15 minutes after the final addition. The clear solution was treated with decolorizing carbon and filtered.

The product was precipitated by the addition of an excess of hydrochloric acid. The crude product was purified by reprecipitation from bicarbonate solution and recrystallization from dilute alcohol. The yield was 20.0 grams (64%) melting at 194°-196°C.

References

Merck Index 7656
Kleeman & Engel p. 761
PDR pp. 705, 830, 993, 1142, 1150, 1606, 1999
OCDS Vol. 1 p. 135 (1977)
I.N. p. 804
REM p. 944
Miller, C.S.; US Patent 2,608,507; August 26, 1952; assigned to Sharp & Dohme, Inc.

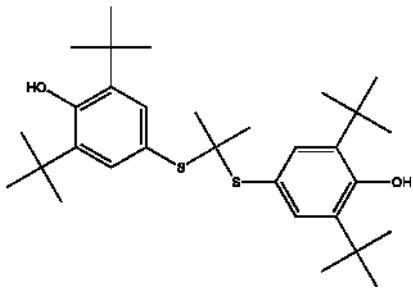
PROBUCOL

Therapeutic Function: Antihyperlipidemic

Chemical Name: Bis(3,5-di-tert-butyl-4-hydroxyphenyl)acetone mercaptole

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 23288-49-5

Trade Name	Manufacturer	Country	Year Introduced
Lorelco	Merrell Dow	US	1977
Lurselle	Lepetit	France	1980
Lurselle	Lepetit	UK	1980
Lurselle	Dow-Lepetit	Switz.	1980
Lurselle	Merrell	W. Germany	1980
Lurselle	Lepetit	Italy	1982
Biphenabid	Merrell Dow	-	-
Lesterol	Lepetit	-	-

Raw Materials

Acetone
2,6-Di-tert-butyl-4-mercaptophenol

Manufacturing Process

Bis(3,5-di-tert-butyl-4-hydroxyphenyl) acetone mercaptole, melting at 125°C to 126°C is prepared by employing 2,6-di-tert-butyl-4-mercaptophenol and acetone as starting materials. In one representative procedure, the 2,6-di-tert-butyl-4-mercaptophenol (47.5 g, 0.2 mol) is dissolved in methanol (50 ml) heated at a temperature of 50°C. A catalytic amount of concentrated hydrochloric acid (1 ml) is added, followed by acetone (5.8 g, 0.1 mol). The temperature of the mixture rises to about 60°C, and is maintained at about 60°C to 65°C for 1.5 hours. The mixture is cooled, diluted with water and about 10 ml of aqueous sodium bicarbonate and extracted with ether. The ether extract is evaporated, and the product is obtained as a residue, which is recrystallized from ethanol and then from isopropanol to obtain the bis(3,5-di-tert-butyl-4-hydroxyphenyl) acetone mercaptole as a crystalline solid melting at about 125°C to 126°C.

In another representative procedure about 2.3 mols of 2,6-di-tert-butyl-4-mercaptophenol is dissolved in about 1,700 ml of methanol under a nitrogen atmosphere; about 100 ml of concentrated hydrochloric acid and 180 ml of acetone are added, and the mixture is stirred and maintained at a temperature of about 35°C to 50°C, for 1.5 hours. The mixture is then cooled to room temperature and filtered, and the bis(3,5-di-tert-butyl-4-hydroxyphenyl) acetone mercaptole product is collected as a colorless crystalline solid filter cake. The product is washed with water and aqueous sodium bicarbonate and purified by recrystallization from ethanol.

References

Merck Index 7657
DFU 2 (2) 128 (1977)
Kleeman & Engel p. 762
PDR p. 1229
OCDS Vol. 2 p. 126 (1980)
DOT 14 (1) 33 (1978)
I.N. p. 804
REM p. 864
Barnhart, J.W. and Shea, P.J.; US Patent 3,862,332; January 21, 1975; assigned to The Dow Chemical Co.

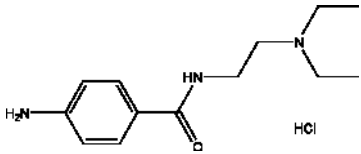
PROCAINAMIDE HYDROCHLORIDE

Therapeutic Function: Antiarrhythmic

Chemical Name: Benzamide, p-amino-N-(2-(diethylamino)ethyl)-, monohydrochloride

Common Name: Amidoprocaine; Novocainamidum; Procainamide hydrochloride; Prokainamid

Structural Formula:



Chemical Abstracts Registry No.: 614-39-1; 51-06-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
PAD	Astra	-	-
Procamide	Zambon	-	-
Procan	Parke-Davis	-	-
Procanbid	Warner Lambert	USA	-
Promine	Major	-	-
Pronestyl	Sarabhai Chemicals	India	-
Roxyl	Star	-	-

Raw Materials

Sodium ethoxide
Diethyl aminoethane
Hydrogen
4-Nitrobenzoyl chloride
Nickel

Manufacturing Process

To the solution of 4-nitro-benzoylchloride the diethyl aminoethane and sodium ethoxide were added and mixed. As a result of reaction a N-(2-diethylamino-ethyl)-4-nitro-benzamide was obtained.

The N-(2-diethylamino-ethyl)-4-nitro-benzamide was reduced by hydrogen Ni as catalyst to give N-(2-diethylamino-ethyl)-4-amino-benzamide (procainamide).

In practice it is usually used as hydrochloride salt.

References

Baltzy R. et al.; J. Am. Chem. Soc. 64, 2231 (1942); Yamazaki M.Y. et al.; J. Pharm. Soc. Japan 73, 294 (1953)

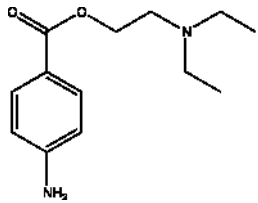
PROCAINE

Therapeutic Function: Local anesthetic, Analgesic, Antiviral

Chemical Name: Benzoic acid, 4-amino-, 2-(diethylamino)ethyl ester

Common Name: Cocainum novum; Factor H_3; Novocainum; PABA-diethylaminoethanol; Procaine; Prokain; Stoff H_3; Vitamin H_3

Structural Formula:



Chemical Abstracts Registry No.: 59-46-1

Trade Name	Manufacturer	Country	Year Introduced
Endocaina	Lafage	-	-
Isocain	Bernburg	-	-
Novadren	Sopharma	-	-
Polocaine	Polfa	-	-
Unicaine	Kay	-	-

Raw Materials

Ethylene chlorohydrin
p-Nitrobenzoyl chloride
Diethyl amine
Tin

Manufacturing Process

The equal quantity of ethylene chlorohydrin and p-nitrobenzoyl chloride was heated on an oil bath at temperature 120°-125°C till the ending of the isolation of hydrogen chloride. The mixture was poured into water to give the oil, which has soon hardened. It was recrystallized from diluted ethanol as white needles of p-nitrobenzoylchloro ethanol; MP: 56°C.

2 g of above prepared product and 2 g of diethyl amine were heated at 100°-120°C for 10 hours in the soldered tube to give 4-nitobenzoic acid diethylaminoethyl ether as an oily viscous mass. It was dissolved in hydrochloric acid and reduced with tin to procaine, which has precipitated as oil after adding sodium carbonate. 4-Aminobenzoic acid diethylaminoethyl

ester crystallized from diluted ethanol with two molecules of water as white needles; MP: 51°C. It crystallized without water from napthaline; MP: 58°-60°C, and formed monohydrochloride with MP: 156°C.

References

Farbwerke vorm. Meister Lucius and Bruning in Hochst a. M.; D.R. Patent No. 179,627; November 27, 1904

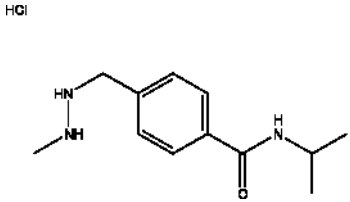
PROCARBAZINE HYDROCHLORIDE

Therapeutic Function: Cancer chemotherapy

Chemical Name: N-(1-Methylethyl)-4-[(2-methylhydrazino)methyl] benzamide hydrochloride

Common Name: Ibenmethyzin

Structural Formula:



Chemical Abstracts Registry No.: 366-70-1; 671-16-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Natulan	Roche	France	1965
Natulan	Roche	W. Germany	1966
Natulan	Roche	UK	1966
Natulan	Roche	Italy	1967
Matulane	Roche	US	1969
Natulan	Nippon Roche	Japan	1973

Raw Materials

Methanol
Sodium hydroxide
Hydrogen bromide
Bromine
Isopropylamine
1-Methyl-1,2-dicarbobenzoxyhydrazine
4-Methylbenzoic acid
Thionyl chloride
Sodium hydride
Hydrogen chloride

Manufacturing Process

544 grams of 4-methylbenzoic acid was boiled with 550 ml of thionyl chloride until a clear solution was obtained. After the excess thionyl chloride was distilled off, the residue was fractionated, yielding 605 g of 4-methylbenzoyl chloride; BP 91°C/9 mm Hg, n_D^{24} = 1.5532. This was dissolved in 550 ml of absolute benzene and the so-formed solution added to a mixture of 248 ml of absolute methanol and 550 ml of absolute benzene. After the exothermic reaction had terminated, the reaction mixture was boiled for a further 20 hours, then concentrated in vacuo and the product, 4-methylbenzoic acid methyl ester, isolated by conventional means. It could be purified by distillation, and the purified product boiled at 91°C/9 mm Hg, MP 32°C.

574 grams of this ester were dissolved in 1200 ml of carbon tetrachloride and, while boiling and exposing to a UV lamp, treated dropwise with a solution of 109 ml of bromine in 400 ml of carbon tetrachloride. After all of the bromine had been dropped in, the mixture was heated for a further hour, concentrated in vacuo and the residue crystallized from low boiling petroleum ether, yielding as colorless fine crystals, 4-(bromo-methyl)-benzoic acid methyl ester, which melted at 52°C. For the reaction of this ester with 1-methyl-1,2-dicarbobenzoxy-hydrazine, the following procedure was followed.

309 grams of a 27% suspension of sodium hydride in an inert solvent was treated with 300 ml of dimethylformamide, and a solution of 1095 grams of 1-methyl-1,2-dicarbobenzoxy-hydrazine in dimethylformamide was added thereto. When all the material had been added and the hydrogen evolution had nearly come to a standstill, the mixture was heated for an hour at about 80°C in order to carry the formation of the sodium salt to completion. A mixture of 759 grams of 4-(bromo-methyl)-benzoic acid methyl ester in 700 ml of dimethylformamide was then dropped in, and finally the reaction mixture was heated for an hour at 80°C. After cooling, the reaction mixture was poured into 10 liters of ice water and the condensation products taken up in ether. The thereby obtained crude methyl ester (n_D^{24} = 1.1558) was used without further purification for the next step. It was dissolved in about 2,200 ml of dioxane, treated with a solution of 133 grams of sodium hydroxide in 870 ml of water, and the resulting mixture stirred for about 24 hours at room temperature. It was then poured into 10 liters of ice water and neutral materials were extracted with ether.

The aqueous phase was rendered acid with concentrated hydrochloric acid (weak Congo red) and the separated acid taken up in ether. The isolated crude acid was recrystallized from dibutyl ether, yielding colorless crystals of 4-[(2-methyl-1,2-dicarbobenzoxy-hydrazino)-methyl]-benzoic acid, which melted at 112°C. The so-obtained product was sufficiently pure for further reaction.

15 grams of 4-[(2-methyl-1,2-dicarbobenzoxy-hydrazino)-methyl]-benzoic acid were boiled with an excess of thionyl chloride for 1 hour under reflux. The unconverted thionyl chloride was distilled off in vacuo, the residue twice dissolved each time in 75 ml of absolute benzene and then concentrated in vacuo. The so-obtained 4-[(2-methyl-1,2-dicarbobenzoxyhydrazino)-methyl]-benzoyl chloride, a viscous light yellow oil, was dissolved in 50 ml of absolute benzene and with stirring mixed with a solution of 4.45 grams of isopropylamine in 100 ml of absolute benzene. By cooling, the temperature of

the reaction mixture was kept below 30°C. After the mixing had been completed, the reaction mixture was maintained first at room temperature for 3 hours and then for ½ hour at 40°C. It was then cooled down and poured into about 100 ml of ice water. After the addition of a mixture of methylene chloride and ether (40 ml + 200 ml), the organic phase was separated and then washed with water, dilute hydrochloric acid, water, dilute sodium hydroxide and again with water.

The solvents were then evaporated, yielding 4-[(2-methyl-1,2-dicarbobenzoxyhydrazino)-methyl]-benzoic acid isopropylamide as a yellow oil, which crystallized upon triturating with ether; MP 90°-92°C. This product was then covered with 70 ml of a 33% solution of hydrogen bromide in glacial acetic acid, and then permitted to stand for 2 hours with occasional swirling, whereupon a thick slurry of crystals was formed. The precipitate was filtered off, washed with 20 ml of glacial acetic acid and finally with ether, yielding crystals of 4-[(2-methyl-hydrazino)-methyl]-benzoic acid isopropylamide hydrobromide, which after recrystallization from methanol/ether melted at 216°-217°C (dec.).

87.5 grams of 4-[(2-methyl-hydrazino)-methyl]-benzoic acid isopropylamide hydrobromide (obtained as described above) were dissolved in 550 ml of water. To this solution, there were added 1,000 ml of methylene chloride and, while cooling with ice and stirring under nitrogen atmosphere, 1,200 grams of potassium carbonate portionwise. The methylene chloride layer was separated and the aqueous slurry extracted three times with 500 ml of methylene chloride in a nitrogen atmosphere. The united methylene chloride extracts were concentrated in vacuo. The residue was dissolved under nitrogen in 100 ml of methanol and treated, while cooling with ice, with 40 ml of a 45% methanolic hydrochloric acid solution, which induces immediate crystallization. The crystals were filtered off and recrystallized from methanol, yielding 4-[(2-methyl-hydrazino)-methyl]-benzoic acid isopropylamide hydrochloride melting at 223°-226°C.

References

Merck Index 7662
Kleeman & Engel p. 763
PDR p. 1491
OCDS Vol. 2 p. 27 (1980)
I.N. p.805
REM p. 1153
Bollag, W., Gutmann, H., Hegedus, B., Kaiser, A., Langemann, A., Muller, M. and Zeller, P.; US Patent 3,520,926; July 21, 1970; assigned to Hoffmann-La Roche Inc.

PROCATEROL

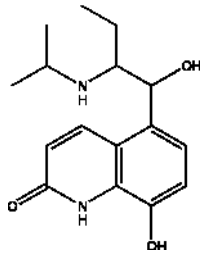
Therapeutic Function: Bronchodilator

Chemical Name: 8-Hydroxy-5-[1-hydroxy-2-[(1-methylethyl)amino]butyl]-2(1H)-quinolinone

2858 Procaterol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 72332-33-3

Trade Name	Manufacturer	Country	Year Introduced
Meptin	Otsuka	Japan	1981

Raw Materials

α-Bromobutyric acid bromide
Isopropylamine
8-Hydroxycarbostyril
Lithium aluminum hydride

Manufacturing Process

50 g of α-bromobutyric acid bromide, 50 g of anhydrous aluminum chloride and 400 ml of carbon disulfide were added to 20 g of 8-hydroxycarbostyril. The resulting mixture was heated at a temperature of 50°C for 13 hours and the carbon disulfide layer was removed by decantation. Crushed ice was added to the residue, and the precipitated crystals were filtered, washed with water and recrystallized from methanol to obtain 27 g of 5-(α-bromobutyryl)-8-hydroxycarbostyril having a melting point of 218°C to 219°C (with coloring and decomposition). To 5 g of the thus obtained 5-(α-bromobutyryl)-8-hydroxycarbostyril was added 100 ml of isopropylamine, and the mixture was heated at a temperature of 50°C for 4 hours followed by concentration to dryness. Crystals which formed upon addition of water were filtered, washed with water and then recrystallized from methanol to obtain 4.6 g of a methanol solvate of 5-(α-isopropylaminobutyryl)-8-hydroxycarbostyril having a melting point of 136°C to 137°C (with foaming and decomposition).

20 g of tetrahydrofuran was added to 1 g of 5-(α-isopropylaminobutyryl)-8-hydroxycarbostyril hydrochloride, and the resulting mixture was added dropwise to a suspension of 0.12 g of lithium aluminum hydride in 10 ml of tetrahydrofuran while stirring at room temperature. After completion of the addition, a small amount of water was added to the reaction mixture to decompose any excess of lithium aluminum hydride. The reaction mixture was then poured into 50 ml of ice-water and the aqueous layer of the resulting solution was separated and concentrated to dryness. The precipitated crystals

were filtered, washed with acetone and dissolved in water. The solution was adjusted to pH of 8 with aqueous sodium hydroxide to precipitate crystals which were then filtered and recrystallized from ethanol to obtain 0.8 g of 5-(1-hydroxy-2-isopropylamino)butyl-8-hydroxycarbostyril monohydrate having a melting point of 141°C to 142°C (with cooling and decomposition).

References

Merck Index 7663
DFU 3 (2) 135 (1978)
OCDS Vol. 3 p. 184 (1984)
DOT 17 (6) 256 (1981)
Nakagawa, K., Yoshizaki, S., Tanimura, K. and Tamada, S.; US Patent 4,026,897; May 3, 1977; assigned to Otsuka Pharmaceutical Co. (Japan)

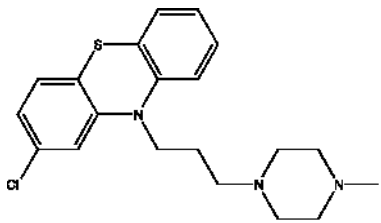
PROCHLORPERAZINE

Therapeutic Function: Antiemetic, Antipsychotic

Chemical Name: 2-Chloro-10-[3-(4-methyl-1-piperazinyl)propyl]-10H-phenothiazine

Common Name: Chlormeprazine

Structural Formula:



Chemical Abstracts Registry No.: 58-38-8; 84-02-6 (Maleate)

Trade Name	Manufacturer	Country	Year Introduced
Compazine	SKF	US	1956
Tementil	Specia	France	1957
Anti-Naus	Protea	Australia	-
Combid	SKF	US	-
Klometil	Farmos	Finland	-
Mitil	Lennon	S. Africa	-
Nibromin-A	Maruko	Japan	-
Normalmin	Sawai	Japan	-
Novamin	Shionogi	Japan	-

Trade Name	Manufacturer	Country	Year Introduced
Pasotomin	Yoshitomi	Japan	-
Stemetil	May and Baker	UK	-
Vertigon	SKF	UK	-

Raw Materials

3-Chloro-10-[3-(di-N-2-chloroethyl)aminopropyl]phenthiazine hydrochloride
1-Methylpiperazine

Manufacturing Process

3-Chloro-10-[3-(di-N-2-chloroethyl)aminopropyl]phenthiazine hydrochloride (1.8 g) is heated in a sealed tube for 4 hours at 140°C with a 290 g/l aqueous solution (9 cc) of monomethylpiperazine. The contents of the tube are treated with chloroform (40 cc). The aqueous layer is decanted and the chloroform layer is shaken with N hydrochloric acid (15 cc followed by 2 cc). The aqueous solution is treated with sodium hydroxide (d = 1.33, 10 cc) and chloroform (20 cc). After evaporation of the solvent, the base (1.5 g) is obtained. A solution of maleic acid (1 g) in ethanol (5 cc) is added and after recrystallization from water, 3-chloro10-[3-(4'-methyl-1'-piperazinyl)propyl]phenothiazine dimaleate is obtained, melting point 228°C (inst .).

References

Merck Index 7665
Kleeman & Engel p. 764
PDR pp. 1606, 1706
OCDS Vol. 1 p. 381 (1977)
DOT 9 (6) 228 (1973)
I.N. p. 806
REM p. 809
Horclois, R.J.; US Patent 2,902,484; September 1, 1959; assigned to Societe des Usines Chimiques Rhone-Poulenc, France

PROCYCLIDINE HYDROCHLORIDE

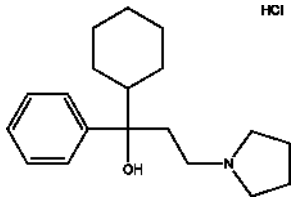
Therapeutic Function: Antiparkinsonian

Chemical Name: α-Cyclohexyl-α-phenyl-1-pyrrolidinepropanol hydrochloride

Common Name: -

Chemical Abstracts Registry No.: 1508-76-5; 77-37-2 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Kemadrin	Burroughs-Wellcome	US	1956
Kemadrine	Wellcome	France	1965
Arpicolin	R.P. Drugs	UK	-
Kemadren	Gayoso Wellcome	Spain	-
Osnervan	Wellcome	W. Germany	-
Procyclid	I.C.N.	Canada	-

Raw Materials

Acetophenone
Magnesium
Paraformaldehyde
Hydrogen
Pyrrolidine
Hydrogen chloride
Bromobenzene

Manufacturing Process

1,1-Diphenyl-3-pyrrolidinopropan-1-ol (30 grams) was dissolved in glacial acetic acid (120 ml), Adams' platinum catalyst (6 grams) added, and the mixture shaken in an atmosphere of hydrogen until the equivalent of 3.4 molecules had been taken up per molecule of compound. Water was added, the catalyst removed by filtration, excess of ammonia added, and the liberated base extracted with ether. The ethereal extract was dried and evaporated and the residue recrystallized from light petroleum (BP 40°-60°C). The 1-cyclohexyl-1-phenyl3-pyrrolidinopropan-1-ol (19.3 grams) so obtained had a melting point of 85.5°-86.5°C. The hydrochloride recrystallized from a mixture of ethanol and ethyl acetate, melted with decomposition at 226°-227°C according to US Patent 2,891,890.

The starting material is prepared by the reaction of acetophenone, paraformaldehyde and pyrrolidine to give ω-pyrrolidinopropiophenone. That is in turn reacted with phenyl magnesium bromide to give 1,1-diphenyl-3-pyrrolidinpropan-1-ol.

References

Merck Index 7667
Kleeman & Engel p. 765
PDR p. 745
OCDS Vol. 1 p. 47 (1977)
DOT 18 (2) 88 (1982)

I.N. p. 806
REM p. 932
Bottorff, E.M.; US Patent 2,826,590; March 11, 1958; assigned to Eli Lilly and Company
Harfenist, M. and Magnien, E.G.; US Patent 2,842,555; July 8, 1958; assigned to Burroughs Wellcome & Co. (U.S.A.) Inc.
Adamson, D.W.; US Patent 2,891,890; June 23, 1959; assigned to Burroughs Wellcome & Co. (U.S.A.) Inc.

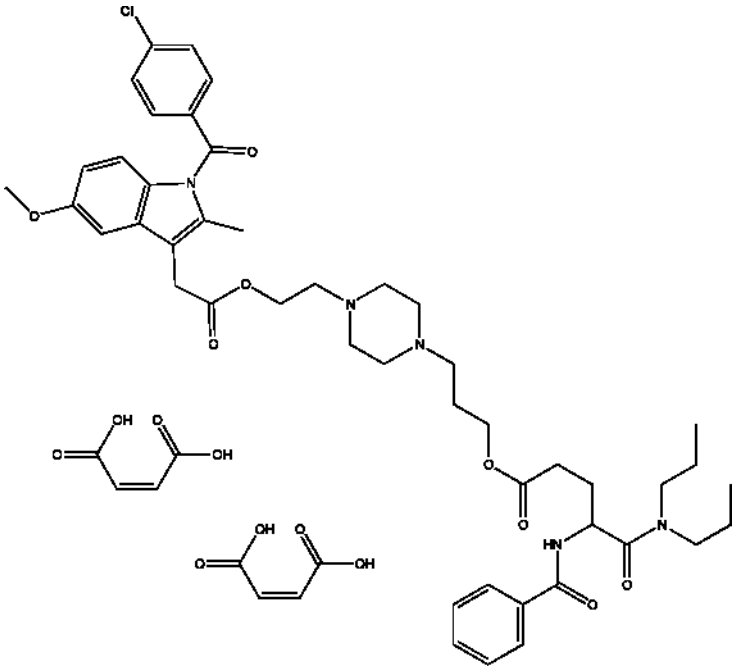
PROGLUMETACIN MALEATE

Therapeutic Function: Antiinflammatory

Chemical Name: N'-2-[1-(p-Chlorobenzoyl)-5-methoxy-2-methyl-3-indoleacetoxy]-ethyl-N-3-(N-benzoyl-N',N'-di-n-propyl-DL-isoglutaminoyl)-oxypropyl piperazine dimaleate

Common Name: Protacine

Structural Formula:



Chemical Abstracts Registry No.: 57132-53-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Afloxan	Rotta	Italy	1981
Proxil	Rorer	Italy	1981

Raw Materials

N'-(2-Hydroxyethyl)-N-3-(N-benzoyl-N',N'-di-n-propyl-DL-isoglutaminoyl)-oxypropylpiperazine
1-(p-Chlorobenzoyl)-5-methoxy-2-methyl-3-indoleacetic acid
N,N'-Dicyclohexylcarbodiimide
Maleic acid

Manufacturing Process

To a titrated solution of 400 cc of ethyl acetate containing 0.1 mol of N'-(2-hydroxyethyl)-N-3-(N-benzoyl-N',N'-di-n-propyl-DL-isoglutaminoyl)-oxypropyl piperazine [obtained by dissolving 71.9 g (0.105 mol) of the corresponding di-oxalate in 500 cc of water, bringing this solution to a pH of between 9 and 10 with sodium bicarbonate and finally extracting the oily emulsion thus formed twice in succession with a total of 400 cc of ethyl acetate], there are added successively 35.8 g (0.1 mol) of 1-(p-chlorobenzoyl)-5-methoxy-2-methyl-3-indoleacetic acid and 20.6 g (0.1 mol) of N,N'-dicyclohexylcarbodiimide. This is left at room temperature for 24 hours, and after having filtered the N,N'-dicyclohexyl urea precipitate the organic phase is then washed with dilute HCl, a solution of sodium bicarbonate and a saturated solution of sodium chloride.

The ethyl acetate is dried with anhydrous sodium sulfate, filtered and dried off. The oily residue is dissolved in 600 cc of methanol; the di-oxalate is precipitated by the addition of a solution of oxalic acid in methanol. Yield 85%, melting point 190°C to 192°C (crystallized by methanol). Microcrystalline substance, creamy white color.

By the same method one can obtain the dimaleate. Yield, 83%; melting point, 146°C to 148°C (crystallized by ethanol). Microcrystalline pale cream colored substance.

References

Merck Index 7679
DFU 5 (3) 142 (1980)
DOT 17 (4) 157 (1981)
Makovec, F., Senin, P. and Rovati, L.; US Patent 3,985,878; October 12, 1976; assigned to Rotta Research Laboratorium S.p.A.

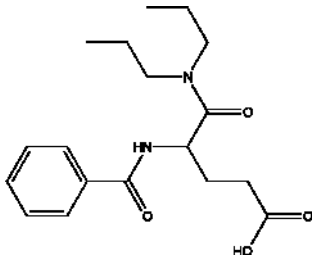
PROGLUMIDE

Therapeutic Function: Gastric antisecretory

Chemical Name: Glutaramic acid, 4-benzamido-N,N-dipropyl-, DL-

Common Name: Proglumide; Xilamida; Xylamide

Structural Formula:



Chemical Abstracts Registry No.: 6620-60-6

Trade Name	Manufacturer	Country	Year Introduced
Milid	Popular	-	-
Milid	Rotta Research Laboratorium spa	-	-
Promid	Kaken	-	-
Promid	Opfermann	-	-
Snol	Inexfa	-	-

Raw Materials

Glutamic acid
Benzoyl chloride
Dipropylamine
Acetic anhydride

Manufacturing Process

588 g L-(+)-glutamic acid [commercial grade], are gradually added, in small portions, while stirring, to 2400 ml 2 N NaOH, in such a manner that the internal temperature does not exceed 5°C by external cooling (ice or brine). When all the glutamic acid has been added and is dissolved there is added to the reaction mixture with continued stirring and in such a manner that the internal temperature does not exceed 15°C, 471 ml benzoyl chloride and 1600 ml 3 N NaOH from two separatory funnels, the addition being made in the following manner: add at once 94.2 ml benzoyl chloride, then, dropwise 160 ml 3 N NaOH (from the other funnel), the speed of addition is regulated so that the pH of the mixture does not exceed 8 (universal indicator paper) and the temperature does not exceed 15°C. When the 160 ml of the 3 N NaOH solution have all been added, add 47.1 ml benzoyl chloride, then slowly add 160 ml 3 N NaOH, again add 47.1 ml of benzoyl chloride, followed by the dropwise addition of the same volume of 3 N NaOH solution. This procedure of alternate addition is continued until the benzoyl chloride and 3 N NaOH solution have all been added. At this point one adds an additional 1125 ml of the 3 N NaOH solution at a speed, which keeps the temperature below 15°C

and the pH under 8, using universal indicator paper for testing the pH. When all has been added, including the last addition of NaOH, stirring is continued for an additional 30 minutes. The reaction mixture is then acidified, dropwise, with concentrated HCl until congo red paper turns blue. The acid solution is stirred for 5 additional minutes, then transferred to a suitable container and stored for 10-18 hours at +5°C. The solids are filtered repulped in a mortar with 600 ml ice water and filtered again. The solids are washed on the filter with 400 ml ice water and pressed dry. The material is then spread out in a thin layer and dried in the air to obtain N-benzoylaminoglutamic acid, MP: 136°-140°C.

1500 g of N-benzoylaminoglutamic acid, obtained above, are added under stirring to 6 liters of acetic anhydride, previously placed in a flask, equipped with a reflux condenser and a stirrer. The stirred mixture is maintained at room temperature for 8 hours without cooling bath and let stand overnight at room temperature. The reaction mixture is filtered, pressed dry, then dried in an air current for one hour at 60°-70°C, and one hour at 100°C to obtain N-benzoylaminoglutamic acid anhydride. Yield: 8.50 g (61%).

To an aqueous solution of dipropylamine (334 ml of amine in sufficient water to yield 1400 ml aqueous solution), are added over a period of 60-75 minutes, under efficient stirring and with cooling to -3°C, 312 g of N-benzoylaminoglutamic acid anhydride in such a manner that the temperature remains between -2°C and -4°C. When the addition is completed, stirring is continued for 10-15 minutes at -3°C and 650 ml glacial acetic acid are added. The temperature is allowed to rise to 6°C. The stirring is continued for 60-80 minutes. The reaction mixture is seeded by adding 2-3 g of previously prepared 4-benzamido-N,N-dipropylglutaramic acid which initiates precipitation of the desired product. The product is purified by dissolving the crude material in 20 times by weight of water and adding a stoichiometric amount of $NaHCO_3$, or a slight excess at 60°-70°C. The mixture is acidified with 20% acetic acid with vigorous stirring at room temperature to obtain a pH of 5.5. The stirring is continued for an additional 10-15 minutes, the product 4-benzamido-N,N-dipropylglutaramic acid is filtered, washed with stirring with 700 ml of water for 15 minutes, filtered again and dried in air current at 25°C to constant weight. Yield 140 g; MP: 142°-145°C.

References

Rotta Research Laboratorium S.p.A., an Italian Joint Stock Company, of San Fruttuoso di Monza, Milan, Italy; G.B. Patent No. 1,108,819; July 31, 1964

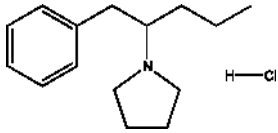
PROLINTANE HYDROCHLORIDE

Therapeutic Function: Analeptic, Stimulant, Antidepressant

Chemical Name: Pyrrolidine, 1-(1-(phenylmethyl)butyl)-, hydrochloride

Common Name: Prolintane hydrochloride; Promotil

Structural Formula:



Chemical Abstracts Registry No.: 1211-28-5

Trade Name	Manufacturer	Country	Year Introduced
Catorid	Boehringer Ingelheim	-	-
Catovit	Boehringer Ingelheim	-	-
Katovit	Thomae	-	-
Promotil	Boehringer Ingelheim	-	-

Raw Materials

Benzyl chloride
Magnesium
α-Pyrrolidinovalero nitrile

Manufacturing Process

390 g benzyl chloride was added dropwise to 72 g of magnesium powder in the mixture of 1:1 of benzene and tetrahydrofuran by stirring and at temperature not above 40°C. The Grignard reagent was diluted with 750 ml of benzene-tetrahydrofuran (1:1). Then a solution of α-pyrrolidinovalero nitrile in 400 ml of benzene-tetrahydrofuran was added dropwise by stirring at temperature not above 40°C. After that the mixture was stirred 3 hours at 40°C and some hours at room temperature. At last the main part of solvents was distilled off in vacuum and ice with hydrochloric acid was added to the residue to an acidic pH. 1 L of benzene was added. The acid layer was separated. Benzene layer was shook with diluted hydrochloric acid. The combined acidic water layers were alkalized with ammonia to alkaline reaction. The oil dropped out was dissolved in benzene.

The solvent was removed and the residue was distilled in vacuum to give 275 g 1-phenyl-2-pyrrolidinylpentane (prolintane); BP: 90-92°C at 0.36 mm.

In practice it is usually used as hydrochloride salt.

References

Kottler A., Seeger E.; D.B. Patent No. 1,088,962; April 26, 1956

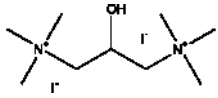
PROLONIUM IODIDE

Therapeutic Function: Iodine source

Chemical Name: 1,3-Propanediaminium, 2-hydroxy-N,N,N,N',N',N'-hexamethyl-, diiodide

Common Name: Diiodomedrine; Hydroxytrimethonium iodide; Ksameprol; Prolonii iododum; Prolonium iodide

Structural Formula:



Chemical Abstracts Registry No.: 123-47-7

Trade Name	Manufacturer	Country	Year Introduced
Prolonium iodide	Yick-Vic Chemicals and Pharmaceuticals (HK) Ltd.	-	-
Prolonium iodide	AJAY NORTH AMERICA, L.L.C.	-	-
Prolonium iodide	Alfa Chem	-	-
Hexajodin	Galenika	-	-
Prolonium iodide	ZYF Pharm Chemical	-	-
Micoiodina	VETEM TECNICA SpA	-	-

Raw Materials

Dimethylamine
Epichlorohydrin
Methyliodide

Manufacturing Process

Tetramethyldiaminoisopropanol can be produced by reaction of dimethylamine with epichlorhydrin.

146 parts of symmetrical tetramethyldiaminoisopropanol are mixed with 600 parts of benzene and 284 parts of methyliodide are slowly added whilst cooling and stirring. An oil which crystallizes after some time separates. It is separated from the benzene and crystallized from hot alcohol. The symmetrical hexamethyldiaminoisopropylalcoholiodide forms white crystals, melting point 270°-275°C (dec.).

References

Callsen J.; US Patent No. 1,526,627; Feb. 17, 1925; Assigned: Farbenfabriken Vorm. Friedr. Bayer and Co., of Leverkusen, near Cologne on the Rhine, Germany
Kleemann A., Engel J.; Pharmazeutische Wirkstoffe, GeorgThieme Verlag Stuttgart, New York, 1982

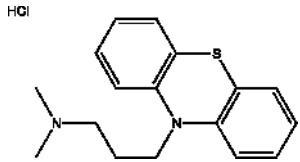
PROMAZINE HYDROCHLORIDE

Therapeutic Function: Tranquilizer

Chemical Name: N,N-Dimethyl-10H-phenothiazine-10-propanamine hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 53-60-1; 58-40-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Sparine	Wyeth	US	1956
Atarzine	Saunders	Canada	-
Calmotal	S.I.T.	Italy	-
Eliranol	Wyeth	Italy	-
Frenil	Polfa	Poland	-
Neuroplegil	Gentili	Italy	-
Promanyl	Paul Maney	Canada	-
Promazettes	Barlow Cote	Canada	-
Promezerine	Barlow Cote	Canada	-
Protactyl	Wyeth	W. Germany	-
Savamine	Banyu	Japan	-
Sediston	Serono	Italy	-
Starazine	Star	Finland	-
Talofen	Pierrel	Italy	-
Tranquazine	Anthony	US	-

Raw Materials

Phenothiazine

3-Dimethylamino-1-chloropropane
Sodium amide
Hydrogen chloride

Manufacturing Process

30 grams of phenothiazine, 120 grams of xylene and 7 grams of sodamide (80%) are mixed and heated under reflux. 23 grams of 3-dimethylamino-1-chloropropane, diluted with its own weight of xylene, is then added little by little during one hour, while maintaining the temperature of the reaction mixture; heating under reflux is then continued for a further hour. After cooling, the mixture is taken up in 400 cc of water and rendered slightly acid with hydrochloric acid. The xylene is decanted, the aqueous layer is rendered strongly alkaline with caustic soda and the base which separates is extracted with ether. On rectification of the ether extract, there is obtained N-(3'-dimethyl-amino-propyl)-phenothiazine which boils at 208°-210°C under 3 mm. The hydrochloride of this base melts at 181°C (Maquenne block).

References

Merck Index 7688
Kleeman & Engel p. 768
PDR p. 1989
OCDS Vol. 1 p. 377 (1977)
I.N. p. 810
REM p. 1090
Charpentier, P.; US Patent 2,519,886; August 22, 1950; assigned to Societe des Usines Chimiques Rhone-Poulenc, France

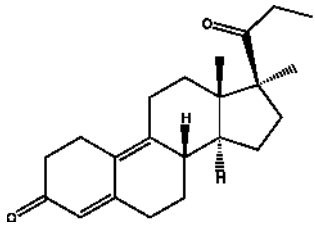
PROMEGESTONE

Therapeutic Function: Progestin

Chemical Name: 17α,21-Dimethyl-19-nor-$\Delta^{4,9}$-pregnadiene-3,20-dione

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 34184-77-5

Trade Name	Manufacturer	Country	Year Introduced
Surgestone	Cassenne	France	1983

Raw Materials

17α-Methyl-19-nor-Δ(5(10))-pregnene-3,20-dione
Bromine
Pyridine

Manufacturing Process

16.3 cc of a solution of 29% of bromine in methanol were added with agitation under a nitrogen atmosphere to a solution of 8.50 g of 17α-methyl-19-nor-Δ5(10)-pregnene-3,20-dionein 85 cc of pyridine cooled to 0°C and the mixture was stirred for 30 minutes at 0°C. The temperature was allowed to return to room temperature and the mixture was stirred for 16 hours.

The mixture was added to 850 cc of water-ice mixture and 82 cc of hydrochloric acid were added thereto. The mixture was extracted with methylene chloride and the combined extracts were washed with water until the wash waters were neutral, were dried over magnesium sulfate and distilled to dryness to obtain 8.480 g of crude product which is purified by crystallion from isopropyl ether to obtain 5.810 g of 17α-methyl-19-nor-Δ4,9-pregnadiene-3,20-dione melting at 106°C.

The mother liquors from the purification of the product were combined and evaporated to dryness. The residue was fractionated by chromatography over silica gel (Kieselgel) and elution with a 7:3 mixture of benzene-ethyl acetate. The first fractions were discarded and the ensuing fraction was evaporated to obtain colorless crystals. The product was purified by mixing with five volumes of boiling isopropyl ether and the crystals formed after cooling were recovered by vacuum filtration, were washed twice with two volumes of isopropyl ether and dried in a ventilated atmosphere to obtain 17α,21-dimethyl-19-nor-Δ4,9-pregnadiene-3,20-dione melting at 152°C.

References

DFU 3 (6) 469 (1978)
DOT 19 (7) 416 (1983)
I.N. p. 810
Warnant, J. and Farcilli, A.; US Patents 3,679,714; July 25, 1972; and 3,761,591; Sept. 25, 1973; both assigned to Roussel UCLAF

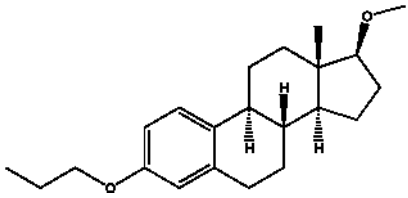
PROMESTRIENE

Therapeutic Function: Glucocorticoid

Chemical Name: 17β-Methoxy-3-propoxyestra-1,3,5(10)-triene

Common Name: Promestriene

Structural Formula:



Chemical Abstracts Registry No.: 39219-28-8

Trade Name	Manufacturer	Country	Year Introduced
Colpotrophine	Chengdu Yuyang Hige-tech Developing Co.,Ltd.	-	-
Colpotrophine 1% creme	Theramex	-	-

Raw Materials

Estradiol
n-Propyl bromide
Dimethyl sulfate
Sodium
Dimethyl sulfoxide

Manufacturing Process

An ethanolic solution of sodium ethoxide is prepared by reacting 3 g of sodium with 300 ml of absolute ethanol. 30 g of estradiol are dissolved in the resultant solution and there are then added thereto, with stirring, 30 ml of n-propyl bromide. Reaction is continued for 3 hours with stirring at 60°C and then the reaction mixture is concentrated under vacuum at 30°C to about 50 ml. The residue is taken up in 500 ml of benzene and then washed twice with 250 ml of a 0.25 N solution of sodium hydroxide and then with distilled water to neutrality. The solution is then dried over sodium sulphate and concentrated to give 32 g of crude product (yield 93%), which on recrystallization from 100 ml of methanol gives 31 g (yield 89%) of pure product; MP: 100°-101°C.

40 g of the 3-propyl-ether obtained above is dissolved in 400 ml of anhydrous dimethyl sulphoxide. Several crystals of triphenylmethane are added to the solution (as a coloured indicator) followed by freshly prepared until a permanent red colour is obtained. There is then added about 50% excess dimethylsulfinyl sodium. The reaction mixture is allowed to stand for about 15 minutes at ambient temperature and is then cooled on an ice bath. 40 ml of redistilled dimethyl sulphate are then slowly added to the mixture, which is then stirred for 15 minutes at room temperature. The excess methyl sulphate is then destroyed by the addition of about 2 L of 2 N sodium hydroxide and the mixture stirred for about 2 hours. The pH of the reaction mixture must be alkaline at the end of the operation. The reaction mixture is extracted with benzene and the benzene fractions are washed with distilled water to neutrality. The benzene extracts are then dried over sodium sulphate and concentrated under vacuum at 33°C to give 42 g of crude product which on

repeated recrystailisation from ethanol gives a pure white product promestriene in a yield of 78%; MP: 66°-67°C. The purity of the end product is controlled by gas phase and thin layer chromatography.

References

Societe Generale de Recherches et Dapplications Sogeras, a French body Corporate, Paris, France G.B. Patent No. 1,337,198; March 17, 1972

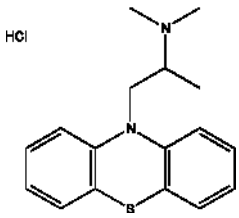
PROMETHAZINE HYDROCHLORIDE

Therapeutic Function: Antihistaminic

Chemical Name: N,N,α-Ttrimethyl-10H-phenothiazine-10-ethanamine hydrochloride

Common Name: Proazamine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 58-33-3; 60-87-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Phenergan	Wyeth	US	1951
Ganphen	Tutag	US	1971
Remsed	Endo	US	1973
Lemprometh	Lemmon	US	1974
Bromethacon	Alcon	US	1981
Baymethazine	Bay	US	1982
Atosil	Bayer	W. Germany	-
Avomine	May and Baker	UK	-
Diphergan	Polfa	Poland	-
Dorme	A.V.P.	US	-
Fargan	Farmitalia	Italy	-
Fellozine	Fellows-Testagar	US	-
Fenazil	Sella	Italy	-
Fenergan	Rhodia Iberica	Spain	-

Trade Name	Manufacturer	Country	Year Introduced
Hiberna	Yoshitomi	Japan	-
Lenazine	Lennon	S. Africa	-
Lergigan	Recip	Sweden	-
Mopergan	Wyeth	US	-
Pelpica	P.C.B.	Belgium	-
Perduretas	Medea	Spain	-
Phencen	Central	US	-
Pipolphen	Nakataki	Japan	-
Progan	Adams	Australia	-
Promet	Legere	US	-
Promethapar	Parmed	US	-
Promethazine	Lederle	US	-
Promine	Laser	US	-
Prorex	Hyrex	US	-
Prothazine	Knoll	Australia	-
Prothia	Kanto	Japan	-
Prothiazine	Novis	Israel	-
Provigan	Reid-Provident	US	-
Pyrethia	Shionogi	Japan	-
Quadnite	Reid-Provident	US	-
Rivozine	Rivopharm	Switz.	-
Sayamol	Cinfa	Spain	-
V-Gan	Hauck	US	-
Zipan	Savage	US	-

Raw Materials

Phenothiazine
1-Dimethylamino-2-propyl chloride
Sodium amide
Hydrogen chloride

Manufacturing Process

30 grams of phenothiazine, 120 grams of xylene, and 7 grams of sodamide (85%) are mixed and heated under reflux. A solution of 23 grams of the base obtained by the action of sodium hydroxide on the hydrochloride of 1-dimethylamino-2-chloropropane, in 25 grams of xylene, is then added little by little during one hour, while maintaining the temperature of the reaction mixture; heating under reflux is then continued for a further hour. After cooling, the mixture is taken up in 400 cc of water and rendered slightly acid with hydrochloric acid. The xylene is decanted, the aqueous layer is rendered strongly alkaline with caustic soda and the base which separates is extracted with ether. The ethereal extract is rectified, the fraction which boils at 190°-192°C under 3 mm being recovered. This is diluted with acetone or ethyl acetate and dry hydrochloric acid is added. The hydrochloride of N-(2'-dimethylamino-2'-methyl-ethyl)-phenothiazine separates, according to US Patent 2,530,451.

References

Merck Index 7691
Kleeman and Engel p. 769
PDR pp.861, 993, 1033, 1959, 1968, 1989
OCDS Vol. 1 pp. 373, 377 (1977)
I.N. p. 811
REM p. 1129
Charpentier, P.; US Patent 2,530,451; November 21, 1950; assigned to Societe des Usines Chimiques Rhone-Poulenc, France
Berg, S.S. and Ashley, J.N.; US Patent 2,607,773; August 19, 1952; assigned to Societe des Usines Chimiques Rhone-Poulenc, France

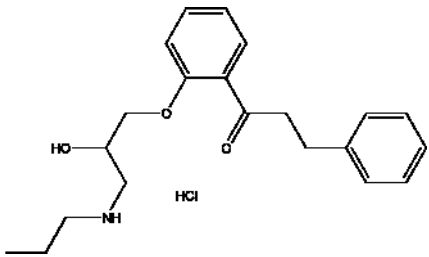
PROPAFENONE HYDROCHLORIDE

Therapeutic Function: Antiarrhythmic

Chemical Name: 2'-(2-Hydroxy-3-propylaminopropoxy)-3-phenylpropiophenone hydrochloride

Common Name: Fenoprain

Structural Formula:



Chemical Abstracts Registry No.: 34183-22-7; 54063-53-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Rytmonorm	Knoll	W. Germany	1978
Rytmonorm	Knoll	Italy	1983
Rytmonorm	Knoll	Switz.	1983
Baxarytmon	Helopharm	W. Germany	-
Normorytmin	Knoll	W. Germany	-

Raw Materials

n-Propylamine
2'-Hydroxy-3-phenylpropiophenone
Epichlorohydrin
Hydrogen chloride

Manufacturing Process

2'-(2,3-epoxypropoxy)-3-phenylpropiophenone - 24.8 g of the sodium salt of 2'-hydroxy-3-phenylpropiophenone were mixed with 40 cm^3 of 1-chloro-2,3-epoxypropane (epichlorohydrin) and the mixture heated on a boiling water bath while stirring, using a reflux condenser. The initially pasty-to-solid mixture liquefied after about 2 hours, sodium chloride separating out. Thereafter it was heated for a further 2 hours while stirring, using a reflux condenser. The mixture was then allowed to cool and subsequently freed, by filtration, from the sodium chloride formed. The filtrate was concentrated in vacuo, and the excess 1-chloro-2,3-epoxypropane thus separated from the desired 2'-(2,3-epoxypropoxy)-3-phenylpropiophenone. The latter remained as a yellowish oil which solidified in the cold, but did not crystallize. Purification of the intermediate product, by distillation in vacuo, was not necessary, particularly as the substance only boiled at a temperature of 280°C/12 mm Hg and at the same time decomposed.

2'-(2-hydroxy-3-propylaminopropoxy)-3-phenylpropiophenone hydrochloride - The above product was treated with 20 cm^3 of n-propylamine and the mixture warmed on a water bath for approximately 4 hours, while stirring, using a reflux condenser. Thereafter, the excess n-propylamine was distilled off. On cooling, the residue solidified to give a viscous yellow mass. 20 cm^3 of 1 M aqueous hydrochloric acid were added to it, and the whole was boiled for 1 hour under reflux, while stirring. The mixture was then poured into a suitable vessel and allowed to crystallize at room temperature. The crude product was drained thoroughly by suction and subsequently crystallized from a mixture of acetone/methanol (80:20, v/v).

Approximately 25 g (66.2% of theory) of a white crystalline substance were obtained. The melting point of the hydrochloride was 173°C to 174°C.

References

Merck Index 7698
DFU 2 (5) 325 (1977)
Kleeman and Engel p. 770
I.N. p. 812
Sachse, R.; British Patent 1,307,455; February 21, 1973; assigned to Helopharm W. Petrick & Co. K.G.

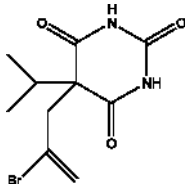
PROPALLYLONAL

Therapeutic Function: Hypnotic

Chemical Name: 2,4,6(1H,3H,5H)-Pyrimidinetrione, 5-(2-bromo-2-propenyl)-5-(1-methylethyl)-

Common Name: Acidum isopropyl-bromallyl-barbituricum; Bromoaprobarbital; Ibomalum; Propallilonalum; Propallylonal; Propyallylonal

Structural Formula:



Chemical Abstracts Registry No.: 545-93-7

Trade Name	Manufacturer	Country	Year Introduced
Noctal	Cassella-Riedel	-	-
Noctal	UCB	-	-

Raw Materials

Isopropylbarbituric acid
Sodium
1,2-Dibrom-2.3-propylene

Manufacturing Process

1). 170 parts of isopropylbarbituric acid are gradually added at room temperature to a sodium ethylate solution prepared from 23 parts of sodium and warming at 80°-85°C with brisk agitation, and finally 240 parts of 1,2-dibrom-2.3-propylene are permitted to flow in slowly. After heating for several hours at 90°-100°C the reaction is completed. After blowing off the alcohol the 5-(2-bromoallyl)-5-isopropylbarbituric acid is recovered in almost quantitative yield in the form of colorless crystals. After re-crystallization from dilute acetic acid the acid shows a melting point of 181°C.

2). 250 parts of dibrompropylene are added to a clear solution of 170 parts of isopropylbarbituric acid in dilute caustic soda solution containing 40 parts of sodium hydroxide, in the cold, and the mixture is briskly shaken. After a short time colorless crystals begin to separate out and the separation continues steadily with further shaking but only gradually. The precipitated 5-(2-bromoallyl)-5-isopropylbarbituric acid is filtered by suction and re-crystallized from water or dilute acetic acid. MP: 181°C.

Any untransformed isopropylbarbituric acid is recovered from the filtrate after separating out the unchanged dibrompropylene, by precipitation with concentrated hydrochloric acid.

References

Boedecker F.; US Patent No. 1,622,129; March 22, 1927; Assigned to the firm I.D. Riedel A.G., of Berlin-Britz, Germany

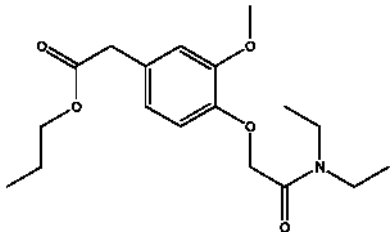
PROPANIDID

Therapeutic Function: Anesthetic

Chemical Name: 4-[2-(Diethylamino)-2-oxoethoxy]-3-methoxybenzene-acetic acid propyl ester

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 1421-14-3

Trade Name	Manufacturer	Country	Year Introduced
Epontol	Bayer	W. Germany	1965
Epontol	Bayer	Italy	1967
Epontol	Theraplix	France	1967
Epontol	Bayer	Japan	1970
Fabontal	Bayer	-	-
Sombrevin	Gedeon Richter	Hungary	-

Raw Materials

Sodium
Homovanillic acid n-propyl ester
Chloracetic acid-N,N-diethylamide

Manufacturing Process

To a solution of 4 g of sodium in 200 ml of n-propanol is added 39 g of homovanillic acid-n-propyl ester (boiling point 160°C to 162°C/4 mm Hg) and the mixture is concentrated by evaporation under vacuum. After dissolving the residue in 200 ml of dimethylformamide and the addition of 0.5 g of sodium iodide,26.2 g of chloracetic acid-N,N-diethylamide are added dropwise with stirring at an internal temperature of 130°C, and the mixture is further heated at 130°C for three hours. From the cooled reaction mixture the precipitated salts are removed by filtering off with suction. After driving off the dimethylformamide under vacuum, the product is fractionated under vacuum, and 44.3 g of 3-methoxy-4-N,N-diethylcarbamido-methoxyphenylacetic acid-n-propylester are obtained as a yellowish oil of boiling point 210°C to 212°C/0.7 mm Hg.

References

Merck Index 7705
OCDS Vol. 2 p. 79 (1980)
DOT 2 (3) 110 (1966)
I.N. p.813
REM p. 1047
Hiltman, R., Wollweber, H., Hoffmeister, F. and Wirth, W.; US Patent 3,086,978; April 23, 1963; assigned to Farbenfabriken Bayer A.G. (Germany)

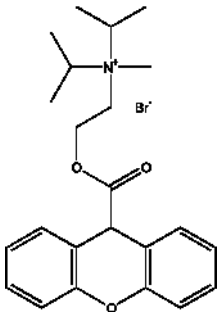
PROPANTHELINE BROMIDE

Therapeutic Function: Spasmolytic

Chemical Name: N-Methyl-N-(1-methylethyl)-N-[2-[(9H-xanthen-9-ylcarbonyl)oxy]ethyl]-2-propanaminium bromide

Common Name: Diisopropylaminoethyl xanthene-9-carboxylate methobromide

Structural Formula:



Chemical Abstracts Registry No.: 50-34-0

Trade Name	Manufacturer	Country	Year Introduced
Pro-Banthine	Searle	US	1953
Probanthine	Searle	France	1981
Apopant	A.L.	Norway	-
Banlin	Paul Maney	Canada	-
Corigast	Searle	W. Germany	-
Ercoril	Erco	Denmark	-
Giquel	Danal	US	-
Ketaman	Desitin	W. Germany	-
Neo-Banex	Neo	Canada	-

Trade Name	Manufacturer	Country	Year Introduced
Neo-Dexabine	Noury Pharma	Netherlands	-
Neo-Gastrosedan	Star	Finland	-
Neo-Metantyl	Zambon	Italy	-
Pantheline	Protea	Australia	-
Panthene	Vangard	US	-
Pervagal	Zambeletti	Italy	-
Probital	Searle	US	-
Prodixamon	A.L.	Norway	-
Propanthel	I.C.N.	Canada	-
Suprantil	Prodotti Erma	Italy	-
Tensilan	Desitin	W. Germany	-

Raw Materials

Xanthene-9-carboxylic acid
β-Diisopropylaminoethyl chloride
Methyl bromide

Manufacturing Process

365 parts of β-diisopropylaminoethyl chloride and 565 parts of xanthene-9-carboxylic acid dissolved in 800 parts of isopropanol is heated to reflux for 5 hours. The solution is then cooled, diluted with dry ether and the crystalline precipitate of β-diisopropylaminoethyl xanthene-9-carboxylate hydrochloride is collected on a filter and dried. This salt melts at 111°-112°C. 38 parts of the foregoing salt are dissolved in the minimum of water and treated with an aqueous solution of potassium carbonate. The suspension of β-diisopropylaminoethylxanthene-9-carboxylate thus formed is extracted with ether and the ether extract is dried and evaporated. There is thus obtained 33 parts of the free base which are treated with 10 parts of methyl bromide in 100 parts of chloroform for 22 hours at 70°-80°C. The reaction mixture is chilled, diluted with anhydrous ether and the quaternary salt thus precipitated is collected on a filter and washed with dry ether and then with butanone. β-Diisopropylaminoethyl xanthene-9-carboxylate methobromide thus obtained melts at 152°-153°C. After recrystallization from isopropanol it melts at 157°-155°C.

References

Merck Index 7708
Kleeman & Engel p. 771
PDR pp. 830, 1569, 1606, 1694, 1723
OCDS Vol. 1 p. 394 (1977)
I.N.p.813
REM p. 919
Cusic, J.W. and Robinson, R.A.; US Patent 2,659,732; November 17, 1953; assigned to G.D. Searle & Co.

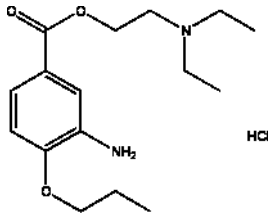
PROPARACAINE HYDROCHLORIDE

Therapeutic Function: Local anesthetic

Chemical Name: Benzoic acid, 3-amino-4-propoxy-, 2-(diethylamino)ethyl ester, monohydrochloride

Common Name: Proparacaine hydrochloride; Proparakain hydrochloride; Proximetacainum hydrochloride; Proxymetacaine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 5875-06-9

Trade Name	Manufacturer	Country	Year Introduced
Alcaine	Alcon	-	-
Ophthaine	AmeriSource	USA	-
Ophthetic	Allergan	-	-

Raw Materials

Thionyl chloride
γ-Diethylaminoethanol
3-Nitro-4-propyl-oxy-benzoic acid
Hydrochloric acid

Manufacturing Process

3-Nitro-4-propyl-oxy-benzoic acid is first converted to the acid chloride by refluxing with thionyl chloride, and after removal of the excess thionyl chloride the acid chloride is reacted with γ-diethylaminoethanol in benzene solution. The γ-diethylaminoethanol-3-nitro-4-propylbenzoate hydrochloride obtained is then reduced in the presence Fe and HCl, to give the γ-diethylaminoethanol-3-amino-4-propylbenzoate.

The hydrochloride of the free base (prepared by reacting the free base with hydrochloric acid) may be recrystallized from acetone.

References

Vliet E. B. et al.; US Patent No. 2,288,334; June 30, 1942; Assigned: Abbott Laboratories, North Chicago, Ill., a corporation of Illinois

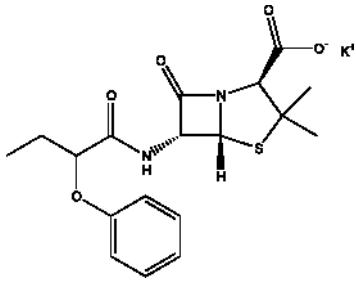
PROPICILLIN POTASSIUM

Therapeutic Function: Antibiotic

Chemical Name: 4-Thia-1-azabicyclo(3.2.0)heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6- (2-phenoxybutyramido)-, monopotassium salt

Common Name: Phenoxypropylpenicillin potassium; Propicillin potassium

Structural Formula:



Chemical Abstracts Registry No.: 1245-44-9; 551-27-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Oracillin	Takeda	-	-

Raw Materials

Triethylamine
2-Phenoxybuturic acid
Isobutyl chloroformate
6-Aminopenicillanic acid

Manufacturing Process

Triethylamine (1.5 ml) was added to a cold solution (10°C) of 2-phenoxybuturic acid (2.16 g, 0.01 mole) in 15 ml of pure dioxane, with stirring and cooling to 5°-10°C, then isobutyl chloroformate (1.36 g, 0.01.mole) in 5 ml of dioxane was added dropwise. Then the mixture was stirred for ten minutes at 5°-8°C. A solution of 6-aminopenicillanic acid (2.16 g, 0.01 mole) in 15 ml of water and 2 ml of triethylamine was then added dropwise while the temperature was maintained below 10°C. The resulting mixture was stirred in the cold for 15 minutes then at room temperature for 30 minutes, diluted with 30 ml of cold water and extracted with ether, which was discarded. The cold aqueous solution was then covered with 75 ml of ether and acidified to pH 2 with 5 N sulfuric acid. After shaking, the ether layer containing the product 6-(2-phenoxybutyramido)penicillanic acid, was separeted, dried over anhydrous sodium sulphate, solvent was removed to give 1.03 g of product propicillin; MP: 175°-179°C (became dark at 170°C),

contained the β-lactam structure as shown by infrared analysis and inhibited Staph. Aureus Smith at concentration 0.05 mcg/ml.

In practice it is usually used as potassium salt.

References

Beecham Research Laboratories Ltd., Brendford, Middlesex, England; G.B. Patent No. 3,316,248; April 25, 1967

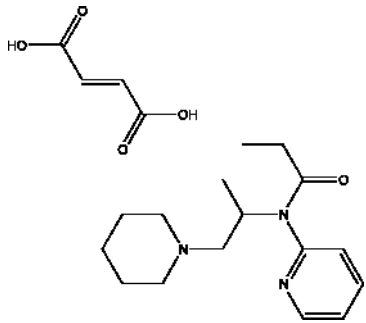
PROPIRAM FUMARATE

Therapeutic Function: Analgesic

Chemical Name: N-[1-Methyl-2-(1-piperidinyl)ethyl]-N-2-pyridinylpropanamide fumarate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 13717-04-9; 15686-91-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Algeril	Bayropharm	Italy	1974
Algeril	Bayer	W. Germany	1974
Dirame	Schering	-	-

Raw Materials

Fumaric acid
2-(1-Piperidine-isopropyl)aminopyridine
Propionic anhydride

Manufacturing Process

20 g of 2-(1-piperidino-isopropyl)aminopyridine and 50 ml of propionic anhydride are heated to 120°C for 8 hours. The mixture is then evaporated under vacuum and the residue taken up in water. The base is precipitated from the solution with a caustic soda solution, taken up in ether and dried with potassium carbonate. After driving off the ether and distillation under vacuum, there are obtained 18 grams of N-propionyl-2-(1-piperidino-isopropyl)aminopyridine of BP 162°-163°C/0.5 mm Hg. The base is then reacted with fumaric acid to give the final product.

References

Merck Index 7733
Kleeman & Engel p. 772
DOT 10 (11) 309 (1974)
I.N. p. 815
Hiltmann, R., Wollweber, H., Hoffmeister, F., Wirth, W. and Kroneberg, H.-G.; US Patent 3,163,654; December 29, 1964; assigned to Farbenfabriken Bayer AG, Germany
Wollweber, H., Hiltmann, R., Hoffmeister, F. and Kroneberg, H.-G.; US Patent 3,594,477; July 20, 1971; assigned to Farbenfabriken Bayer AG, Germany

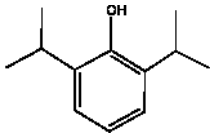
PROPOFOL

Therapeutic Function: Anesthetic

Chemical Name: Phenol-2,6-diisopropyl

Common Name: Disoprofol; Propofol

Structural Formula:



Chemical Abstracts Registry No.: 2078-54-8

Trade Name	Manufacturer	Country	Year Introduced
Cleofol Inj.	Themis Pharmaceuticals Ltd.	India	-
Diprivan	AstraZeneca UK Limited	Italy	-
Diprivan	Zeneca	Italy	-
Diprivan	ICI India Limited	India	-

Trade Name	Manufacturer	Country	Year Introduced
Pofol	Dong Kook Pharmaceutical Co.	Korea	-
Propofol	Baxter	-	-
Propofol Abbott	Abbott Laboratories	USA	-
Propofol 1% Fresenius	Fresenius Kabi	Austria	-
Propofol Lipuro	B. Braun Melsungen AG	Germany	-
Propovan	Bharat Serum and Vaccines Pvt. Ltd.	India	-
Recofol	Leiras OY	Germany	-

Raw Materials

Phenol
Aluminum turnings
Propylene
Isopropyl (2-isopropylphenyl) ether
Fluorided alumina

Manufacturing Process

2 Methods of preparation of 2,6-diisopropylphenol

1. To vessel with flushed nitrogen at an elevated temperature to 165°C 490 parts of phenol was placed, then 4.5 parts of aluminum turnings were added in small increments.The reaction mixture was accompanied by evolution of hydrogen for 15 min, then the mixture was allowed to cool to about 60°C and agitation discontinued. Aluminum phenoxide catalyst mixture was ready.

The reaction vessel was heated to 150°C and pressurized with propylene. The temperature then increased slowly. The start of the reaction was evidenced by a drop in the propylene pressure at 190°C and at a pressure of 21-35 atm. The product was hydrolyzed and fractionated to yield 105 parts of 2,6-diisopropylphenol. Boiling point: 135.5-136.5°C.

2. To 15 g of isopropyl (2-isopropylphenyl) ether was added 8 g of 1% fluorided alumina. The mixture was placed in a 300 cc stirred autoclave and the system was flushed with nitrogen and left under a nitrogen atmosphere. The autoclave was heated to 150°C for 1 h with stirring during which time the pressure reached 200 psig. The cooled reaction mixture was taken up in acetone, filtered, and the solvent was removed on a rotary evaporator. The residue was analyzed by gas-liquid phase chromatography (glpc) which showed the presence of 2,6-diisopropylphenol (60%).

References

Ecke G.G., et al.; US Patent No. 2,831,898; April 22, 1958; Assigned: Ethyl Corporation, New York, N.Y., a corporation of Delaware
Firth B.E., Rosen T.J.; US Patent No. 4,447,657; May 8, 1984; Assigned: UOP Inc., Des Plaines, III

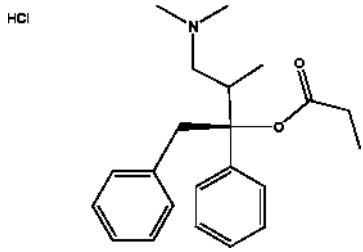
PROPOXYPHENE HYDROCHLORIDE

Therapeutic Function: Analgesic

Chemical Name: (S)-α-[2-(Dimethylamino)-1-methylethyl]-α-phenylbenzeneethanol propanoate hydrochloride

Common Name: Dextropropoxyphene hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 1639-60-7; 469-62-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Darvon	Lilly	US	1957
Antalvic	Houde	France	1963
SK-65	SKF	US	1973
Propoxychel	Rachelle	US	1973
Dolene-65	Lederle	US	1973
Prophen 65	Halsey	US	1981
Darvocet-N	Lilly	US	-
Depronal SA	Warner	UK	-
Develin	Goedecke	W. Germany	-
Doloxene	Lilly	UK	-
Erantin	Boehringer Mannheim	W. Germany	-
Liberen	Lisapharma	Italy	-
Lorcet	U.A.D. Labs	US	-
Wygesic	Wyeth	US	-

Raw Materials

Benzyl chloride
Magnesium
Hydrogen chloride
Propionic anhydride
α-Methyl-β-dimethylaminopropiophenone

Manufacturing Process

A solution of benzylmagnesium chloride prepared from 63.3 grams (0.5 mol)

of benzyl chloride, 30.5 grams (1.25 mol) of magnesium and 750 cc of ether was added dropwise with stirring to a solution of 61.9 grams (0.35 mol) of α-methyl-β-dimethylaminopropiophenone (prepared by the method of Burchalter et al, JACS 70 page 4186, 1948), in 150 cc of ether. When all of the Grignard reagent had been added, the solution was refluxed for about 1 hour. The reaction mixture was then decomposed by the addition of saturated aqueous ammonium chloride solution. The ether solution containing the 1,2-diphenyl-2-hydroxy-3-methyl-4-dimethylaminobutane formed in the reaction was decanted from the granular precipitate and dried over anhydrous magnesium sulfate.

Dry hydrogen chloride gas was passed into the ether solution until precipitation was completed. The solid was removed by filtration and was recrystallized from a mixture of methanol and ethyl acetate. The α-dl-1,2-diphenyl-2-hydroxy-3-methyl-4-dimethylaminobutane hydrochloride thus obtained melted at about 231° to 232°C.

A mixture of 50 grams of α-dl-1,2-diphenyl-2-hydroxy-3-methyl-4-dimethylaminobutane hydrochloride, 50 grams of propionic anhydride and 50 cc of pyridine was refluxed for about 5 hours. The reaction mixture was cooled to 50°C and ethyl ether was added to the point of incipient precipitation. The hydrochloride salt of α-dl-1,2-diphenyl-2-propionoxy-3-methyl-4-dimethylaminobutane formed in the reaction precipitated upon cooling and was removed by filtration and washed with anhydrous ether. On recrystallization from a mixture of methanol and ethyl acetate, α-dl-1,2-diphenyl-2-propionoxy-3-methyl-4-dimethylaminobutane hydrochloride melted at 170°-171°C.

References

Merck Index 7739
Kleeman & Engel p. 285
PDR pp. 993, 1044, 1606, 1723, 1808, 1996, 1999
OCDS Vol. 1 pp. 50, 298 (1977) and 2, 57 (1980)
I.N. p. 816
REM p.1114
Pohland, A.; US Patent 2,728,779; December 27, 1955; assigned to Eli Lilly and Company

PROPRANOLOL HYDROCHLORIDE

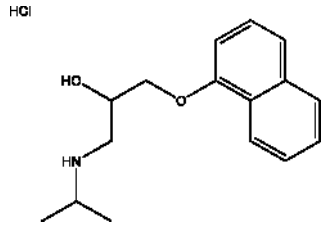
Therapeutic Function: Beta-adrenergic blocker

Chemical Name: 1-(Isopropylamino)-3-(1-naphthyloxy)-2-propanol hydrochloride

Common Name: -

Chemical Abstracts Registry No.: 318-98-9; 525-66-6 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Inderal	I.C.I.	UK	1965
Dociton	Rhein Pharma	W. Germany	1965
Avlocardyl	I.C.I.	France	1967
Inderal	Ayerst	US	1968
Angilol	D.D.S.A.	UK	-
Arcablock	Arcana	Austria	-
Bedranol	Berk	Switz.	-
Berkolol	Lagap	UK	-
Beta-Neg	Ellem	Italy	-
Beta-Tablinen	Sanorania	W. Germany	-
Cardinol	Protea	Australia	-
Caridolol	Sankyo	Japan	-
Corotrend	Siegfried	Switz.	-
Deralin	Abic	Israel	-
Detensol	Desbergers	Canada	-
Dideral	Dif-Dogu	Turkey	-
Frekven	Ferrosan	Denmark	-
Herzbase	Nichiiko	Japan	-
Herzul	Ono	Japan	-
Inderide	Ayerst	US	-
Indobloc	Homburg	W. Germany	-
Kemi	Otsuka	Japan	-
Nedis	Omega	Argentina	-
Noloten	Beta	Argentina	-
Novopranol	Novopharm	Canada	-
Obsidan	Iris-Chemie	E. Germany	-
Oposim	Richet	Argentina	-
Pranolol	A.L.	Norway	-
Pronovan	A.L.	Norway	-
Propranolol	Lederle	US	-
Propranur	Henning	W. Germany	-
Pur-Bloka	Lennon	S. Africa	-
Pylapron	Kyorin	Japan	-
Reducor	Leiras	Finland	-
Sawatal	Sawai	Japan	-
Tonum	Tubi Lux Pharma	Italy	-

Raw Materials

1-Naphthol
Isopropylamine
Epichlorohydrin
Hydrogen chloride

Manufacturing Process

In a first step, 1-naphthol was reacted with epichlorohydrin to give 1-chloro-3-(1-naphthoxy)-2propanol. A mixture of 4.4 parts of 1-chloro-3-(1-napntnoxy)-2-propano and 16 parts of isopropylamine is heated in a sealed vessel at 70°-80°C for 10 hours. The vessel is cooled and to the contents there are added 50 parts of water. The mixture is acidified with 2 N hydrochloric acid, and washed with 50 parts of ether. The aqueous phase is decolorized with carbon, and then added to 50 parts of 2 N sodium hydroxide solution at 0°C. The mixture is filtered, The solid residue is washed with water, dried, and crystallized from cyclohexane. There is thus obtained 1-isopropylamino-3-(1-naphthoxy)-2-propanol, MP 96°C.

The base may be converted into the hydrochloride as follows. 4.65 parts of the base are dissolved in 60 parts of warm acetone. To the warm solution there are added 2 parts of 10 N hydrochloric acid. The mixture is allowed to cool, and is then filtered. The solid residue is washed with acetone and then dried. The solid is crystallized from propanol, and there is thus obtained 1-isopropylamino-3-(1-naphthoxy)-2-propanol hydrochloride MP 163°C.

References

Merck Index 7740
Kleeman & Engel p. 773
PDR pp. 622, 993, 1999
OCDS Vol. 1 p. 117 (1977) and 2, 105, 107, 212 (1980)
DOT 19 (3) 172 (1983)
I.N. p. 816
REM p. 906
Crowther, A.F. and Smith, L.H.; US Patent 3,337,628; August 22, 1967; assigned to Imperial Chemical Industries Limited, England

PROPYLHEXEDRINE

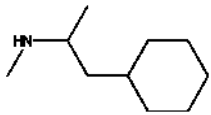
Therapeutic Function: Nasal decongestant

Chemical Name: N,α-Dimethylcyclohexaneethanamine

Common Name: Hexahydrodesoxyephedrine

Chemical Abstracts Registry No.: 101-40-6; 6192-98-9 (Hydrochloride salt)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Benzedrex	SKF	US	1949
Dristan	Whitehall	US	-
Eggobesin	Fahlberg-List	E. Germany	-
Eventin	Minden	W. Germany	-

Raw Materials

Cyclohexylacetone
N-Methylformamide
Sulfuric acid
Sodium hydroxide

Manufacturing Process

33.6 grams of cyclohexylacetone, a compound known to the art, dissolved in 13 grams of 85% formic acid is caused to interact with 72.0 grams of N-methyl formamide at 160°-180°C for 4 hours. This results in the formation of the formyl derivative of the amine, according to the following reaction:

C_6H_{11}-CH_2-C(O)-CH_3+ 2HCONHCH_3 => C_6H_{11}-CH_2-CH(NCH_3-CHO)-CH_3+ CH_3NH_2+ CO_2

The formyl derivative is then hydrolyzed by refluxing with 50% sulfuric acid for about 4 hours, after which the hydrolysate is extracted with ether to remove the acid-insoluble material and the aqueous solution made strongly alkaline with any suitable alkalizing agent, for example, sodium hydroxide, to liberate the amine.

The amine is then taken up in ether, dried over potassium hydroxide and purified by distillation, preferably under reduced pressure. β-cyclohexylisopropylmethylamine thus obtained boils at 90.0°-92°C at 22 mm Hg.

References

Merck Index 7761
Kleeman & Engel p. 774
OCDS Vol. 1 p. 37 (1977)
I.N. p. 817
REM p. 890
Ullyot, G.E.; US Patent 2,454,746; November 23, 1948; assigned to Smith, Kline and French Laboratories

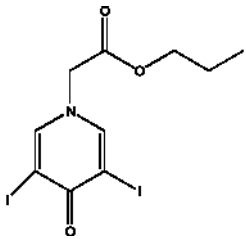
PROPYLIODONE

Therapeutic Function: Diagnostic aid

Chemical Name: 1(4H)-Pyridineacetic acid, 3,5-diiodo-4-oxo-, propyl ester

Common Name: Propiliodon; Propyliodone

Structural Formula:



Chemical Abstracts Registry No.: 587-61-1

Trade Name	Manufacturer	Country	Year Introduced
Propyliodone	GlaxoSmithKline	-	-
Dionosil oily	GlaxoSmithKline	-	-

Raw Materials

Chloroacetic acid
3,5-Diiodo-4-1H-pyridone
Isopropanol

Manufacturing Process

15 parts of 3,5-diiodo-4-pyridone-N-acetic acid, (prepared from 3,5-diiodo-4-1H-pyridone and chloroacetic acid), 60 parts of isopropanol, and 1 part of concentrated sulfuric acid are boiled for an hour in a vessel fitted with a reflux condenser. The solution is then cooled, whereupon crystals of isopropyl 3,5-diiodo-4-pyridone-N-acetate separate out by filtration, washed with ethanol and dried. MP: 215°C.

References

Branscombe D.J.; G.B. Patent No. 517,382; July 25, 1938; Imperial Chemical Industries Limited, of Imperial Chemical House, Millbank, London

Pharmazeutishe Wirkstoffe von A. Kleemann und J. Engel. 2., neubearbeitete und erweiterte Auflage; Georg Thime Verlag Stuttgart New York 1982; p. 775

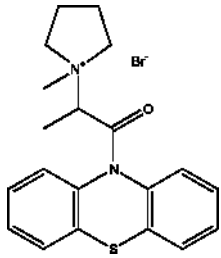
PROPYROMAZINE BROMIDE

Therapeutic Function: Spasmolytic, Anticholinergic

Chemical Name: 1-Methyl-1-(1-phenothiazin-10-ylcarbonylethyl) pyrrolidinium bromide

Common Name: Diaspasmyl; Propyromazine bromide

Structural Formula:



Chemical Abstracts Registry No.: 145-54-0

Trade Name	Manufacturer	Country	Year Introduced
Propyromazine bromide	Astra (AstraZeneca)	-	-

Raw Materials

Pyrrolidine
2-Bromo-1-phenothiazin-10-yl-propan-1
Methyl bromide

Manufacturing Process

185 g pyrrolidine and 334 g 2-bromo-1-phenothiazin-10-yl-propan-1 were refluxed in 2500 ml toluene for three hours. On cooling the solution the precipitated pyrrolidine hydrochloride was separated and collected, and the filtrate was evaporated to dryness. The crystalline residue 272 g was recrystallized from a mixture of five parts of light petroleum. MP of 1-phenothiazin-10-yl-2-pyrrolidin-1-yl-propan-1-one 94.5-95.5°C. Its brommethylate 1-methyl-1-(1-methyl-2-oxo-2-phenothiazin-10-yl-ethyl)pyrrolidinium, bromide was prepared by reaction with equivalent quantity of methyl bromide.

References

Dahlbom J.R., T.K.I. B. Ekstrand; US Patent No. 2,615,886; January 10, 1951; Assigned to Aktiebolaget Astra, Apotekarnes Kremiska Fabriker, Sodertalje, Sweden

Pharmazeutishe Wirkstoffe von A. Kleemann und J. Engel; 2., neubearbeitete und erweiterte Auflage, p. 776, 1982; Georg Thime Verlag Stuttgart New York

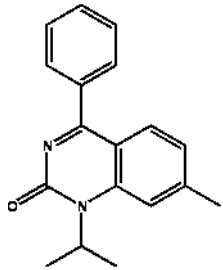
PROQUAZONE

Therapeutic Function: Antiinflammatory

Chemical Name: 1-Isopropyl-7-methyl-4-phenyl-2(1H)-quinazolinone

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 22760-18-5

Trade Name	Manufacturer	Country	Year Introduced
Biarison	Sandoz	Italy	1977
Biarison	Sandoz	Japan	1977
Biarison	Sandoz	France	1977
Biarison	Sandoz	Switz.	1977
Biarison	Wander	W. Germany	1979

Raw Materials

4-Methyl-2-isopropylaminobenzophenone
Urethane

Manufacturing Process

A mixture of 5.9 g of 4-methyl-2-isopropylaminobenzophenone, 13.9 g urethane and 500 mg of zinc chloride is heated at a temperature of 190°C for 1½ hours. There is then additionally added 7 g of urethane and 250 mg of zinc chloride, and the heating continued at a temperature of 190°C for an additional 2½ hours. The resulting mixture is cooled to about 100°C and diluted with chloroform. The resulting mixture is then filtered and the filtrate washed first with water and then with brine. The organic phase is separated,

dried over anhydrous sodium sulfate and concentrated in vacuo to remove substantially all of the chloroform and obtain an oily residue which is dissolved in a small amount of about 20 ml of methylene chloride. The resulting solution is then diluted with about 40ml of ethyl acetate and concentrated in vacuo to crystallize 1-isopropyl-7-methyl-4-phenyl-2(1H)-quinazolinone; melting point 137°C to 138°C.

References

Merck Index 7775
DFU 1 (11) 540 (1976)
Kleeman and Engel p. 777
OCDS Vol. 2 p. 386 (1980)
DOT 8 (3) 116 (1972) and 13 (12) 534 (1977)
I.N. p. 818
Linder, J., Mattner, P.G. and Salmond, W.G.; US Patent 3,759,720; September 18, 1973; assigned to Sandoz-Wander Inc.
Denzer, M.; US Patent 3,793,324; February 19, 1974
Ott, H.; US Patent 3,925,548; December 9,1975; assigned to Sandoz, Inc.

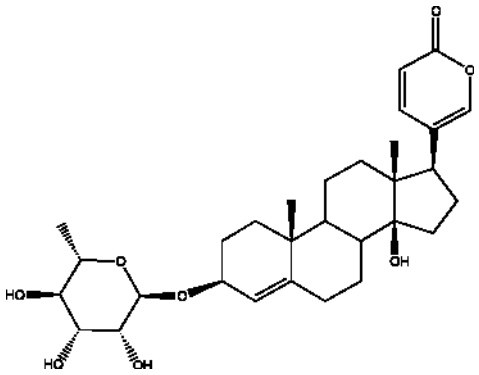
PROSCILLARIDIN

Therapeutic Function: Cardiotonic

Chemical Name: 3-[(6-Deoxy-α-L-mannopyranosyl)oxy]-14-hydroxybufa-4,20,22-trienolide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 466-06-8

Trade Name	Manufacturer	Country	Year Introduced
Talusin	Knoll	W. Germany	1964
Talusin	Biosedra	France	1968
Apocerpin	Kotani	Japan	-
Bunosquin	Seiko	Japan	-
Caradrin	Kowa	Japan	-
Cardimarin	Santen	Japan	-
Cardiolidin	Nichiiko	Japan	-
Cardion	Nippon Chemiphar	Japan	-
Cardon	Kanto	Japan	-
Herzo	Toho	Japan	-
Mitredin	Nippon Shoji	Japan	-
Procardin	Mohan	Japan	-
Procillan	Hokuriku	Japan	-
Proherz	Shinshin	Japan	-
Proscillan	Streuli	Switz.	-
Proscillar	Toyo Jozo	Japan	-
Prosiladin	Sawai	Japan	-
Prostosin	Iwaki	Japan	-
Proszin	Teisan	Japan	-
Protasin	Bayropharm	W. Germany	-
Purosin-TC	Tatsumi	Japan	-
Sandoscill	Sandoz	W. Germany	-
Scillaridin	Morishita	Japan	-
Silamarin A	Wakamoto	Japan	-
Stellarid	Tobishi-Mochida	Japan	-
Talusin	Dainippon	Japan	-
Urgilan	Simes	Italy	-
Wirnesin	Inpharzam	W. Germany	-

Raw Materials

Squill

Manufacturing Process

350 g of dried and cut squill were fermented at 50°C for two hours in 1.1 liters of water. The suspension was then extracted three times with 1.1 liters of ethyl acetate. The extracts were united and evaporated to dryness, the residue was dissolved in 2 ml of dioxane and chromatographed in a twenty-fold quantity (based on the amount of dried residue) of silica gel. The proscillaridin was then eluated with toluene to which increasing quantities of a methanol-dioxane mixture were added. The main fraction, containing proscillaridin, was evaporated to dryness. The residue was crystallized out of methanol. Pure proscillaridin was obtained with a melting point of 227°C to 230°C; α_{20}^{D} = -93.5°C (in methanol).

The same result was obtained by fermentation on the aqueous suspension of the cut squill at room temperature for 24 hours and working up in the manner described.

References

Merck Index 7776
Kleeman & Engel p. 777
DOT 3 (3) 97 (1967)
I.N. p.819 Steidle, W. US Patent 3,361,630; January 2, 1968; assigned to Knoll A.G. (Germany)

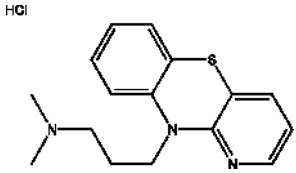
PROTHIPENDYL HYDROCHLORIDE

Therapeutic Function: Sedative, Antihistaminic

Chemical Name: N,N-Dimethyl-10H-pyrido[3,2-b][1,4]benzothiazine-10-propanamine hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 1225-65-6; 303-69-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Timovan	Ayerst	US	1960
Dominal	Homburg	W. Germany	-
Prosyl	Kanto	Japan	-
Tolnate	SKF	UK	-

Raw Materials

1-Azaphenothiazine
Sodium amide
3-Dimethylaminopropyl chloride
Hydrogen chloride

Manufacturing Process

A mixture of 20 g (0.1 mol) of 1-azaphenothiazine, 4.3 g (0.11 mol) of sodamide and 300 ml of dry toluene is stirred and refluxed for eight hours. A slow stream of dry nitrogen gas is used to sweep out the ammonia as formed. The mixture is cooled and 110 ml of a 1 M solution of 3-dimethylaminopropyl chloride in toluene is added dropwise, with stirring. Subsequently, the mixture

is stirred and refluxed for fifteen hours, cooled, and concentrated in vacuo. The viscous residue is refluxed with 500 ml of chloroform and filtered hot. The chloroform filtrate is treated with activated charcoal and again filtered. The filtrate is concentrated and the residue distilled to give about 19.8 g (69% yield) of product, an oil distilling at about 195°C to 198°C (under 0.5 mm pressure of mercury).

To a solution of 16.4 g (0.058 mol) of the free base in 75 ml of dry acetonitrile is added dropwlse while cooling (ice bath) and stirring 14.5 ml (0.053 mol) of 3.6 N ethereal hydrogen chloride. An equal volume of anhydrous ether is added and the product altered, dried and recrystallized from monochlorobenzene. The product melts at about 177°C to 178°C with sintering at about 176°C. The yield is about 11.0 g (60%).

References

Merck index 7789
Kleeman & Engel p. 779
OCDS Vol. 1 p. 430 (1977)
I.N. p. 821
Yale, H.L. and Bernstein, J.; US Patent 2,943,086; June 28, 1960; assigned to Olin Mathieson Chemical Corp.

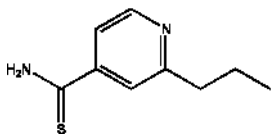
PROTIONAMIDE

Therapeutic Function: Antitubercular

Chemical Name: 2-Propyl-4-pyridinecarbothioamide

Common Name: α-Propyl-isonicotinic thioamide

Structural Formula:



Chemical Abstracts Registry No.: 14222-60-7

Trade Name	Manufacturer	Country	Year Introduced
Ektebin	Bayer	W. Germany	1969
Protionizina	Farmitalia	Italy	1970
Entelohi	Kyowa	Japan	-
Peteha	Saarstickstoff-Fatol	W. Germany	-
Promid	Biofarma	Turkey	-

Trade Name	Manufacturer	Country	Year Introduced
Prothionamide	Toho	Japan	-
Trevintix	Theraplix	France	-
Tuberamin	Meiji	Japan	-
Tuberex	Shionogi	Japan	-
Tubermide	Sankyo	Japan	-

Raw Materials

Ethyl oxalate
Hydrogen chloride
Phosphoric anhydride
Cyanacetamide
Ammonia
Sodium ethylate
Hydrogen
Methyl-n-propyl ketone
Phosphorus oxychloride
Hydrogen sulfide

Manufacturing Process

(A) Ethyl Butyryl-Pyruvate: 146 grams of ethyl oxalate are condensed with 86 grams of methyl-(n)-propyl-ketone in the presence of sodium ethylate prepared from 25 grams of sodium. 135 grams of product, having a boiling point of 113°C/6 mm, are obtained.

(B) 3-Cyano-4-Carbethoxy-6-(n)-Propyl-2-Pyridone: The 135 grams of the product just obtained are condensed with 62 grams of cyanacetamide in the presence of 24 cc of piperidine in 1200 cc of 95% alcohol. 64 grams of a product, melting at 152°C, are obtained.

(C) 6-(n)-Propyl-2-Pyridone-4-Carboxylic Acid: The 64 grams of the product just obtained are treated with 500 cc of concentrated hydrochloric acid at boiling point. 40 grams of a product, having a melting point of 285°C, are obtained.

(D) Ethyl 2-Chloro-6-(n)-Propyl-Isonicotinate: The 40 grams of the acid just obtained are treated with 80 grams of phosphorus oxychloride and 95 grams of phosphorus pentachloride. The phosphorus oxychloride is distilled and the reaction mixture is treated with 400 grams of absolute alcohol. 40 grams of chlorinated ester, having a BP of 115°-116°C/2 mm, are obtained.

(E) Ethyl 2-(n)-Propyl-Isonicotinate: The product just obtained is dechlorinated by catalytically hydrogenating it in an alcoholic medium in the presence of palladium black and potassium acetate. 30 grams of ester, having a boiling point of 121°-125°C/7 mm, are obtained.

(F) 2-(n)-Propyl-Isonicotinamide: The 30 grams of the ester just obtained are treated with 40 cc of concentrated ammonia saturated with gaseous ammonia. 20 grams of product, having a melting point of 135°C, are obtained.

(G) 2-(n)-Propyl-Isonicotinic-Nitrile: The 20 grams of the amide just obtained are treated with 32 grams of phosphoric anhydride. 11 grams of nitrile, having a BP of 90°-95°C/4 mm, are obtained.

(H) 2-(n)-Propyl-Isonicotinic Thioamide: The 11 grams of nitrile just obtained,

dissolved in 40 cc of ethanol containing 4 grams of triethanolamine, are treated with hydrogen sulfide. 8 grams of the desired product, having a melting point of 142°C, are obtained.

References

Merck Index 7791
Kleeman & Engel p. 780
DOT 3 (1) 24 (1967)
I.N. p. 821
Chimie et Atomistique, France; British Patent 800,250; August 20, 1958

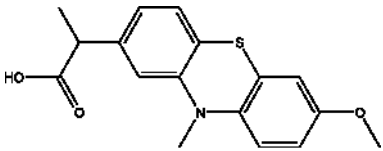
PROTIZINIC ACID

Therapeutic Function: Antiinflammatory

Chemical Name: 7-Methoxy-α,10-dimethylphenothiazine-2-acetic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 13799-03-6

Trade Name	Manufacturer	Country	Year Introduced
Pirocrid	Theraplix	France	1974
Pirocrid	Mochida	Japan	1979
P.R.T.	Mochida	Japan	-

Raw Materials

Sodium
thanol
Diethyl carbonate
Methyl (7-methoxy-10-methyl-3-phenthiazinyl)acetate
Hydrogen chloride
Methyl iodide
Sodium hydroxide

Manufacturing Process

Methyl ethyl (7-methoxy-10-methyl-3-phenthiazinyl)malonate is prepared by reacting a solution of sodium (4.37 grams) in anhydrous ethanol (110 cc) with a solution of methyl (7-methoxy-10-methyl-3-phenthiazinyl)acetate (59 grams) in ethyl carbonate (180 cc). The reaction mixture is heated at about

105°-110°C for 3 hours and the ethanol formed is distilled off as it is formed.

The reaction mixture is acidified with N hydrochloric acid (200 cc) and the oil formed is extracted with methylene chloride (200 cc). The methylene chloride solution is washed with water (210 cc), treated with decolorizing charcoal (5 grams), dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure (20 mm Hg) giving an oil (77 grams) which is crystallized from methanol (300 cc) to yield methyl ethyl (7-methoxy-10-methyl-3-phenthiazinyl)-malonate (62.4 grams) melting at 80°-82°C.

Methyl ethyl (7-methoxy-10-methyl-3-phenthiazinyl)malonate (62.2 grams) followed by methyl iodide (45.7 grams) is added to a solution of sodium (4.45 grams) in anhydrous ethanol (500 cc). The reaction mixture is heated under reflux for 1 hour at 45°C, then for 6 hours at 55°C, and finally concentrated to dryness under reduced pressure (20 mm Hg). The residue is taken up in methylene chloride (300 cc) and water (250 cc), filtered in the presence of a filtration adjuvant, washed with methylene chloride (150 cc) and water (150 cc), and decanted. The aqueous solution is extracted once again with methylene chloride (100 cc), and the combined organic solutions washed with water (100 cc), aqueous 0.1 N sodium hyposulfite solution (200 cc) and finally with water (200 cc). After drying over anhydrous sodium sulfate and evaporation to dryness under reduced pressure (20 mm Hg), there is obtained an oil (64.8 grams) which is dissolved in methylene chloride (100 cc) and chromatographed over alumina (650 grams). After elution with methylene chloride, a fraction of 2.5 liters is recovered and concentrated to dryness under reduced pressure (20 mm Hg) to give methyl ethyl methyl-(7-methoxy-10-methyl-3-phenthiazinyl)malonate (59.7 grams) melting at 70°-72°C.

1 N sodium hydroxide solution (296 cc) is poured over a period of 3 hours into a solution of methyl ethyl methyl-(7-methoxy-10-methyl-3-phenthiazinyl)malonate (59.7 grams) in ethanol (600 cc) heated under reflux in an atmosphere of nitrogen. The reaction mixture is concentrated to dryness under reduced pressure (20 mm Hg), the residue obtained acidified with N hydrochloric acid (300 cc) and the gum formed extracted with methylene chloride (150 cc). The organic solution is washed with water (200 cc), treated with decolorizing charcoal (10 grams), dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure (20 mm Hg). The oil obtained (48 grams) is dissolved in N sodium hydroxide solution (200 cc) and the aqueous solution washed with diethyl ether (300 cc), treated with decolorizing charcoal (5 grams) and acidified with N hydrochloric acid (200 cc). The oil formed is dissolved in methylene chloride (350 cc), the solution washed with water (100 cc), treated with decolorizing charcoal (5 grams) and dried over anhydrous sodium sulfate. The solution is concentrated to dryness under reduced pressure (20 mm Hg) to give an oil (35.6 grams) which crystallizes slowly. On recrystallization from diisopropyl ether (180 cc) a product (19.5 grams), melting at 123°-124°C, is obtained. Further recrystallization from diisopropyl ether (290 cc) yields 2-(7-methoxy-10-methyl-3-phenthiazinyl)propionic acid (12.9 grams) melting at 124°-125°C.

References

Merck Index 7792
Kleeman & Engel p. 782
DOT 8 (12) 452 (1972)

I.N. p. 36
Farge, D., Jeanmart, C. and Messer, M.N.; US Patent 3,450,698; June 17, 1969; assigned to Rhone-Poulenc SA, France

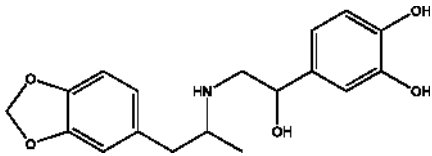
PROTOKYLOL

Therapeutic Function: Bronchodilator

Chemical Name: 4-[2-[[2-(1,3-Benzodioxol-5-yl)-1-methylethyl]amino]-1-hydroxyethyl]-1,2-benzenediol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 136-70-9; 136-69-6 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Caytine	Lakeside	US	1959
Ventaire	Marion	US	1974
Asmetil	Benvegna	Italy	-
Atma-Sanol	Sanol	W. Germany	-
Beres	Simes	Italy	-
Biturix	Nemi	Argentina	-
Palison	Farmasimes	Spain	-

Raw Materials

Chloroacetylcatechol
3,4-Methylenedioxyphenylisopropanolamine
Hydrogen

Manufacturing Process

3,4-Methylenedioxyphenylisopropanolamine is reacted with chloroacetylcatechol in a 3:1 mol ratio in 60% ethanol at reflux temperature with continuous stirring. Stirring and refluxing were continued for another five hours after which the reaction mixture was cooled and then acidified with 20 cc of concentrated aqueous HCl. The acid solution was concentrated in vacuo to a viscous consistency and the residue dissolved in acetone. On standing, the aminoketone precipitated and was filtered. The precipitate was dissolved in isopropyl alcohol and permitted to recrystallize. An alcoholic solution of this

aminoketone precipitate was reduced with PtO_2 and hydrogen, clarified by filtration, concentrated to dryness in vacuo and the residue crystallized from acetone giving the desired product.

References

Merck Index 7798
Kleeman and Engel p. 783
I.N. p.821
Biel, J.H.; US Patent 2,900,415; August 18, 1959; assigned to Lakeside Laboratories, Inc.

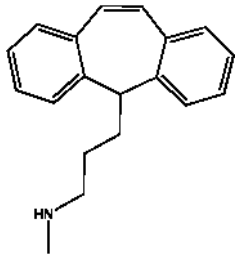
PROTRIPTYLINE

Therapeutic Function: Psychostimulant

Chemical Name: N-Methyl-5H-dibenzo[a,d]cycloheptene-5-propylamine

Common Name: Amimetilina; 5-(3-Methylaminopropyl)-5H-dibenzo[a,d]cycloheptene

Structural Formula:



Chemical Abstracts Registry No.: 438-60-8; 1225-55-4 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Vivactil	MSD	US	1967
Maximed	Sharp and Dohme	W. Germany	1968
Concordin	MSD	Italy	1972
Concordine	MSD	France	1973
Triptil	Merck-Frosst	Canada	-

Raw Materials

Formamide	3-Methylaminopropanol-1
Thionyl chloride	5H-Dibenzo[a,d]cycloheptene
Potassium amide	Potassium hydroxide

Manufacturing Process

Preparation of 3-(N-Formyl-N-Methyl)-Aminopropanol-1: A mixture of 40 grams of 3-methylaminopropanol-1 and 20 grams of formamide is heated while stirring for 4 hours at 165°C. The crude product is fractionated in vacuo using a Widmer column yielding substantially pure 3-(N-formyl-N-methyl)-aminopropanol-1.

Preparation of 3-(N-Formyl-N-Methyl)-Aminopropyl Chloride: 50 grams of 3-(N-formyl-N-methyl)-aminopropanol-1 obtained above is dissolved in a mixture of 100 ml of chloroform and 25 grams of pyridine. 40 grams of thionyl chloride is then slowly added while maintaining the temperature below 65°C. After 6 hours of refluxing, the mixture is washed with water, then with sodium bicarbonate solution and again with water and then dried over magnesium sulfate and the solvent distilled off in vacuo. Fractional distillation at 1 mm pressure yields substantially pure 3-(N-formyl-N-methyl)-aminopropyl chloride.

Preparation of 5-[3-(N-Formyl-N-Methyl)-Aminopropyl]-5H-Dibenzo[a,d]Cycloheptene: To a suspension of 3.9 grams of potassium amide is slowly added a solution of 19.2 grams (0.1 mol) of 5H-dibenzo[a,d]cycloheptene in 600 ml of ether with stirking. The suspension is refluxed with stirring for 3 hours, then cooled to room temperature and a solution of 0.1 mol of 3-(N-formyl-N-methyl)-aminopropyl chloride in 100 ml of ether added. The mixture is then refluxed with stirring for 5 hours and then 100 ml of water added. The ether layer is then washed with dilute hydrochloric acid, then water and then dried over magnesium sulfate and evaporated to dryness yielding 5-[3-(N-formyl-N-methyl)-aminopropyl]-5H-dibenzo[a,d]cycloheptene.

Preparation of 5-(3-Methylaminopropyl)-5H-Dibenzo[a,d]Cycloheptene from 5-[3-(N-Formyl-N-Methyl)-Aminopropyl]-5H-Dibenzo[a,d]Cycloheptene: 29.5 grams of 5-[3-(N-formyl-N-methyl)aminopropyl]-5H-dibenzo[a,d]cycloheptene is refluxed for 24 hours under nitrogen in a solution of 36.3 grams of potassium hydroxide in 378 ml of n-butanol. After cooling to room temperature, the solvent is evaporated in vacuo, the residue is stirred with 200 ml of water, 300 ml of n-hexane, the layers separated, the water layer extracted with 100 ml of n-hexane and the combined hexane layers washed with water (2 x 100 ml) and then with 0.5 N sulfuric acid (100, 80, 80 ml). The acid solution is then alkalized and extracted with ether (2 x 150 ml and 1 x 100 ml), dried over $MgSO_4$ and the solution evaporated to dryness yielding substantially pure 5-(3-methylarninopropyl)-5H-dibenzo[a,d]cycloheptene according to US Patent 3,244,748.

References

Merck Index 7804
Kleeman & Engel p. 783
PDR p. 1220
OCDS Vol. 1 p. 152 (1977)
I.N. p. 822
REM p. 1097
Tishler, M., Chemerda, J.M. and Kollonitsch, J.; US Patent 3,244,748; April 5, 1966; assigned to Merck & Co., Inc.

Tishler, M., Chemerda, J.M. and Kollonitsch, J.; US Patent 3,271,451; September 6, 1966; assigned to Merck & Co., Inc.

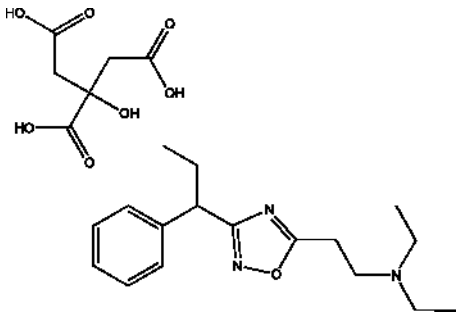
PROXAZOLE CITRATE

Therapeutic Function: Spasmolytic

Chemical Name: N,N-Diethyl-3-(1-phenylpropyl)-1,2,4-oxadiazole-5-ethanamine citrate

Common Name: Propaxoline citrate

Structural Formula:



Chemical Abstracts Registry No.: 132-35-4; 5696-49-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Recidol	Lampugnani	Italy	1967
Pirecin	Yoshitomi	Japan	1970
Mendozal	Beaufour	France	1976
Flou	Elea	Argentina	-
Solacil	Finadiet	Argentina	-
Toness	Angelini	Italy	-

Raw Materials

α-Ethylbenzamidoxime
Citric acid
β-Chloropropionyl chloride
Diethylamine

Manufacturing Process

α-Ethylbenzamidoxime and anhydrous potassium carbonate are suspended in chloroform. To this mixture, under continuous stirring and controlling of the reaction temperature to remain beyond 15°C, there is slowly added β-chloropropionyl chloride. After addition of the acid chloride, stirring is

continued for a further hour. Then with cooling there is added portionwise a small amount of water. Further amounts of water are introduced into the reaction mixture and the chloroform solution containing the β-chloropropionyl α-ethylbenzamidoxime is separated.

To this solution there is added in about 20 minutes a solution of diethylamine in $CHCl_3$ while the temperature is kept below 35°C. The reacting mixture is heated to boiling, water formed during the reaction being distilled off thereby. After two hours the distillate contains no more water and the reaction is finished. Water is added to dissolve diethylamine hydrochloride formed during the reaction, and the chloroform layer containing the product is separated from the aqueous layer. The product may be purified by distillation; it boils at 132°C at 0.2 mm pressure. It is converted to the citrate by reaction with citric acid.

References

Merck Index 7805
Kleeman & Engel p. 784
OCDS Vol. 2 p. 271 (1980)
I.N. p. 822
Palazzo, G. and Silvestrini, B.; US Patent 3,141,019; July 14, 1964; assigned to Angelini Francesco, Aziende Chimiche Riunite, Italy

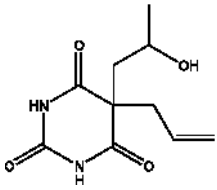
PROXIBARBAL

Therapeutic Function: Sedative

Chemical Name: 5-(2-Hydroxypropyl)-5-(2-propenyl)-2,4,6(1H,3H,5H) pyrimidinetrione

Common Name: Proxibarbital

Structural Formula:



Chemical Abstracts Registry No.: 2537-29-3

Trade Name	Manufacturer	Country	Year Introduced
Axeen	Hommel	W. Germany	1962
Centralgol	Valpan	France	1965
Ipronal	Polfa	Poland	-
Vasalgin	Chinoin	Hungary	-

Raw Materials

Diallylbarbituric acid
Sulfuric acid
Water

Manufacturing Process

9 Parts of diallyl-barbituric acid are added to a precooled mixture of 15.5 parts of concentrated sulfuric acid and 0.5 part of water while stirring intensively, the mixture being cooled so that its temperature does not exceed 25°C. The honey-colored viscous solution is stirred vigorously and all at once into 45 parts of water, whereupon the mixture warms up to 35°C to 40°C and, after several seconds, solidifies into a thick pulp, which is then heated as quickly as possible to 95°C, at which temperature a clear solution is formed. This is cooled slowly until the 5-allyl-5-(β-hydroxypropyl)-barbituric acid begins to form coarse-grained crystals, after which the mass is cooled rapidly to 20%.

The crystallized 5-allyl-5-(β-hydroxypropyl)-barbituric acid is centrifuged off, 55 to 58 parts of mother liquor and 10 to 13 parts of crude product being obtained. The latter is dispersed in 20 parts of saturated aqueous sodium chloride solution and after two hours is again centrifuged off.

The thus-washed crude product is dissolved in a mixture of 12 parts of ethanol and 20 parts of benzene, with mild warming if necessary. 1 Part of sodium chloride and 1.5 parts of saturated aqueous sodium chloride solution are added to the obtained solution in ethanol-benzene, and whole thoroughly admixed. When the brine layer has settled, it is separated and the afore-described washing repeated. The clear solution is concentrated under reduced pressure until incipient formation of crystals and is then poured into 30 parts of benzene, whereupon a thick crystalline pulp is forthwith formed which, after being cooled to room temperature, is centrifuged off. The so-obtained 5-allyl-5-(β-hydroxypropyl)-barbituric acid is dried at 70°C under reduced pressure and can be used for therapeutic purposes without further purification. Melting point 164°C to 165°C. Yield: 5 parts.

References

Merck Index 7806
I.N. p. 822
Hommel A.G.; British Patent 953,387; March 25, 1964

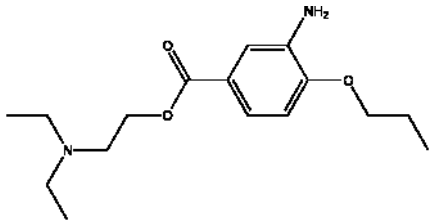
PROXYMETACAINE

Therapeutic Function: Local anesthetic

Chemical Name: 3-Amino-4-propoxybenzoic acid 2-(diethylamino)ethyl ester

Common Name: Proparacaine; Proxymetacaine

Structural Formula:



Chemical Abstracts Registry No.: 499-67-2

Trade Name	Manufacturer	Country	Year Introduced
Diocaine	Dioptic	-	-

Raw Materials

4-Propoxynitrobenzoyl chloride
Diethylaminoethanol
Granulated tin

Manufacturing Process

Equal molecular proportions of 4-propoxynitrobenzoyl chloride and diethylaminoethanol are mixed. They react forming hydrochloride of (diethylamino)ethyl 4-propoxy-3-nitrobenzoate as a pale yelllow leaflets; MP: 124.8-126.8°C. The reaction is completed when there is no further tendency to warm itself spontaneously. Ten parts by weight of the latter substance are dissolved in a mixture of twenty-five parts by weight of hydrochloric acid and twenty parts by weight of alcohol, and the solution treated with twelve parts by weight of granulated tin, keeping the temperature at about 35°C.

A colorless solution is obtained from which the tin is removed by precipitation with hydrogen sulfide. On addition of sodium carbonate solution, 3-Amino-4-propoxybenzoic acid 2-(diethylamino)ethyl ester separates as an oil. When treated with one equivalent of hydrochloric acid it forms a hydrochloride, which is readily soluble in water and crystallizes from a mixture of absolute alcohol and ethyl acetate in white prisms MP: 182.0-183.3°C.

References

Wildman E.A.; US Patent No. 1,317,250; September 30, 1919; Assigned to Parke Davis and Company, of Detroit,Michigan, a corporation
Climton R.O. et al.; J.A.C.S. v.74 p. 592-598, 1952

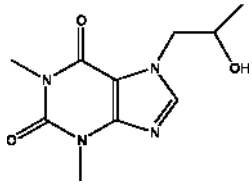
PROXYPHYLLINE

Therapeutic Function: Diuretic, Cardiac stimulant, Smooth muscle relaxant, Vasodilator

Chemical Name: 1H-Purine-2,6-dione, 3,7-dihydro-7-(2-hydroxypropyl)-1,3-dimethyl

Common Name: Hydroxypropyltheophylline; Proxifillina; Proxiphyllinum; Proxyphylline

Structural Formula:



Chemical Abstracts Registry No.: 603-00-9

Trade Name	Manufacturer	Country	Year Introduced
Monophyllin	AFI	-	-
Monophyllin	Yoshitomi	-	-
Neofyllin	Abigo	-	-
Neofyllin	Pharmacia	-	-
Purophyllin	Siegfried	-	-
Spasmolysin	Kade	-	-
Theon	Draco	-	-

Raw Materials

Theophylline
1-Chloro-2-propanol
Sodium hydroxide

Manufacturing Process

A mixture of 270 g (1.5 moles) of anhydrous theophylline and 213 g (2.25 moles) of 1-chloro-2-propanol in 750 ml of water is heated to boiling in an apparatus equipped with a mechanical agitator, reflux condenser, thermometer, and dropping funnel. A 25 per cent solution of sodium hydroxide in water, containing 90 g (2.25 moles) of sodium hydroxide, is added to the refluxing mixture over a period of 2 hours. Refluxing is continued for 1 hour after all the sodium hydroxide has been added. The water is removed as completely as possible by distillation under reduced pressure, using a boiling water bath as the source of heat. The residue, consisting of a sticky, resinous mass or white solid, is treated with 700 ml of anhydrous ethyl alcohol and heated until the remaining insoluble solid is loose and granular. The solid is separated by filtering of the hot mixture. When the filtrate cools, a white, crystalline mass separates which is filtered off and washed with cold anhydrous ethyl alcohol. The material is purified by crystallization from anhydrous ethyl alcohol. The purified product is 7-β-hydroxypropyl theophylline, M. P. 135-136°C. The pH of a 5% per cent solution in distilled

water falls within the range of 5.5 to 7.0. 1 g dissolves in approximately 1 ml of water at 20°C and in about 14 ml of anhydrous ethyl alcohol. It is considerably more soluble in boiling anhydrous ethyl alcohol.

References

Rice R. V.; US Patent No. 2,715,125; Aug. 9, 1955; Assigned to N. J., assignor to Gane's Chemical Works, Inc., Carlstadt, N. J., a corporation of New York

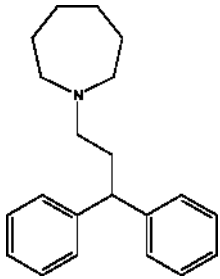
PROZAPINE

Therapeutic Function: Choleretic, Spasmolytic

Chemical Name: 1-(3,3-Diphenylpropyl)cyclohexamethyleneimine

Common Name: Prozapine; Hexadiphane

Structural Formula:



Chemical Abstracts Registry No.: 3426-08-2

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

Raw Materials

Hydrochloric acid	α,α-Diphenyl-7-hexamethyleneimino butyronitrile
Phenyl magnesium bromide	
Sodium amide	Sodium hydroxide
Hydrogen	Hexamethyleneiminoethyl phenyl ketone
Thionyl chloride	Palladium on charcoal

Manufacturing Process

The 1st method of preparation of the 1,1-diphenyl-3-hexamethyleneimino propane:

A vigorously stirred suspension of 0.2 to 1 mole of sodium amide in 200 ml of xylene, in which were dissolved 0.1 mole of α,α-diphenyl-7-hexamethyleneimino butyronitrile was boiled for 12 hours. Thereupon the excess of sodium amide was decomposed with water and the xylene layer was separated, washed with water and extracted with hydrochloric acid. This acidic extract was made strongly alkaline with concentrated lye and the separated base was extracted with ether. After drying, the ether was evaporated and the 1,1-diphenyl-3-hexamethyleneimino propane distilled in vacuo. The boiling point was 170-174°C/1 mm, the refractive index n_D^{20} = 1.5636, and the density d_4^{20} = 1.009. From the oil obtained several acid additions and quaternary ammonium salts can be obtained by reaction with acids containing a non-toxic anion or esters thereof. The hydrochloric acid salt, for instance, melts at 189-192°C, the methiodide at 174-177°C under decomposition.

Another method of preparation of the 1,1-diphenyl-3-hexamethyleneimino propane:

To a solution of 0.4 mole of phenyl magnesium bromide in ether were added 42.3 g (0.183 mole) of hexamethyleneiminoethyl phenyl ketone, dissolved in dry ether, followed by 250 ml of dry benzene. The temperature of the mixture was slowly raised until all the ether had been driven off, after which the solution was heated to boiling under reflux of the benzene for 6 hours. The reaction mixture was then cooled and a solution of ammonium chloride was added. The benzene layer was washed with water and dried on potassium carbonate, filtered from the potassium carbonate, and the solvent was then evaporated. Recrystallization of the residue from petroleum ether (B.P. 60-80°C) yielded 44 g of 1,1-diphenyl-3-hexamethyleneimino propanol-1 with a melting point of 81°C.

To 31 g of 1,1-diphenyl-3-hexamethyleneimino propanol-1, dissolved in chloroform, an excess of thionyl chloride was added and the mixture was heated under reflux for 3 hours. Thereupon the reaction mixture was evaporated to dryness under reduced pressure and the residue was recrystallized by dissolving in warm ethanol and diluting this solution with ethyl acetate. An aqueous solution of the 1,1-diphenyl-1-chloro-3-hexamethyleneimino propane hydrochloride thus obtained was hydrogenated with hydrogen gas in the presence of a buffered palladium-charcoal catalyst at a pressure of 3 atm. The 1,1-diphenyl-3-hexamethyleneimino propane obtained was purified by distillation under reduced pressure. The boiling point was 170-174°C/1 mm.

References

Paul A. J. Janssen, David K. De Jongh; US Patent No. 2,881165; Apr. 7, 1959; Assigned to N. V. Nederlandsche Cornbinatie voor Chemische Industrie, Amsterdam, Netherlands, a limited liability company of the Netherlands

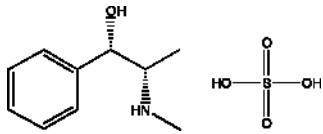
PSEUDOEPHEDRINE SULFATE

Therapeutic Function: Bronchodilator

Chemical Name: Benzenemethanol, α-((1S)-1-(methylamino)ethyl)-, (αS)-, sulfate (2:1) (salt)

Common Name: Pseudoephedrine sulfate

Structural Formula:



Chemical Abstracts Registry No.: 7460-12-0; 90-82-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Afrinol	Schering	-	-
Demazin sinus	Schering-Plough	-	-
Drixora	Magpharm Pharmaceuticals	S. Africa	-
Lertamine-D	White Pharma	-	-
Pseudoephedrine sulfate	BASF AG	Germany	-
Pseudoephedrine sulfate	Knoll AG	Germany	-

Raw Materials

Hydrobromic acid
Bromine
Methylamine
Propionaldehyde
Phenyl magnesium bromide

Manufacturing Process

Propionaldehyde was brominated by bromine and the propanoilbromide was obtained. Then propanoilbromide reacted with methanol and hydrobromic acid yielding 1,2-dibromo-1-methoxypropane.

1,2-Dibromo-1-methoxypropane in turn with phenylmagnesium-bromide gave the product, which after hydrolysis yielded 1-phenyl-1-methoxy-2-bromopropane.

To the solution of 1-phenyl-1-methoxy-2-bromopropane methylamine was added and as a result of the reaction 1-phenyl-1-methoxy-2-methylaminopropane was obtained. After that 1-phenyl-1-methoxy-2-methylaminopropane on hydrolysis with hydrobromic acid yielded 1-phenyl-1-hydroxy-2-methylaminopropane, i.e. racemic pseudoephedrine. The racemic base was resolved, by crystallization of their tartrates, into l- and d-pseudoephedrine. The base l-pseudoephedrine forms white rhombic crystals, melting point 118°C. The salt pseudoephedrine sulfate may be prepeared by

treatment of pseudoephedrine base with sulfuric acid.

References

Manske and Holmes, The Alkaloids, Vol III, pp.343-344, 351-361, Academic Press (1953)

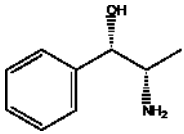
PSEUDONOREPHEDRINE

Therapeutic Function: Sympathomimetic, Anorexic

Chemical Name: Benzenemethanol, α-((1S)-1-aminoethyl)-, (αS)-

Common Name: Cathine, Katine; ψ-Norephedrine; Norisoephedrine; Norpseudoephedrine; Pseudonorephedrine

Structural Formula:



Chemical Abstracts Registry No.: 492-39-7

Trade Name	Manufacturer	Country	Year Introduced
Beloform	Neue Formulierung	-	-
Cathine	BlueRunners Trading Dev. Co.	-	-
Norpseudoephedrine	Shanghai Lansheng Corporation	-	-

Raw Materials

Thionyl chloride
Norephedrine hydrochloride, (+)-

Manufacturing Process

60 ml thionylchloride was added to 20 g (+)-norephedrine hydrochloride by cooling. Then the mixture was gradually heated to +35°C. Finally it was heated 20 minutes at 45°C. After that the excess thionylchloride was removed in vacuum, the residue was stirred with 100 ml acetone and 2-amino-1-chloro-1-phenylpropane hydrochloride was filtered off. It was dissolved in 100 ml 2 N hydrochloric acid, heated to reflux for 3 hours, and distilled to dryness in vacuum. The crystalline residue was mixed with acetone, filtered off and dried. Yield was 17.5 g crude product, which was cleaned by fractional

crystallization to give 13 g (65%) (+)-norpseudoephedrine hydrochloride 166°-168°C. The may be converted to the base by adding of equivalent of any base.

References

Pfanz H., Wieduwilt H.; D.D. Patent No. 13,785; Feb. 8, 1956

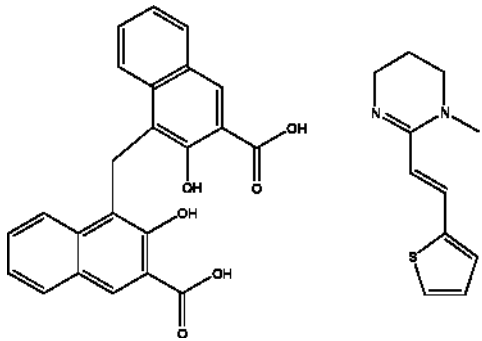
PYRANTEL PAMOATE

Therapeutic Function: Anthelmintic

Chemical Name: E-1,4,5,6-Tetrahydro-1-methyl-2-[2-(2-thienyl)vinyl] pyrimidine pamoate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 22204-24-6; 15686-83-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Antiminth	Roerig	US	1972
Helmex	Roerig	W. Germany	1972
Cobantrin	Pfizer Taito	Japan	1973
Combantrin	Pfizer	France	1973
Combantrin	Pfizer	Italy	1975
Lombriareu	Areu	Spain	-
Piranver	ICN-Usafarma	Brazil	-

Raw Materials

Tartaric acid	Thiophene-2-carboxaldehyde
Pamoic acid	1,2-Dimethyl-1,4,5,6-tetrahydropyrimidine

Manufacturing Process

A solution of 0.1 mol of each of thiophene-2-carboxaldehyde and 1,2-dimethyl-1,4,5,6-tetrahydropyrimidine in dimethyl carbonate (0.2 mol) is held at 27°C for 48 hours. The reaction mixture is then stripped to give a 65% yield of product as the free base.

The base may be isolated as the tartrate as follows: A portion of reaction mixture is added to a well stirred solution of tartaric acid in ethanol at 27°C. The mixture is stirred for two hours and the product recovered by filtration. The filter cake is washed with cold ethanol followed by ether and air-dried. MP 144°-147°C.

The tartrate salt is recrystallized by dissolving in hot methanol, filtering, adding hot ethanol to the filtrate and cooling. The product is collected and air-dried. MP 148°-150°C. A second crop is obtained from the filtrate for a total yield of 59%. The tartrate is then metathesized with pamoic acid (Merck Index #6867) to give pyrantel pamoate as the product.

References

Merck Index 7856
Kleeman & Engel p. 786
PDR p. 1403
OCDS Vol. 1 p. 266 (1977) and 2, 303 (1980)
DOT 8 (11) 431 (1972); 17 (1) 41 (1981); and (6) 262 (1981)
I.N. p. 825
REM D. 1237
Kasubick, R.V. and McFarland, J.W.; US Patent 3,502,661; March 24,1970; assigned to Chas. Pfizer & Co., Inc.

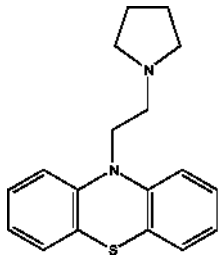
PYRATHIAZINE

Therapeutic Function: Antihistaminic

Chemical Name: 10-[2-[1-(Pyrrolidinyl)ethyl]phenothiazine

Common Name: Parathiazine

Structural Formula:



Chemical Abstracts Registry No.: 84-08-2

Trade Name	Manufacturer	Country	Year Introduced
Pyrrolazote	Upjohn	US	1949

Raw Materials

Phenothiazine
Sodium amide
β-Pyrrolidinoethyl chloride

Manufacturing Process

To a stirred suspension of 4.29 g (0.11 mol) of sodium amide in 100 ml of dry toluene was added 19.9 g (0.1 mol) of phenothiazine. The solution was heated at reflux for two hours, the sodium salt of phenothiazine precipitating from solution. The toluene suspension of the sodium salt of phenothiazine was cooled to room temperature, whereupon there was added dropwise with continued stirring 13.36 g (0.1 mol) of β-pyrrolidinoethyl chloride in 50 ml of dry toluene. After addition was complete, the solution was heated under reflux, with stirring, for an additional 15 hours. Upon cooling, the toluene was extracted with dilute hydrochloric acid and the toluene then discarded. The aqueous acid solution was made alkaline with dilute sodium hydroxide, the crude N-(β-pyrrolidinoethyl)-phenothiazine separating as a brownish oil.

The oil was extracted with ether, the ether solution dried with anhydrous magnesium sulfate, and then filtered. Dry hydrogen chloride was passed into the ether solution and a semisolid mass, which crystallized after scratching, separated therefrom. The crude N-(β-pyrrolidinoethyl)-phenothiazine was separated from the ether and, after two crystallizations from isopropanol, 17.0 g of desired product, melting at 196°C to 197°C (uncorr.), was obtained.

References

Merck Index 7857
OCDS Vol. 1 p. 373 (1977)
I.N. p. 731
Hunter, J.H. and Reid, W.B. Jr.; US Patent 2,483,999; October 4, 1949; assigned to The Upjohn Co.

PYRAZINAMIDE

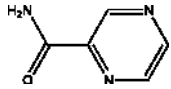
Therapeutic Function: Antibacterial (tuberculostatic)

Chemical Name: Pyrazinecarboxamide

Common Name: -

Chemical Abstracts Registry No.: 98-96-4

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Aldinamide	MSD	US	1955
Pirilene	Lepetit	France	1981
Eprazin	Krugmann	W. Germany	-
Isopyratsin	Leiras	Finland	-
Pezatamid	Hefa-Frenon	W. Germany	-
Piraldina	Bracco	Italy	-
Pirazimida	Madaus Cerafarm	Spain	-
Pyrafat	Saarstickstoff-Fatol	W. Germany	-
Pyrazide	SCS Pharmalab	S. Africa	-
P.Z.A.	Servipharm	Switz.	-
Tebrazid	Continental Pharma	Belgium	-
Tisamid	Orion	Finland	-
Zinamide	MSD	UK	-

Raw Materials

Pyrazine-2,3-dicarboxamide
Sodium hydroxide

Manufacturing Process

166 Parts of pyrazine-2,3-dicarboxamide (1 mol) is slurried in 1,000 parts of 1 N aqueous sodium hydroxide. The reaction mixture is heated at 95°C to 98°C until a clear solution results. Thereupon the mixture is cooled with ice to about 5°C and acidified to approximately a pH of 1. The cold reaction mixture is allowed to stand until precipitation of the pyrazine-2-carboxamide-3-carboxylic acid is substantially complete whereupon it is recovered by filtration and dried at 50°C to 60°C.

100 Parts of pyrazine-2-carboxamide-3-arboxylic acid is heated in a reaction vessel provided with an intake for inert gas. The reaction mixture is heated in a bath held at 220°C and nitrogen is introduced. The solid material melts and effervesces and sublimed pyrazinamide vapors are carried out of the reaction vessel in the nitrogen stream. They are introduced into a suitably cooled condenser, condensing in the form of a white sublimate. After the reaction is proceeding vigorously the bath temperature is raised to 255°C and then gradually and slowly allowed to drop to 190°C over a period of time sufficient to permit the reaction to go substantially to completion. The sublimed pyrazinamide, if desired, is further purified by recrystallization from water or alcohol.

References

Merck Index 7858
Kleeman & Engel p. 787
OCDS Vol. 1 p. 277 (1977)
I.N. p. 826
REM p. 1216
Webb, J.S. and Ark, H.G. Jr.; US Patent 2,780,624; February 5, 1957; assigned to American Cyanamid Co.

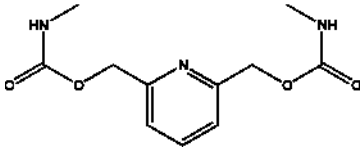
PYRIDINOL CARBAMATE

Therapeutic Function: Antiarteriosclerotic

Chemical Name: Bis[methylcarbamic acid]-2,6-pyridinediyldimethylene diester

Common Name: Pyricarbate

Structural Formula:



Chemical Abstracts Registry No.: 1882-26-4

Trade Name	Manufacturer	Country	Year Introduced
Movecil	Erba	Italy	1969
Angioxine	Roussel	France	1971
Anginin	Banyu	Japan	-
Angiovital	I.S.M.	Italy	-
Angioxil	Firma	Italy	-
Angiperl	Sawai	Japan	-
Arteriolangal	Lanzas	Spain	-
Aterin	Ilsan	Turkey	-
Aterofal	Nativelle	Italy	-
Atero-Flavin	Indelfar	Spain	-
Aterollano	Llano	Spain	-
Ateronova	Cheminova	Spain	-
Atover	Oti	Italy	-
Carbatona	Turro	Spain	-
Cicloven	A.G.I.P.S.	Italy	-
Colesterinex	Galenika	Switz.	-
Dual-Xol	Lifepharma	Spain	-

Trade Name	Manufacturer	Country	Year Introduced
Duaxol	Argentia	Argentina	-
Duvaline	Almirall	Spain	-
Gasparol	Castejon	Spain	-
Meduxal	Allard	France	-
Plavolex	Wolner	Spain	-
Prodectin	Kobanyai	Hungary	-
Ravenil	Caber	Italy	-
Sospitan	Kali-Chemie	W. Germany	-
Vasagin	Sidus	Italy	-
Vasapril	Cifa	Italy	-
Vasmol	Lifasa	Spain	-
Vasocil	Magis	Italy	-
Vasoverin	Biochimica	Switz.	-
Veranterol	Asla	Spain	-

Raw Materials

Methyl isocyanate
2,6-Dihydroxymethylpyridine hydrochloride

Manufacturing Process

(A) 15.7 g (0.1 mol) of 2,6-dihydroxymethylpyridine hydrochloride are suspended in 176 ml of acetonitrile, and 20.8 ml (0.15 mol) of triethylamine are added to the suspension. Thereafter 13 ml (0.22 mol) of methyl isocyanate are added dropwise to the reaction mixture at 20°C to 25°C. The reaction mixture is stirred at 20°C to 30°C for one hour, thereafter boiled for 3 hours, and finally the solvent is evaporated under reduced pressure. 35 to 40 g of a greyish, crystalline residue are obtained, which is a mixture of 2,6-dihydroxymethylpyridine-bis-(N-methylcarbamate) and triethylamine hydrochloride. The obtained residue is dissolved in 80 ml of hot water, decolorized with 2 g of activated carbon when hot, and filtered after 30 minutes of stirring. The filtrate is cooled, the resulting crystal suspension is stirred at 0°C to 5°C for 3 hours, the solids are filtered off, and dried at 50°C to 60°C.

23.3 g (94.4%) of 2,6-dihydroxymethylpyridine-bis(N-methylcarbamate) are obtained. The product melts at 134°C to 135°C; its purity is 99.8% (determined by UV spectrophotometry). When examined by thin layer chromatography, the product is uniform.

(B) 23.3 g of 2,6-dihydroxymethylpyridine-bis(N-methylcarbamate), prepared as described above, are dissolved in a boiling mixture of 46.6 ml of methanol and 46.6 ml of water. When the dissolution is complete, the solution is allowed to cool under slow stirring, without applying any external cooling means. The crystals start to separate at 48°C to 50°C. When the temperature of the mixture falls spontaneously below 35°C, it is cooled externally to 0°C to 5°C, and allowed to stand at this temperature for about 8 hours. The separated substance is filtered off and dried at 50°C to 100°C. 22.65 g of 2,6-dihydroxymethylpyridine-bis(N-methylcarbamate) are obtained. The quality of the product meets pharmaceutical requirements.

The yield of this crystallization procedure is 95.7%. The above process provides the γ_2 modification of 2,6-dihydroxymethylpyridine-bis(N-methylcarbamate), which can be tabletted directly. The substance melts at 134°C to 136°C, its purity is 99.9% (determined by UV spectrophotometry).

References

Merck Index 7874
Kleeman & Engel p. 787
DOT 5 (1) 16 (1969)
I.N. p. 826
Sprung, M., Toth, J., Kovatsits, M., Sztrokay, K., Szen, T., Gorgenyi, K., Boor, A., Forgacs, L.,Szabo, J. and Kruzics, A.; British Patent 1,548,334; July 11, 1979; assigned to Richter Gedeon Vegyeszeti Gyar R.T. (Hungary)

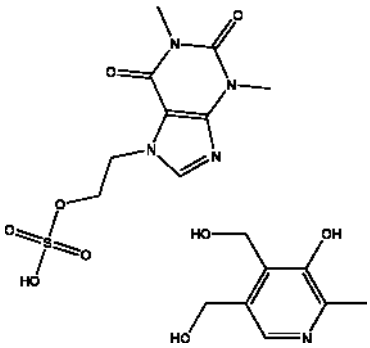
PYRIDOFYLLINE

Therapeutic Function: Coronary vasodilator

Chemical Name: 1H-Purine-2,6-dione, 3,7-dihydro-1,3-dimethyl-7-(2-(sulfooxy)ethyl)-, compd. with 5-hydroxy-6-methyl-3,4-pyridinedimethanol (1:1)

Common Name: Pyridofylline; Theodoxine

Structural Formula:



Chemical Abstracts Registry No.: 53403-97-7

Trade Name	Manufacturer	Country	Year Introduced
Pyridofylline	Debarge	-	-

Raw Materials

Theophylline
Chlorosulfonic acid
Pyridoxine
Potassium hydroxide
Monochlorhydrin ethylene glycol

Manufacturing Process

A solution of 100 g of theophylline in 500 ml 1 M solution of KOH was prepared potassium theophylline. To that potassium theophylline was added 120 ml monochlorhydrin ethylene glycol, a mixture was heated at 130°C for 4 hours. The product was dissolved in ethanol and filtered. After crystallization was obtained 7-(2-hydroxyethyl)theophylline.

100 g of 7-(2-hydroxyethyl)-theophylline was refluxed in 2.1 L of dry chloroform, then was added dropwise 47 g of HSO_3Cl and mixture was refluxed for 2 hours. After filtration the solid product [O-(7-theophyllinylethyl) sulfuric acid] was washed with chloroform and ether and dried in vacuum for 4 hours at 80°C.

Pyridofylline was obtained by mixing 110 g o-(7-theophyllinylethyl) sulfuric acid and 72 g pyridoxine in ethanol.

References

Albert M., Debarge E.J.J.; Brevet Special de Medicament; FR 828M, Dec. 23, 1960

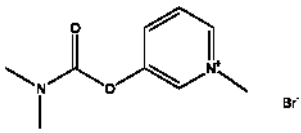
PYRIDOSTIGMINE BROMIDE

Therapeutic Function: Cholinergic

Chemical Name: 3-[[(Dimethylamino)carbonyl]oxy]-1-methylpyridinium bromide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 101-26-8

Trade Name	Manufacturer	Country	Year Introduced
Mestinon	Roche	US	1955
Mestinon	Roche	Japan	1970
Regonol	Organon	US	1973
Mestinon	Roche	France	1981
Kalymin	Arzneimittelwerk Dresden	E. Germany	-

Raw Materials

3-Hydroxypyridine
Dimethyl carbamic acid chloride
Methyl bromide

Manufacturing Process

12 parts by weight of dimethyl-carbamic acid chloride, dissolved in 20 parts by weight of xylol, are added dropwise to a boiling solution of 19 parts by weight of 3-hydroxypyridine in 120 parts by weight of xylol. Heating is continued under reflux for 3 hours. When the solution has cooled down, it is separated from the precipitated 3-hydroxypyridine hydro chloride and washed with water. After drying over sodium sulfate, the xylol is distilled off and the residue fractionated under reduced pressure. The N,N-dimethyl-carbamic acid ester of 3-hydroxypyridine distills at 148°C under a pressure of 15 mm.

A solution of 20 parts by weight of methyl bromide in 30 parts by weight of acetone is added to a solution of 35 parts by weight of N,N-dimethyl-carbamic acid ester of 3-hydroxypyridine in 70 parts by weight of acetone. After standing for a lengthy period (1 or 2 days), the N,N-dimethyl-carbamic acid ester of 3-hydroxy-1-methyl-pyridinium-bromide separates. It can be recrystallized from absolute alcohol. The colorless, strongly hygroscopic crystals melt at 151°-152°C.

References

Merck Index 7877
Kleeman and Engel p. 789
PDR pp. 1289, 1491
I.N. p. 826
REM p. 900
Urban, R.; US Patent 2,572,579; October 23,1951; assigned to Hoffmann-La Roche Inc.

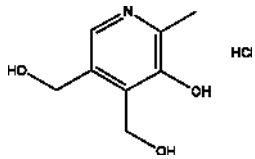
PYRIDOXINE HYDROCHLORIDE

Therapeutic Function: Enzyme cofactor vitamin

Chemical Name: 3,4-Pyridinedimethanol, 5-hydroxy-6-methyl-, hydrochloride

Common Name: Adermine hydrochloride; Piridossina hydrochloride; Piridoxina hydrochloride; Pyridoxine hydrochloride; Pyridoxinium chloride; Pyridoxol hydrochloride; Vitamin B_6 hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 58-56-0; 65-23-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Pyridoxine hydrochloride	Roche	-	-
Pyridoxine hydrochloride	Takeda Chemical Industry	Japan	-

Raw Materials

Formamide
Maleic anhydride
Sodium bicarbonate
Ethyl α-alaninate hydrochloride
Hydrogen chloride
Lithium aluminum hydride

Manufacturing Process

To 35 g of ethyl α-alaninate hydrochloride is added 10 g of formamide and the resulting mixture is heated slowly to 105°C over a period of 30 to 45 min. After heating at 105°C for 10 min, about 75 ml of toluene is added. After standing for about 1 h, the mixture is then refluxed for about 6 h. After cooling the ammonium chloride formed is removed and the resulting solution is evaporated to remove the solvent. The ethyl N-formyl-α-alaninate is obtained by distillation at 100°C.

To a moxture of 25 ml of alcohol free chloroform and 11.36 g of P_2O_5 is added over 20 min a solution of 5.81 g of ethyl N-formyl-α-alaninate in 15 ml of alcohol free chloroform at about 30°C the resulting reaction mixture is refluxed for 1 h, cooled and the solvent decanted. The hard mass remaining is broken up and a solution of 27 g of potassium hydroxide in 27 ml of water and 34 ml of methanol is gradually added keeping the temperature at 10-20°C. The resulting solution is refluxed for 1 h, cooled and extracted with 10 x 15 ml of methylene chloride. The 4-methyl-5-ethoxy oxazole is recovered, after removing the solvent, by distilling at 75-80°C at 10 mm pressure.

Upon mixing 1.27 g of 4-methyl-5-ethoxy oxazole (0.01 mole), 0.98 g of maleic anhydride (0.01 mole) and 2.5 ml of dry benzene, a yellow color appears and heat is evolved, requiring cooling. After 3-4 min the evolution of heat ceases and the color fades. The mixture is then refluxed for about 18 h, after which the solvent is decanted and the residue treated with a small

quantity of water. To the residue is added 40 ml of ethanol and the solution is then saturated with gaseous HCl. The acidic solution is refluxed for 3.5 h. After cooling the solvent is evaporated and crystalline residue containing diethyl 2-methyl-3-hydroxy-pyridine-4,5-dicarboxylate hydrochloride is converted to the free base by reaction with aqueous sodium bicarbonate. The resulting solution is extracted with ether and the ether extacts dried.

The ether solution containing diethyl 2-methyl-3-hydroxy-pyridine-4,5-dicarboxylate is treated with 0.5 g of lithium aluminum hydride. The resulting mixture is stirred for 2 h and allowed to stand overnight. The ether layer is removed and the aqueous layer is saturated with carbon dioxide. The resulting residue is extracted three times with hot ethanol and gaseous HCl is passed into the ethanol extracts. After allowing the acidified ethanol solution to stand for 2-3 h, crystals of pyridoxine hydrochloride are deposited and recovered by filtration. Melting point 203.5°-205°C, dec.

References

Chase G.O.; US Patent No. 3,222,374; Dec. 7, 1965; Assigned: Hoffmann-La Roche Inc., Nutley, N. J.
Coffen D.L.; US Patent No. 4,026,901; May 31, 1977; Assigned: Hoffmann-La Roche Inc., Nutley, N. J.

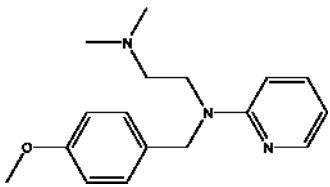
PYRILAMINE

Therapeutic Function: Antihistaminic

Chemical Name: N-[(4-Methoxyphenyl)methyl]-N',N'-dimethyl-N-2-pyridinyl-1,2-ethanediamine (often used as the maleate)

Common Name: Mepyramine; Pyranisamine

Structural Formula:



Chemical Abstracts Registry No.: 91-84-9; 6036-95-9 (Hydrochloride salt); 59-33-6 (Maleate salt)

Trade Name	Manufacturer	Country	Year Introduced
Neo-Antergan	MSD	US	1948
Thylogen	Rorer	US	1949
Statomin	Bowman	US	1950

Trade Name	Manufacturer	Country	Year Introduced
Pyra-Maleate	Mallinckrodt Inc.	US	1950
Copsmine	Durst	US	1950
Stamine	Tutag	US	1951
Albatussin	Bart	US	-
Allergan	Wiedenmann	Switz.	-
Amfeta	Bama-Geve	Spain	-
Anthisan	May and Baker	UK	-
Citra Forte	Boyce	US	-
Codimal	Central	US	-
Copsamine	Durst	US	-
Fiogesic	Sandoz	US	-
Histalet	Reid-Rowell	US	-
Histavet-P	Burns-Biotec	US	-
Kontristin	Eczacibasi	Turkey	-
Kriptin	Whitehall	US	-
Kronohist	Ferndale	US	-
Midol PMS	Glenbrook	US	-
Poly-Histine	Bock	US	-
Primatene	Whitehall	US	-
PV-Tussin	Reid-Rowell	US	-
Pyra	Mallinckrodt Inc.	US	-
Pyramal	Columbus	US	-
Statomin	Bowman	US	-
Triaminic	Dorsey	US	-

Raw Materials

4-Methoxybenzaldehyde
2-Aminopyridine
1-Dimethylamino-2-chloroethane
Sodium amide

Manufacturing Process

43 g of α-p-methoxybenzylaminopyridine (from 4-methoxybenzaldehyde reaction with 2-aminopyridine) are heated in 60 cc of toluene to 95°C to 100°C. 18 g of sodamide (85%) and 110 cc of a 40% toluene solution of 1-dimethylamino-2-chloroethane are added in small amounts alternately with shaking; the addition takes 1 hour. Toluene is distilled off, first at normal pressure, then under reduced pressure, until there remains a pasty mass. The mass is taken up with dilute hydrochloric acid and ether, neutralized to pH 7, and p-methoxybenzylaminopyridine separates. After making alkaline using excess of potash, it is extracted with benzene, dried and distilled. The product thereby obtained, N',N'-dimethylaminoethyl-N-p-methoxybenzyl-α-aminopyridine boils at 185°C to 190°C/2 mm. The monohydrochloride melts at 135°C (block Maquenne).

References

Merck Index 7883
Kleeman and Engel p. 561

PDR pp. 654, 674, 692, 784, 850, 875, 925, 1447, 1583, 1900
OCDS Vol. 1 p.51 (1977)
I.N. p. 597
REM p. 1129
Horclois, R.J.; US Patent 2,502,151; March 28, 1950; assigned to Societe des Usines Chimiques Rhone-Poulenc

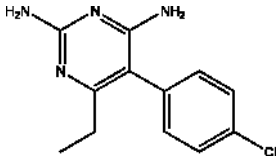
PYRIMETHAMINE

Therapeutic Function: Antimalarial

Chemical Name: 5-(4-Chlorophenyl)-6-ethyl-2,4-pyrimidinediamine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 58-14-0

Trade Name	Manufacturer	Country	Year Introduced
Daraprim	Burroughs-Wellcome	US	1953
Daraprim	Burroughs-Wellcome	W. Germany	1969
Erbaprelina	Erba	Italy	-
Fansidar	Roche	France	-
Malocide	Specia	France	-
Pirimecidan	Cidan	Spain	-
Pyrimethamin-Heyl	Heyl	W. Germany	-
Tindurin	EGYT	Hungary	-

Raw Materials

p-Chlorophenylacetonitrile
Guanidine
Diazomethane
Sodium ethoxide
Ethyl propionate

Manufacturing Process

p-Chlorophenylacetonitrile (36.5 grams) and ethyl propionate (25.5 grams) were added to a solution of sodium ethoxide (from 5.75 grams sodium) in absolute ethanol (150ml). The solution was heated on a steam bath for 6 hours. After cooling, the whole was poured into water and the oil extracted

well with ether, the ether solution was discarded and the aqueous solution neutralized with 1 N sulfuric acid. A heavy oil separated which was taken into ether, washed with water, bicarbonate solution and again with water. After drying, the ether was removed to give a thick oil which solidified on standing (34.6 grams). After recrystallization from an ether-petroleum ether mixture it formed needles, MP 108°-112°C.

The above keto-nitrile (15 grams) was methylated with a solution of diazomethane in ether. (The diazomethane solution was prepared using 20 grams of N-nitrosomethylurea.) The ether and excess diazomethane were evaporated on the steam bath and the oil dissolved in ethanol (50 ml). To this was added a solution of guanidine in ethanol (100 ml) (prepared from 8.1 grams of the hydrochloride). The solution was refluxed for 5 hours, the alcohol removed and the residue treated with 5 N sodium hydroxide. The insoluble material was then filtered. After purification by precipitation from dilute acetic acid with sodium hydroxide and by recrystallization from ethanol the product formed clear colorless needles (8.0 grams), MP 218°-220°C as described in US Patent 2,602,794.

References

Merck Index 7884
Kleeman & Engel p. 791
PDR pp. 741, 1484
OCDS Vol. 1 p. 262 (1977)
DOT 16 (5) 174 (1980)
I.N. p.827
REM p. 1219
Hitchings, G.H., Russell, P.B. and Falco, E.A.; US Patent 2,576,939; December 4, 1951; assigned to Burroughs Wellcome & Co. (USA.) Inc.
Hitchings, G.H. and Falco, E.A.; US Patent 2,579,259; December 18, 1951; assigned to Burroughs Wellcome & Co. (USA.) Inc.
Hitchings, G.H., Russell, P.B. and Falco, E.A.; US Patent 2,602,794; July 8, 1952; assigned to Burroughs Wellcome & Co. (USA.) Inc.
Jacob, R.M.: US Patent 2,680,740; June 8,1954; assigned to Societe des Usines Chimiques Rhone-Poulenc (France)

PYRISUCCIDEANOL DIMALEATE

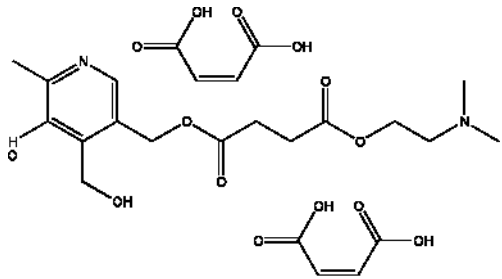
Therapeutic Function: Cerebrotonic

Chemical Name: 2-(Dimethylamino)ethyl(5-hydroxy-4-(hydroxymethyl)-6-methyl-3-pyridyl)methyl succinate salt with maleic acid (1:2)

Common Name: Pirisuccideanoli maleas; Pirisudanol maleate; Pyrisuccideanol dimaleate

Chemical Abstracts Registry No.: 53659-00-0; 33605-94-6 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Nadex Forte	Novartis Pharma	-	-

Raw Materials

Succinic anhydride
Thionyl chloride
Formic acid
Pyridoxine hydrochloride
Dimethylamino ethanol
Pyridine
Maleic acid

Manufacturing Process

Process of preparation of 2-(dimethylamino)ethyl(5-hydroxy-4-(hydroxymethyl)-6-methyl-3-pyridyl)methyl succinate includes four steps.

a. Into a 4 liter flask provided with a stirrer there were poured 2.1 liters of pure and anhydrous acetone, and 100 g of dried pyridoxine hydrochloride were added under stirring. The mixture was cooled whilst stirring at 0°C and then gaseous HCl was bubbled through the solution for 6 hours. After another hour the temperature was allowed to rise to room temperature and the stirring was maintained for a further hour. The mixture was then cooled to -15°C and the 3,4-isopropylidene pyridoxine was obtained in the form of its hydrochloride (100 g). The free base was obtained by treatment above hydrochloride with a solution of Na_2CO_3. 82 g of base was obtained melting at 111°C.

b. 100 g of succinic anhydride, 100 g of dimethylaminoethanol and 100 ml of anhydrous acetone were placed into a 2 liter flask and were refluxed for 3 hours. The solution was then concentrated to one third of its original volume by evaporation and cooled. A precipitate appeared, which was separated and recrystallized from acetone. 140 g of product was obtained, with a melting point of 78°C.

The chloride was prepared from this compound by treatment of 420 g of the compound with freshly distilled $SOCl_2$ 1.85 liter. After elimination of non-reacted $SOCl_2$, the product obtained was treated by benzene and dried, to yield 620 g of the hydrochloride of the chloride acid. 120 g of the compound

of step (a) above (0.57 mole) were dissolved in 0.5 liter of pyridine. After cooling there were slowly added at about 5°C, during 90 minutes, 170 g (0.69 mole) of the hydrochloride previously obtained, dissolved in 0.2 liter of chloroform. The solution was stirred for 10 hours, then evaporated to dryness (350 g). The residue was dissolved in 0.3 liter of water and was neutralized by an aqueous solution of NH_3 saturated by K_2CO_3. There was obtained an oily substance which was extracted with chloroform. The extract was concentrated to dryness (170 g).

c. In this step the blocking group linking the OH in position 3 to the CH_2OH in position 4 of the pyridoxine ring was broken by hydrolysis with formic acid. 52 g of the product of step (b) above were treated with 1.650 liter of 1% solution of formic acid and 0.250 liter of ethyl alcohol. The mixture was boiled for 30 minutes, evaporated again treated with ethyl alcohol and evaporated. There were obtained 37 g of an oily substance.

d. Maleate was obtained by reacting 37 g (0.115 mole) of above product of step (c) dissolved in 120 ml of acetone with 27 g (0.230 mole) of maleic acid dissolved in 130 ml of acetone. Yield 51 g. MP: 134°C.

References

Esanu A.; US Patent No. 3,717,636; Feb. 20, 1973; Assigned to Societe d'Etudes Produits Chimiques Issy-Les-Moulineaux, France

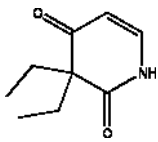
PYRITHYLDIONE

Therapeutic Function: Hypnotic, Sedative

Chemical Name: 3,3-Diethyl-2,4-(1H,3H)pyridinedione

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 77-04-3

Trade Name	Manufacturer	Country	Year Introduced
Presidon	Roche	US	1948
Persedon	Roche	W. Germany	-

Raw Materials

Methyl formate
Diketene
Ethyl bromide
Sodium methylate
Ammonia

Manufacturing Process

108 g of sodium methylate were suspended in 500 ml of toluene. 120 g of methyl formate were dropped into the sodium methylate suspension thus formed at a rate so that temperature did not exceed 30°C. Thereafter a solution of 157 g of α,α-diethylacetoacetamide in 500 ml of toluene were added so that the temperature did not exceed 50°C. The mixture was stirred for one hour at 50°C and then overnight at room temperature. The reaction mixture was poured into 700 ml of ice water, permitted to stratify, the aqueous layer was separated, covered with a layer of 200 ml of toluene and then treated while stirring with 200 g of 50% sulfuric acid. Finally the reaction mixture, which was acid to congo red, was warmed at 50°C and the toluene containing layer was separated. The aqueous layer was extracted with four 200 ml portions of toluene at 50°C and then discarded. The toluene extracts were combined and then concentrated in vacuo at 60°C. There were obtained 135 g of crystalline residue which was recrystallized from 200 ml of toluene. The 3,3-diethyl-2,4-dioxo-1,2,3,4-tetrahydropyridine thus obtained melted at 96°C.

The α,α-diethylacetoacetamide used as starting material was obtained by converting diketene with aqueous ammonia to acetoacetamide and alkylating twice with ethyl bromide in the presence of sodium alcoholate.

References

Merck Index 7893
Kleeman & Engel p. 793
I.N. p. 828
Hinderling, R .,Lutz, A.H. and Schnider, O.; U.S. Patent 3,019,230; January 30, 1962; assigned to Hoffmann-La Roche Inc.

PYRITINOL

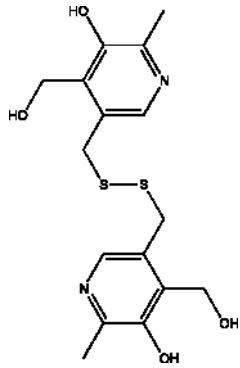
Therapeutic Function: Neurotropic

Chemical Name: 3,3'-(Dithiodimethyiene)bis[5-hydroxy-6-methyl-4-pyridine methanol]

Common Name: Pyrithioxin

Chemical Abstracts Registry No.: 1098-97-1; 10049-83-9 (Dihydrochloride salt)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Encephabol	Merck	W. Germany	1963
Enbol	Chugai	Japan	1971
Biocefalin	Benvegna	Italy	-
Bonol	Ikapharm	Israel	-
Cefalogen	Montefarmaco	Italy	-
Cerebropirina	Chemil	Italy	-
Cerebrotrofina	N.C.S.N.	Italy	-
Cervitalin	Savoma	Italy	-
Chioebon	Kyowa Yakuhin Osaka	Japan	-
Divalvon	Nippon Kayaku, Co.	Japan	-
Encebrovit	Sierochimica	Italy	-
Encefabol	Bracco	Italy	-
Encefort	Intersint	Italy	-
Encerebron	Pulitzer	Italy	-
Enerbol	Polfa	Poland	-
Evolubran	A.B.C.	Italy	-
Fulneurina	Fulton	Italy	-
Gladius	SKF	Italy	-
Leonar	Kalopharma	Italy	-
Life	S.I.T.	Italy	-
Maind	Also	Italy	-
Miriplex	Poli	Italy	-
Musa	Poli	Italy	-
Neurotin	Nakataki	Japan	-
Neuroxin	Yamanouchi	Japan	-
Piritinol	Magis	Italy	-
Piritiomin	Hishiyama	Japan	-
Sawaxin	Sawai	Japan	-
Scintidin	I.C.I.	Italy	-
Tonobrein	C.T.	Italy	-
Tonomentis	Ion	Italy	-

Raw Materials

Methanol
Potassium xanthogenate
Ammonia
3,4-Bisbromoethyl-4-hydroxy-5-methyl-pyridinium bromide

Manufacturing Process

To a solution of 60 g of potassium xanthogenate in 240 cc of water there is added dropwise, while being cooled with ice, a solution of 42 g of 3,4-bis-bromomethyl-4-hydroxy-5-methyl-pyridinium-bromide in 1 liter of water so that the temperature remains between 2°C and 5°C. After stirring for 1 hour at the same temperature, the water is decanted off and the residue is triturated with acetone. Yield: 25 g of 4-hydroxymethyl-5-hydroxy-6-methyl-pyridyl-(3)-methylxanthogenate; melting point: 170°C to 171°C (alcohol, decomposition).

40 g of 4-hydroxymethyl-5-hydroxy-6-methyl-pyridyl-(3)-methylxanthogenate are left standing at room temperature for 5 days in a mixture of 800 cc of alcohol and 400 cc of aqueous NH_3-solution, and subsequently concentrated under vacuum to about 50 cc. The precipitated bis(4-hydroxymethyl-5-hydroxy-6-methyl-3-pyridylmethyl) disulfide is sucked off. Yield: 20 g of the disulfide; melting point: 218°C to 220°C (butanol, decomposition).

References

Merck Index 7894
Kleeman & Engel p. 793
DOT 9 (6) 215 (1973)
I.N. p. 828
Zima, O. and Schorre, G.; US Patent 3,010,966; November 28, 1961; assigned to E. Merck A.G. (Germany)

PYROVALERONE HYDROCHLORIDE

Therapeutic Function: Psychostimulant

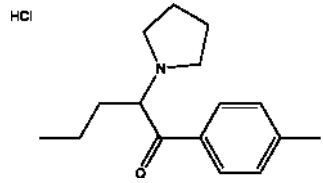
Chemical Name: 1-(4-Methylphenyl)-2-(1-pyrrolidinyl)-1-pentanone hydrochloride

Common Name: -

Chemical Abstracts Registry No.: 1147-62-2; 3563-49-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Thymergix	Joullie	France	1973

Structural Formula:



Raw Materials

p-Methylvalerophenone
Bromine
Pyrrolidine
Hydrogen chloride

Manufacturing Process

23.1 grams of α-bromo-p-methyl-valerophenone, obtained by bromination of p-methyl-valerophenone, are dissolved in 50 ml of benzene and 25 ml of pyrrolidine are added at 0°C. The whole is boiled for 20 minutes, cooled, washed twice with water, dried and acidified with about 50 ml of 2 N hydrochloric acid. After evaporation, it is recrystallized from methanol-acetone-ether. 22.6 grams of α-pyrrolidino-p-methyl-valerophenone hydrochloride, melting point 178°C, equivalent to a yield of 88.5% of the theoretical are obtained according to British Patent 927,475.

References

Merck Index 7914
Kleeman and Engel p. 794
OCDS Vol. 2 p. 124 (1980)
DOT 10 (5) 188 (1974)
I.N. p. 829
Dr. A. Wander SA, Switzerland; British Patent 927,475; May 29, 1963
Dr. Karl Thomae, GmbH, Germany; British Patent 933,507; August 8, 1963

PYRROBUTAMINE

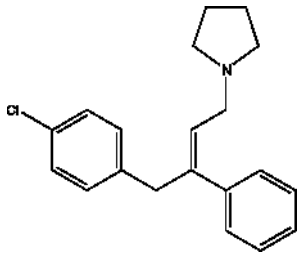
Therapeutic Function: Antihistaminic

Chemical Name: 1-[4-(4-Chlorophenyl)-3-phenyl-2-butenyl]-pyrrolidine

Common Name: -

Chemical Abstracts Registry No.: 91-82-7

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Pyronil	Lilly	US	1952
Co-Pyronil	Lilly	UK	-
Proladyl	Lilly	-	-

Raw Materials

Pyrrolidine
Paraformaldehyde
Magnesium
Acetophenone
p-Chlorobenzyl chloride
Hydrogen chloride

Manufacturing Process

A mixture of 1,800 ml of absolute ethanol, 427 g (6 mols) of pyrrolidine, and a trace of methyl orange is cooled in an ice bath and gaseous hydrogen chloride is bubbled through the mixture until a red color develops, indicating that all of the amine has been converted to the hydrochloride. The addition of hydrogen chloride is stopped, the ice bath is removed and to the solution are added 720 g of acetophenone, 270 g of paraformaldehyde and 10 ml of concentrated hydrochloric acid. The mixture is stirred and refluxed vigorously for one hour. An additional 180 g of paraformaldehyde are then added, and refluxing is continued for about three hours. The hot solution is poured into 6 liters of acetone and the mixture is chilled overnight. A precipitate of ω-(N-pyrrolidino)-propiophenone hydrochloride separates. The precipitate is filtered off, washed with cold acetone, and dried in air.

ω-(N-pyrrolidino)-propiophenone hydrochloride thus prepared melted at about 163°C to 164°C after recrystallization from acetone.

To a suspension of 4 mols of ω-(N-pyrrolidino)-propiophenone hydrochloride in 1,500 ml of water and 100 g of ice in a separatory funnel are added a 50% aqueous solution containing 200 g of sodium hydroxide, and 2 liters of ether. The mixture is shaken vigorously until all of the suspended matter dissolves. The ether is then removed, washed with 1 liter of water and dried over anhydrous magnesium sulfate. The anhydrous ether solution of ω-(N-pyrrolidino)-propiophenone thus prepared is added to a Grignard reagent prepared from 6 mols of p-chlorobenzyl chloride and 6 mols of magnesium turnings in 3,000 ml of anhydrous ether. The ethereal solution of the ketone is added to the Grignard reagent at such a rate that rapid refluxing is

maintained. After all of the ketone has been added, the reaction mixture is stirred for 2 hours and is decomposed by pouring it over a mixture of 500 g of ice and 6 mols of concentrated hydrochloric acid. The hydrochloric acid addition salt of 1-p-chlorophenyl-2-phenyl-4-N-(pyrrolidino)-butanol-2 formed in the reaction separates at the ether-water interface as a white crystalline material. The aqueous phase is removed and discarded, and the mixture of ether and hydrochloride salt is converted to 1-p-chlorophenyl-2-phenyl-4-(N-pyrrolidino)-butanol-2 by treatment with 10% sodium hydroxide solution. The base is removed by extraction with ether, and the ether extracts are dried over magnesium sulfate.

1-p-chlorophenyl-2-phenyl-4-(N-pyrrolidino)-butanol-2 melted at about 109°C to 110°C after recrystallization from petroleum ether.

A solution of 200 g of 1-p-chlorophenyl-2-phenyl-4-(N-pyrrolidino)-butanol-2 in 750 ml of concentrated hydrochloric acid is refluxed for 9 hours thereby causing a dehydration of the butanol compound. and the formation of the hydrochloric acid addition salt of a 1-p-chlorophenyl-2-phenyl-4-(N-pyrrolidino)-butene. The hydrochloride salt formed crystallizes in the oily lower layer of the two phase reaction mixture and is removed therefrom by filtration. The filtrate is again refluxed for 9 hours, cooled to 0°C, and a second crop of the hydrochloric acid addition salt of the dehydration product is obtained and filtered off. The filtrate containing residual amounts of 1-p-chlorophenyl-2-phenyl-4-(N-pyrrolidino)-butanol-2 is again refluxed for 9 hours to yield an additional crop of the salt of the dehydration product. The several fractions of the butene compound are combined and triturated with several small portions of hot acetone and recrystallized from alcohol-ether mixture. The hydrochloric acid addition salt of the dehydration product, 1-p-chlorophenyl-2-phenyl-4-(N-pyrrolidino)-butene hydrochloride, melts at about 227°C to 228°C.

References

Merck Index 7916
Kleeman & Engel p. 794
OCDS Vol. 1 p. 78 (1977)
I.N. p. 829 Mills, J.; US Patent 2,655,509; October 13, 1953; assigned to Eli Lilly & Co.

PYRROLNITRIN

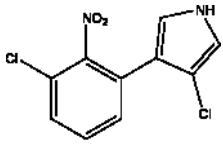
Therapeutic Function: Antifungal

Chemical Name: 1H-Pyrrole, 3-chloro-4-(3-chloro-2-nitrophenyl)-

Common Name: Pyrrolnitrin

Chemical Abstracts Registry No.: 1018-71-9

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Micutrin	Searle Farmaceutici	-	-
Lilly 52230	Eli Lilly and Company	-	-

Raw Materials

Piperidine
Sodium
Sulfuryl chloride
1-(2-Nitro-3-chlorophenyl)-1,3-butanedione
Diethyl aminomalonate

Manufacturing Process

A mixture of 2.0 g of 1-(2-nitro-3-chlorophenyl)-1,3-butanedione, 1.9 g of diethyl aminomalonate, 1.5 ml of absolute ethyl alcohol and two drops of piperidine was refiuxed for 5 hours. After cooling, the reaction mixture was allowed to stand and then crystals were separated. The crystals were collected by filtration and then dried to obtain 2.5 g of colorless crystals. The crystals were recrystallized from a mixed solvent of benzene and ether to obtain diethyl N-[1-methyl-3-(2-nitro-3-chlorophenyl)-3-oxopropylidene]aminomalonate as colorless needles having MP: 134°-136°C.

A solution of 0.8 g of diethyl N-[1-methyl-3-(2-nitro-3-chlorophenyl)-3-oxopropylidene]aminomalonate in 4 ml of absolute tetrahydrofuran was added dropwise with stirring to a solution prepared with 8 ml of absolute ethanol and 100 mg of metallic sodium. After the reaction mixture was refluxed for 4.5 hours, the solvents were distilled off under reduced pressure. The residue was added with an ice-water and the solution was extracted with ether. The extract was washed with water, dried over anhydrous magnesium sulfate, after which ether was distilled off. The residue was recrystallized from benzene to obtain ethyl 3-(2-nitro-3-chlorophenyl)-5-methylpyrrole-2-carboxylate as colorless needles having MP: 220°-223°C.

1.2 g of ethyl 3-(2-nitro-3-chlorophenyl)-5-methyl-pyrrole-2-carboxylate is suspended in 12 ml of acetic acid. A solution of 2.1 g of sulfuryl chloride in 3 ml of acetic acid is added dropwise to the suspension with stirring at about 200°C. The reaction mixture stood overnight is stirred for one hour at 30°C, one hour at 40°C, and then two hours at 50°C. Thereafter, this mixture is poured into ice water. The mixture is extracted with ethyl acetate. The extract is washed with an aqueous solution of potassium hydrogen carbonate and dried over anhydrous magnesium sulfate, and then the solvent was distilled off. Ethyl 3-(2-nitro-3-chlorophenyl)-4-chloro- 5-trichloromethylpyrrole-2-carboxylate is obtained as pale-brown viscous oil.

A mixture of ethyl 3-(2-nitro-3-chlorophenyl)-4-chloro-5-

trichloromethylpyrrole-2-carboxylate, prepared from 40 mg of ethyl 3-(2-nitro-3-chlorophenyl)-4-chloro- 5-methylpyrrole-2-carboxylate and sulfuryl chloride, and 5 ml of 10% sodium hydroxide aqueous solution was heated for two hours on a water bath. The reaction mixture was acidified with 10% sulfuric acid and the resultant acidic solution was extracted with ethyl acetate and the extract was dried. The solvent was distilled off to yield 370 mg of 3-(2-nitro-3-chlorophenyl)-4-chloro-pyrrole-2,5-dicarboxylic acid having a melting point of 298°C. (decomp.).

Decarboxylation of this dicarboxylic acid gave almost quantitavily the disered 3-chloro-4-(2'-nitro-3'-chlorophenyl)pyrrole; MP: 125°C. (recrystallized from benzene).

References

Umio S. et al.; US Patent No. 3,428,648; Feb. 18, 1969; Assigned to Fujisawa Pharmaceutical Co., Ltd., Osaka, a comoany of Japan
Nakano H., Umio S. et al., Tetrahedron Letters No 7 pp. 737-740, 1966

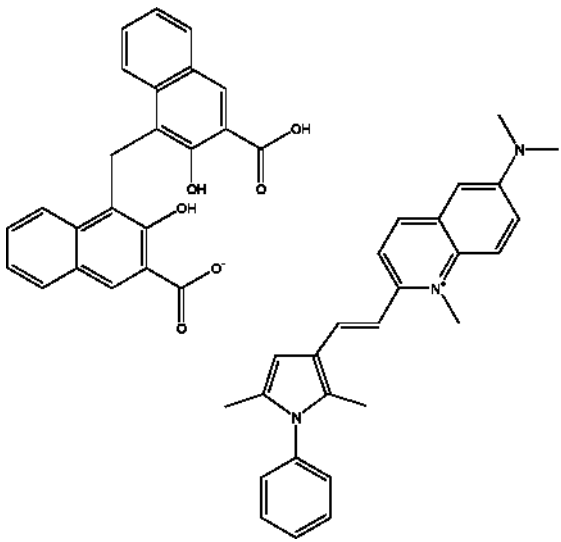
PYRVINIUM PAMOATE

Therapeutic Function: Anthelmintic

Chemical Name: 6-(Dimethylamino)-2-[2-(2,5-dimethyl-1-phenyl-1H-pyrro-3-yl)ethenyl]-1-methylquinolium salt with pamoic acid (2:1)

Common Name: Pyrvinium embonate; Viprynium embonate

Structural Formula:



Chemical Abstracts Registry No.: 3546-41-6

Trade Name	Manufacturer	Country	Year Introduced
Povan	Parke Davis	US	1959
Povanyl	Parke Davis	France	1981
Antioxur	Esteve	Spain	-
Molevac	Parke Davis	W. Germany	-
Neo-Oxypaat	Katwijk	Netherlands	-
Oxialum	Wolner	Spain	-
Pamovin	Merck-Frosst	Canada	-
Pamoxan	Uriach	Spain	-
Pirok	Bilim	Turkey	-
Poquil	Parke Davis Sankyo	Japan	-
Privonium	Rivopharm	Switz.	-
Pyrcon	Jenapharm	E. Germany	-
Pyrvin	Farmos	Finland	-
Tolapin	Taro	Israel	-
Tru	Elea	Argentina	-
Vanquin	Parke Davis	Italy	-
Vermitiber	Tiber	Italy	-

Raw Materials

Pyrvinium chloride
Sodium pamoate

Manufacturing Process

A hot, filtered solution of 2.27 grams of pyrvinium chloride dihydrate in 250 ml of water is added slowly to a solution of 2.25 grams of sodium pamoate monohydrate in 50 ml of water. A red precipitate immediately forms. The mixture is heated at about 90°-100°C for 5 minutes more and then filtered. The reaction product is washed with hot water and dried at about 75°C in a vacuum. This preparation melts at about 210°-215°C with prior softening from about 190°C.

References

Merck Index 7927
Kleeman & Engel p. 796
PDR p. 1384
I.N. p. 830
REM p. 1237
Van Lare, E. and Brooker, L.G.S.; US Patent 2,515,912; July 18, 1950; assigned to Eastman Kodak Company
Elslager, E.F. and Worth, D.F.; US Patent 2,925,417; February 16, 1960; assigned to Parke, Davis & Company