T

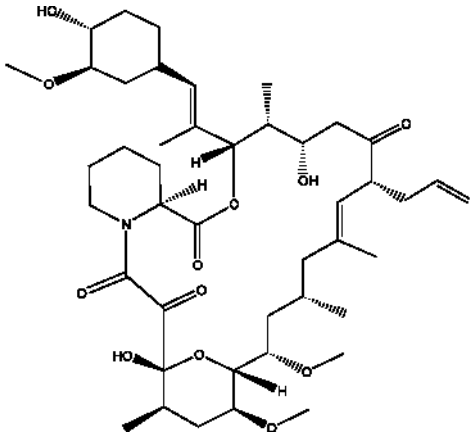
TACROLIMUS

Therapeutic Function: Immunosuppressive

Chemical Name: Tsukubaenolide

Common Name: Efrimus; Tacrolimus; Tsukubaenolide

Structural Formula:



Chemical Abstracts Registry No.: 104987-11-3

Trade Name	Manufacturer	Country	Year Introduced
FK-506	Fujisawa	Japan	-
Fujimycin	Fujisawa	Japan	-
Protopic	Fujisawa	USA	-
Protopic Ointment	Fujisawa	USA	-
Tacrolimus	Fujisawa	Japan	-

Raw Materials

Glycerin Calcium carbonate

Starch	Soluble starch
Glucose	Cottonseed meal
Adekanol	Corn steep liquor
Peanut powder	Gluten meal
Yeast	Streptomyces tsukubaensis No. 9993, FERM BP-927

Manufacturing Process

The novel 17-allyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatrcyclo[22.3.1.04,9]octacos-18-ene-2,3,10,16-tetraone (FR-900506), substance can be produced by culturing a FR-900506 substance(s)-producing strain belonging to the genus Streptomyces (e.g. Streptomyces tsukubaensis No. 9993, FERM BP-927) in a nutrient medium.

Fermentation

A culture medium (160 ml) containing glycerin (1%), corn starch (1%), glucose (0.5%), cottonseed meal (1%), dried yeast (0.5%), corn steep liquor (0.5%) and calcium carbonate (0.2%) (adjusted to pH 6.5) was poured into each of ten 500 ml-Erlenmeyer flasks and sterilized at 120°C for 30 min. A loopful of slant culture of Streptomyces tsukubaensis No. 9993 was inoculated to each of the medium and cultured at 30°C for 4 days on a rotary shaker. The resultant culture was inoculated to a medium containing soluble starch (5%), peanut powder (0.5%), dried yeast (0.5%), gluten meal (0.5%), calcium carbonate (0.1%) and Adekanol (deforming agent, Trade Mark, maker Asasi Denka Co.) (0.1%) (150 liters) in a 200-liter jar-fermentor, which had been sterilized at 120°C for 20 min in advance, and cultured at 30C for 4 days under aeration of 150 liters/minutes and agitation of 250 rpm.

Isolation and Purification

The cultured broth thus obtained was filtered with an aid of diatomaseous earth (5 kg). The mycelial cake was extracted with acetone (50 liters), yielding 50 liters of the extract. The acetone extract from mycelium and the filtrate (135 L) were combined and passed through a column of a non-ionic adsorption resin "Diaion HP-20" (Trade Mark, maker Mitsubishi Chemical Industries Ltd.) (10 L). After washing with water (30 L) and 50 % aqueous acetone (30 L), elution was carried out with 75 aqueous acetone. The eluate (30 liters) was evaporated under reduced pressure to give residual water (2 L). This residue was extracted with ethyl acetate (2 L) three times. The ethyl acetate extract was concentrated under reduced pressure to give an oily residue. The oily residue was mixed with twice weight of acidic silica gel (special silica gel grade 12, maker Fuji Devison Co.), and this mixture was slurried in ethyl acetate. After evaporating the solvent, the resultant dry powder was subjected to column chromatography of the same acidic silica gel (800 ml) which was packed with n-hexane. The column was developed with n-hexane (3 L), a mixture of n-hexane and ethyl acetate (4:1 v/v, 3 L) and ethyl acetate (3 L). The fractions containing the object compound were collected and concentrated under reduced pressure to give an oily residue. The oily residue was dissolved in a mixture of n-hexane and ethyl acetate (1:1 v/v, 30 ml) and subjected to column chromatography of silica gel (maker Merck Co., Ltd. 230-400 mesh) (500 ml) packed with the same solvents system. Elution was carried out with a mixture of n-hexane and ethyl acetate

(1:1 v/v, 2 liters and 1:2 v/v, 1.5 L) and ethyl acetate (1.5 L). Fractions containing the first object compound were collected and concentrated under reduced pressure to give crude FR-900506 substance (3 g) in the form of yellowish powder.

This powder of the FR-900506 substance could be transformed into a form of white crystals by recrystallization thereof from acetonitrile. Melting point: 127°-129°C.

References

Okuhara M. et al.; US Patent No. 5,110,811; May 5, 1992; Assigned: Fujisawa Pharmaceutical Company, Ltd., Osaka, Japan

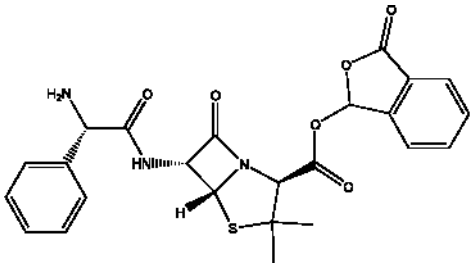
TALAMPICILLIN

Therapeutic Function: Antibacterial

Chemical Name: (2S)-6-[(Aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid 1,3-dihydro-3-oxo-1-isobenzofuranyl ester

Common Name: Phthalidyl-D-α-aminobenzylpenicillanate

Structural Formula:



Chemical Abstracts Registry No.: 47747-56-8; 39878-70-1 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Talpen	Beecham	US	1975
Yamacillin	Yamanouchi	Japan	1977
Talampicillina	Midy	Italy	1980
Talat	Polifarma	Italy	-
Talmen	Prodes	Spain	-

Raw Materials

Ampicillin 3-Bromophthalide

Manufacturing Process

A fine suspension of 25.18 grams (0.05 mol) of potassium salt of enamine protected ampicillin and 10.65 grams (0.05 mol) 3-bromophthalide were reacted in a 1:2 mixture of acetone/ethyl acetate (1,500 ml) for 24 hours. After filtration the organic layer was washed twice with 250 ml portions of 1 N sodium bicarbonate and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. Addition of ether crystallized the phthalide enamine protected α-aminophenylacetamido penicillanate in 85% yield.

The enamine protecting group was removed by dissolving 10 grams in aqueous acetone (250 ml water to 250 ml acetone) and vigorously stirring this solution at pH 2.5 for 1 hour. The acetone was removed in vacuo and the ester, which was salted out of the aqueous phase as a sticky yellow gum, was dissolved in ethyl acetate (200 ml) and washed twice with 200 ml portions of 1 N sodium bicarbonate and brine and dried over anhydrous magnesium sulfate. Careful addition of dry ester (about 50 ml) to the dry ethyl acetate layer yielded the ampicillin phthalide ester as hydrochloric salt as a fine white amorphous solid in 80% yield.

References

Merck Index 8912
Kleeman and Engel p. 854
OCDS Vol. 2 p. 438 (1980)
DOT 12 (7) 283 (1976) & 15 (8) 349 (1979)
I.N. p. 919
REM p. 1201
Ferres, H.; US Patent 3,860,579; January 14, 1975; assigned to Beecham Group Limited, England
Murakami, M., Isaka, I., Kashiwagi, T., Matsui, H., Nakano, K., Takahashi, K., Horiguchi, H. and Koda, A.; US Patent 3,951,954; April 20, 1976; assigned to Yamanouchi Pharmaceutical Co., Ltd., Japan

TALNIFLUMATE

Therapeutic Function: Antiinflammatory, Analgesic

Chemical Name: 2-[[3-(Trifluoromethyl)phenyl]amino]-3-pyridine carboxylic acid 1,3-dihydro-3-oxo-1-isobenzofuranyl ester

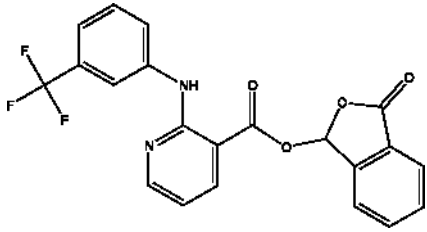
Common Name: -

Chemical Abstracts Registry No.: 66898-62-2

Raw Materials

2-(3'-Trifluoromethylanilino)nicotinic acid
3-Bromophthalide

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Somalgen	Bago	Argentina	1972

Manufacturing Process

49 ml of triethylamine were added to a suspension of 2-(3'-trifluoromethylanilino)nicotinic acid (70.6 g in 250 ml of dimethylformamide). After stirring for 30 minutes 53.3 g of 3-bromophthalide were added. The reaction mixture was maintained at 25°C to 30°C during 4 hours. Ethyl acetate (750 ml) was poured into the reaction mixture. This solution was filtered and extracted with water (4 x 250 ml), discarding the water layer.

The organic layer was dried with anhydrous magnesium sulfate and then filtered. The solution was concentrated under vacuum at 30°C to 35°C until reduced to half of its original volume and then cooled to 5°C to allow the crystallization of the compound. Thus, the cake was filtered, washed with cool ethyl acetate, and dried under vacuum. Yield: 74% (76.7 g) of phthalidyl ester of 2-(3'-trifluoromethylanilino)-pyridin-3-carboxylic acid, melting point: 165°C to 167°C.

References

Merck Index 8921
DFU 4 (6) 448 (1979)
OCDS Vol. 3 p. 146 (1984)
DOT 19 (7) 99 (1983)
I.N. p. 919
Bago, S.; US Patent 4,168,313; September 18, 1979

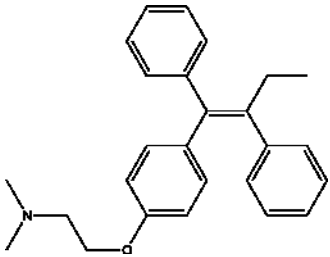
TAMOXIFEN

Therapeutic Function: Antiestrogen, Antineoplastic

Chemical Name: 2-[4-(1,2-Diphenyl-1-butenyl)phenoxy]-N,N-dimethylethanamine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 10540-29-1; 54965-24-1 (Citrate)

Trade Name	Manufacturer	Country	Year Introduced
Nolvadex	I.C.I.	UK	1973
Nolvadex	I.C.I.	W. Germany	1976
Nolvadex	I.C. Pharma	Italy	1976
Nolvadex	I.C.I.	France	1977
Nolvadex	I.C.I.	Switz.	1978
Nolvadex	Stuart	US	1978
Nolvadex	Sumitomo	Japan	1981
Tamofen	Rhone Poulenc	-	-
Valodex	Abic	Israel	-

Raw Materials

Bromobenzene
Magnesium
4-(β-Dimethylaminoethoxy)-α-ethyldesoxybenzoin

Manufacturing Process

To the Grignard reagent prepared from 0.59 part of magnesium, 3.95 parts of bromobenzene and 50 parts of ether there are added 7.5 parts of 4-(β-dimethylaminoethoxy)-α-ethyldesoxybenzoin in 50 parts of ether. After heating under reflux for 3 hours, the mixture is decomposed by the addition of a solution of 60 parts of ammonium chloride in 150 parts of water. The mixture is separated, and the ethereal layer is dried with anhydrous sodium sulfate, and the ether is evaporated. The residue is crystallized from methanol. There is thus obtained 1-(p-β-dimethylaminoethoxyphenyl)-1,2-diphenylbutan-1-ol, melting point 120°C to 121°C.

2.15 parts of 1-(p-β-dimethylaminoethoxyphenyl)-1,2-diphenylbutan-1-ol, 25 parts of ethanol and 0.8 part of 10 N hydrochloric acid are heated together under reflux for 3 hours. The solution is evaporated to dryness under reduced pressure and the residue is extracted with methylene chloride. The methylene chloride extract is decolorized with charcoal and then evaporated to dryness. The residue is dissolved in 100 parts of water, the solution is basified by the addition of sodium hydroxide solution, and the precipitated solid is extracted three times, each time with 50 parts of ether. The combined extracts are dried

with anhydrous sodium sulfate and then evaporated. The residue is crystallized from aqueous methanol, and there is thus obtained 1-(p-β-dimethylaminoethoxyphenyl)-1,2-diphenylbut-1-ene, melting point 95°C to 96°C.

References

Merck Index 8923
Kleeman and Engel p. 854
PDR p. 1783
OCDS Vol. 2 p. 127 (1980) & 3, 70 (1984)
DOT 10 (2) 71 (1974)
I.N. p. 920
REM p. 990
Harper, M.J.K., Richardson, D.N. and Walpole, A.L.; British Patent 1,013,907; December 22, 1965; assigned to Imperial Chemical Industries, Ltd. (UK)

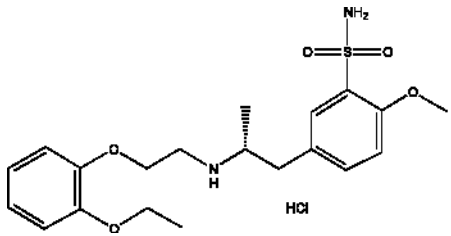
TAMSULOSIN HYDROCHLORIDE

Therapeutic Function: Antihypertensive

Chemical Name: 5-[2-[[2-(2-Ethoxyphenoxy)ethyl]amino]propyl]-2-methoxy-benzenesulfonamide monohydrochloride, (R)-

Common Name: Amsulosin hydrochloride; Tamsulosin hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 106463-17-6; 106133-20-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Contiflo OD	Ranbaxy Laboratories Limited	India	-
Flomax	Medvantx	-	-
Flomax	Abbott Laboratories	-	-
Flomax	Physicians TC.	-	-
Flomax	Allscripts	-	-
Flomax	Yamanouchi	-	-
Flomax	Boehringer-Ingelheim	-	-
Flomax	GlaxoWellcome	-	-

Trade Name	Manufacturer	Country	Year Introduced
Omnic	Yamanouchi	Netherlands	-
Tamsulosin Hydrochloride	Yamanouchi	Netherlands	-

Raw Materials

5-{2-[2-(2-Ethoxyphenoxy)ethylamino]-1-hydroxy-2-methylethyl}-2-methoxybenzenesulfonamide hydrochloride
Thionyl chloride
Palladium on carbon
Hydrogen

Manufacturing Process

In 1,000 ml of acetonitrile was suspended 17 g of 5-{2-[2-(2-ethoxyphenoxy)ethylamino]-1-hydroxy-2-methylethyl}-2-methoxybenzenesulfonamide hydrochloride and while stirring the suspension, 9 g of thionyl chloride was added dropwise to the suspension at room temperature, whereby the product first dissolved and then began to crystallize gradually. After stirring the mixture for two days, the crystals formed were recovered by filtration, washed with chloroform and dried to provide 15 g of 5-{1-chloro-2-[2-(2-ethoxyphenoxy)ethylamino]-2-methylethyl}-2-methoxybenzenesulfonamide hydrochloride. Melting point: 197°-200°C.

In methanol was dissolved the 5-{1-chloro-2-[2-(2-ethoxyphenoxy)ethylamino]ethyl}-2-methoxybenzenesulfonamide hydrochloride and after adding thereto 10% palladium carbon, dechlorination was performed under hydrogen stream at normal temperature and pressure. The palladium carbon was filtered away and the filtrate was concentrated under reduced pressure to provide the 2-methoxy-5-{2-[2-(2-ethoxyphenoxy)ethylamino]ethyl}benzenesulfonamide hydrochloride, which was recrystallized from 120 ml of a mixture of methanol and ethanol (1:4 by volume ratio) to provide the colorless crystals thereof. The melting point of the 5-{2-[2-(2-ethoxyphenoxy)ethylamino]-2-methylethyl}-2-methoxybenzenesulfonamide hydrochloride: 254°-256°C.

References

Niigata K., Fujikura T.; US Patent No. 5,447,958; Sep. 5, 1995; Assigned: Yamanouchi Pharmaceutical Co., Ltd., Tokyo, Japan

TANPHETAMIN

Therapeutic Function: Antiobesity

Chemical Name: d-Amphetamine tannate

Common Name: Dexamphetamine tannate

Structural Formula: A complex of amphetamine, $C_6H_5CH_2CH(CH_3)NH_2$and tannic acid

Chemical Abstracts Registry No.: 1407-85-8

Trade Name	Manufacturer	Country	Year Introduced
Synatan	Neisler	US	1955
Obotan	Mallinckrodt Inc.	US	-
Proptan	Irwin, Neisler	US	-

Raw Materials

d-Amphetamine
Tannic acid

Manufacturing Process

Approximately 75 grams of d-amphetamine as a free base was dissolved in 300 ml of isopropanol (solution A). Approximately 200 grams of NF tannic acid was dissolved in 700 milliliters of slightly warmed isopropanol (solution B). Solution B was poured, with rapid stirring, into solution A to provide an almost immediate precipitation of the insoluble tannate complex. The solution was cooled to room temperature and the product filtered off and dried. During the filtration, most of the isopropanol was removed by washing with acetone, and the precipitate dried at 140°F to yield a light tan product. The amount of precipitate was approximately 200 grams of tannate salt but more could be obtained by concentration of the mother liquors.

References

Merck Index 8930
I.N. p. 301
Cavallito, C.J.; US Patent 2,950,309; August 23, 1960; assigned to Irwin, Neisler and Company

TAZAROTENE

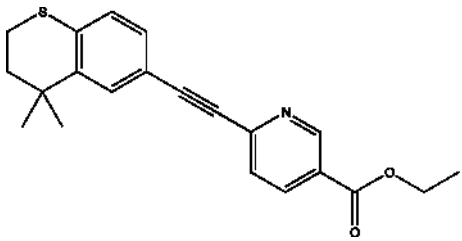
Therapeutic Function: Keratolytic

Chemical Name: 3-Pyridinecarboxylic acid, 6-((3,4-dihydro-4,4-dimethyl-2H-1-benzothiopyran-6-yl)ethynyl)-, ethyl ester

Common Name: Tazarotene

Chemical Abstracts Registry No.: 118292-40-3

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Avage	Allergan	-	-
Tazorac	Allergan	-	-
Zorac	Allergan	-	-

Raw Materials

Thiophenol	1-Bromo-3-methyl-2-butene
Phosphoric acid	Phosphorus pentoxide
Acetyl chloride	Stannic chloride
Hydrogen chloride	Butyl lithium
Chlorophosphate	Diisopropylamine
Hydrogen chloride	6-Chloronicotinic acid
Dicyclohexylcarbodiimide	Dimethylaminopyridine
Copper iodide	Sodium hydroxide
Diethyl chlorophosphate	Bis(triphenylphosphine)palladium(II) chloride

Manufacturing Process

A mixture of 14.91 g (135.324 mmol) of thiophenol and 5.5 g (137.5 mmol) of NaOH in 100 ml acetone was heated at reflux for 2.5 h and then treated dropwise with a solution of 20 g (134.19 mmol) of 1-bromo-3-methyl-2-butene in 20 ml acetone. This solution was refluxed for 40 h and then stirred at room temperature for 24 h. Solvent was then removed in vacuo, the residue taken up in water, and extracted with 3 times 50 ml ether. Ether extracts were combined and washed with 3 times 30 ml of 5% NaOH solution, then water, saturated NaCl solution and dried. Solvent was then removed in vacuo and the residue further purified by kugelrohr distillation (80°C, 0.75 mm) to give the phenyl-3-methylbut-2-enylsulfide as a pale yellow oil.

To a solution of 15.48 g (86.824 mmol) of phenyl-3-methylbut-2-enylsulfide in 160 ml benzene were added successively 12.6 g (88.767 mmol) of phosphorus pentoxide and 11 ml of 85% phosphoric acid. This solution was refluxed with vigorous stirring under argon for 20 h, then cooled to room temperature. The supernatant organic layer was decanted and the syrupy residue extracted with 3 times 50 ml ether. Organic fractions were combined and washed with water, saturated $NaHCO_3$ and saturated NaCl solution and then dried. Solvent was removed in vacuo and the residue purified by kugelrohr distillation (80°C, 0.5 mm) to give the 4,4-dimethylthiochroman as a pale yellow oil.

A solution of 14.3 g (80.21 mmol) of 4,4-dimethyl thiochroman and 6.76 g (86.12 mmol) of acetyl chloride in 65 ml benzene was cooled in an ice bath and treated dropwise with 26.712 g (102.54 mmol) of stannic chloride. The mixture was stirred at room temperature for 12 h, then treated with 65 ml water and 33 ml conc. hydrogen chloride and heated at reflux for 0.5 h. After being cooled to room temperature, the organic layer was separated and the aqueous layer extracted with 5 times 50 ml benzene. The recovered organic fractions were combined and washed with 5% sodium carbonate solution, water, saturated NaCl solution and then dried. The solvent was removed in vacuo and the residue purified by flash chromatography (silica; 5% ethyl acetate in hexanes) followed by kugelrohr distillation (150°C, 0.7 mm) to give the 4,4-dimethyl-6-acetylthiochroman as a pale yellow oil.

To a solution of 1.441 g (14.2405 mmol) of diisopropylamine in 30 ml dry tetrahydrofuran under argon at -78°C was added dropwise 9 ml of 1.6 M (14.4 mmol) n-butyl lithium in hexane. After stirring this solution at -78°C for 1 h, it was treated dropwise with a solution of 2.95 g (13.389 mmol) of 4,4-dimethyl-6-acetylthiochroman in 5 ml of dry tetrahydrofuran. After another hour of stirring at -78°C, the solution was treated with 2.507 g (14.53 mmol) of diethyl chlorophosphate and brought to room temperature, where it was stirred for 3.75 h. This solution was then transferred using a double ended needle to a solution of lithium diisopropylamide (prepared as above using 2.882 g (28.481 mmol) of diisopropylamine and 18 ml of 1.6 M (28.8 mmol) n-butyl lithium in hexane) in 60 ml dry tetrahydrofuran at -78°C. The cooling bath was removed and the solution stirred at room temperature for 15 h, then quenched with water and acidified to pH 1 with 3 N hydrogen chloride. The mixture was stirred at room temperature for 12 h, then treated with 65 ml water and 33 ml conc. hydrogen chloride and heated at reflux for 0.5 h. After being cooled to room temperature, the organic layer was separated and the aqueous layer extracted with 5 times 50 ml benzene. The recovered organic fractions were combined and washed with 5% sodium carbonate solution, water, saturated NaCl solution and then dried. The solvent was removed in vacuo and the residue purified by flash chromatography (silica; 5% ethyl acetate in hexanes) followed by kugelrohr distillation (150°C, 0.7 mm) to give the 4,4-dimethyl-6-ethynylthiochroman as a pale yellow oil.

A mixture of 15.75 g (0.1 mol) 6-chloronicotinic acid, 6.9 g (0.15 mol) ethanol, 22.7 g (0.11 mol) dicyclohexylcarbodiimide and 3.7 g dimethylaminopyridine in 200 ml methylene chloride was heated at reflux for 2 h. The mixture was allowed to cool, solvent removed in vacuo and residue subjected to flash chromatography to give the ethyl 6-chloronicotinate as a low-melting white solid.

2 Methods of preparation of the ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate.

1. Reaction vessels used in this procedure were flame dried under vacuum and all operations carried out in an oxygen-free, argon or nitrogen atmosphere. To a solution of 465.7 mg (2.3019 mmol) of 4,4-dimethyl-6-ethynyl-thiochroman in 4 ml of dry tetrahydrofuran at 0°C was added dropwise 1.5 ml of 1.6 M (2.4 mmol) n-butyl lithium in hexane. This was stirred at 0°C for 10 min and at room temperature for 10 min, cooled again to 0°C and then treated with a solution of 330 mg (2.4215 mmol) of fused $ZnCl_2$ in 4 ml dry tetrahydrofuran using a double ended needle. Thereafter the

solution was stirred at 0°C for 30 min, then at room temperature for 10 min. A solution of 426.3 mg (2.2967 mmol) of ethyl 6-chloronicotinoate in 4 ml dry tetrahydrofuran was transferred by double ended needle into a suspension of 430 mg (0.37 mmol) of tetrakistriphenylphosphine palladium in 4 ml dry tetrahydrofuran and stirred at room temperature for 10 min, then treated by double ended needle with the solution of the alkynylzinc prepared above. This mixture was stirred at room temperature for 18 h, then quenched with 100 ml water. Product was recovered by extraction with 3 times 75 ml ether. Ether fractions were combined and washed with saturated NaCl solutions and dried. Solvent was removed in vacuo and the residue purified by flash chromatography (silica; 5% ethyl acetate in hexane) followed by HPLC (Whatman Partisil M-9 10/50; 4% ethyl acetate in hexane) to give the ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate.

2. A solution of 15.4 g (76.2 mmol) of 4,4-dimethyl-6-ethynylthiochroman and 14.0 g (75.5 mmol) of ethyl-6-chloronicotinate in 35 ml of freshly distilled triethylamine was degassed and then treated under nitrogen with a finely powdered mixture of 1 g (5.25 mmol) of high purity cuprous iodide and 2 g (2.85 mmol) of bis(triphenylphosphine) palladium (II) chloride. The mixture was heated under nitrogen at 55°C for 20 h and then cooled to room temperature. The triethylamine was then removed under vacuum and the residue was diluted with 200 ml of a 1:4 mixture of ethyl acetate and hexanes. This mixture was filtered through silica and the filtrate concentrated in vacuo. The resultant residue was purified by flash chromatography (silica gel; 15% ethyl acetate in hexanes) and recrystallized from a mixture of ethyl acetate and hexanes to give the ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate as a pale yellow solid.

References

Chandraratna R.A.S.; US Patent No. 5,089,509; Feb. 18, 1992; Assigned: Allergan, Inc., Irvine, Calif.

TAZOBACTAM SODIUM

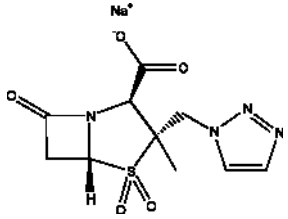
Therapeutic Function: Antibiotic

Chemical Name: 4-Thia-1-azabicyclo(3.2.0)heptane-2-carboxylic acid, 3-methyl-7-oxo-3-(1H-1,2,3-triazol-1-ylmethyl)-, 4,4-dioxide, (2S,3S,5R)-, sodium salt

Common Name: Tazobactam sodium

Chemical Abstracts Registry No.: 89785-84-2; 89786-04-9 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
CL-307579	China Pharm Chemical Co., Ltd.	China	-
Tazobactam Sodium	Shandong Qilu Medicines Imp. and Exp. Co., Ltd.	China	-

Raw Materials

Sodium azide	Potassium permanganate
Acetic acid	Palladium on charcoal
Vinyl acetate	Benzhydryl 2-β-chloromethyl-2-α-methylpenam-3-α-carboxylate

Manufacturing Process

A known β-lactam type antibiotic (for example, benzhydryl 2-β-chloromethyl-2-α-methylpenam-3-α-carboxylate) was used for synthesis of new penicillinic derivatives.

A solution of 5.00 g of sodium azide in 53 ml of water was added to a solution of benzhydryl 2-β-chloromethyl-2-α-methylpenam-3-α-carboxylate (5.13 g) in dimethylformamide (155 ml). The mixture was stirred at room temperature for 4 h. The resulting reaction mixture was poured into cooled water and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried over magnesium sulfate and concentrated to provide 4.87 g of the benzhydryl 2-β-azidomethyl-2-α-methylpenam-3-α-carboxylate as oil in 93% yield.

To a solution of benzhydryl 2-β-azidomethyl-2-α-methylpenam-3-α-carboxylate (7.03 g) in a mixture of acetic acid (240 ml) and water (40 ml) was added potassium permanganate (6.02 g) over a period of more than 1 h. The mixture was stirred at room temperature for 2.5 h. The resulting reaction mixture was diluted with ice water. The precipitate was collected by filtration, and washed with water. The resulting product was dissolved in ethyl acetate and the solution was washed with an aqueous solution of sodium hydrogen carbonate and dried over magnesium sulfate. Concentration gave 5.48 g of the benzhydryl 2-β-azidomethyl-2-α-methylpenam-3-α-carboxylate-1,1-dioxide in 72% yield.

A 200 mg quantity of benzhydryl 2-β-azidomethyl-2-α-methylpenam-3-α-carboxylate-1,1-dioxide was reacted with 10 ml of vinyl acetate in a sealed

reactor at 100° to 110°C for 30 h. The reaction mixture was concentrated at reduced pressure. The residue was crystallized with cooled chloroform. The white crystals of benzhydryl 2-α-methyl-2-β-(1,2,3-triazol-1-yl)methylpenam-3-α-carboxylate-1,1-dioxide have a melting point 206°-208°C, dec.

Hydrogenation was conducted in 10 ml of ethyl acetate and 10 ml of water at room temperature for 30 min by using 45 mg of benzhydryl 2-α-methyl-2-β-(1,2,3-triazol-1-yl)methylpenam-3-α-carboxylate-1,1-dioxide, 15 mg of 10% palladium charcoal and 16 mg of sodium hydrogen carbonate. The aqueous layer was separated from the reaction mixture and washed once with ethyl acetate. The aqueous solution was then purified with an MCl gel, CHP-20P (product of Mitsubishi Kasei Co., Ltd., Japan). After freeze-drying, there was obtained an amorphous product of sodium 2-α-methyl-2-β-(1,2,3-triazol-1-yl)methylpenam-3-α-carboxylate-1,1-dioxide with a melting point 170°C, dec.

References

Micetich R.G. et al.; US Patent No. 4,562,073; Dec. 31, 1985; Assigned: Taiho Pharmaceutical Company Limited, Tokyo, Japan

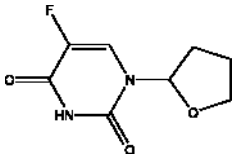
TEGAFUR

Therapeutic Function: Antineoplastic

Chemical Name: 1-(Tetrahydro-2-furanyl)-5-fluorouracil

Common Name: Ftorafur

Structural Formula:



Chemical Abstracts Registry No.: 17902-23-7

Trade Name	Manufacturer	Country	Year Introduced
Futraful	Taiho	Japan	1974
Ftorafur	Gruenenthal	W. Germany	1977
Citofur	Lusofarmaco	Italy	1981
Futraful	Simes	Italy	1981
Coparogin	Nippon Chemiphar	Japan	-
Daiyalose	Daito	Japan	-
Exonal	Toyama	Japan	-
Fental	Kanebo, Ltd.	Japan	-

Trade Name	Manufacturer	Country	Year Introduced
F.H.	Mitsui	Japan	-
Filacul	Torii	Japan	-
Flopholin	Tsuruhara	Japan	-
Franroze	Hishiyama	Japan	-
Ftoral	Abic	Israel	-
F.T.R.	Tenyosha	Japan	-
Fulaid	Takeda	Japan	-
Fulfeel	Kyorin	Japan	-
Furofluor	Green Cross	Japan	-
Furofutran	Taiyo	Japan	-
Futraful Zupo	Taiho	Japan	-
Geen	Tatumi	Japan	-
Helpa	Teikoku	Japan	-
Icalus	Isei	Japan	-
Lamar	Tokyo Tanabe	Japan	-
Lifril	Kissei Pharmaceutical Co., Ltd.	Japan	-
Lunacin	Sawai	Japan	-
Natira	Mohan	Japan	-
Neberk	Fuji	Japan	-
Nitobanil	Ohta	Japan	-
Pharmic	Toyo	Japan	-
Rescrel	Nikken	Japan	-
Richina	Taiyo	Japan	-
Riol	Toa Eiyo	Japan	-
Sinoflurol	Kaken	Japan	-
Sunfural	Toyo Jozo	Japan	-
Tefsiel	Towa	Japan	-
THF-FU	Taiho	Japan	-
Utefos	Almirall	Spain	-
Videcocan	Unifa	Argentina	-
Youfural	Showa	Japan	-

Raw Materials

Ammonia
2-Chlorofuranidin
5-Fluorouracilmercury
2,4-Bis(trimethylsilyl)-5-fluorouracil
2,3-Dihydrofuran

Manufacturing Process

One process from US Patent 4,107,162: 27.4 g of 2,4-bis(trimethylsilyl)-5-fluorouracil and 7.7 g of 2,3-dihydrofuran are dissolved in 70 ml of acetonitrile, and 30 ml of an acetonitrile solution containing 1.3 g of anhydrous stannic chloride are added thereinto with cooling and stirring. 50 ml of acetonitrile containing 1.3 ml of water dissolved therein are then dropwise added over 15 minutes. After return to room temperature, the reaction is further effected with stirring at 40°C for 5 hours. The reaction mixture is neutralized by adding 1 N aqueous ammonia with cooling and

stirring (conversion 83%). After the nondissolved substances are removed by filtration, the filtrate is concentrated and dried under reduced pressure. 100 ml of water and 300 ml of dichloromethane are added to the residue to completely dissolve the residue by stirring. The obtained dichloromethane layer is separated. The water layer is subjected to extraction twice with dichloromethane. The thus obtained extracts are combined with the separated dichloromethane layer and the combined extracts, after drying with anhydrous magnesium sulfate, are concentrated and dried. The obtained residue is dissolved in ethanol, and the nondissolved substances are removed by filtration. The filtrate is subjected to recrystallization to give white crystals, followed by further recrystallization of the mother liquor. There are totally obtained 15.6 g of N_1-(2'-furanidyl)-5-fluorouracil.Yield: 78% of theory, with respect to 2,4-bis(trimethylsilyl)-5-fluorouracil.

An alternative process from US Patent 3,635,946: A vigorously stirred reaction mixture consisting of 32.87 g (0.1 mol) of 5-fluorouracilmercury, 100 ml of dimethylformamide and 50 ml of toluene is dried by azeotropic distillation of toluene. It is then cooled to -40°C in a stream of dry nitrogen, and a solution of 21.3 g (0.2 mol) of 2-chlorofuranidin in 20 ml of dried dimethylformamide is gradually added to the stirred mixture, the temperature being maintained between -40°C and -30°C. After completion of the reaction (which is marked by complete dissolution of the starting 5-fluorouracilmercury) i.e. after about 3 to 4 hours, 60 to 80 ml of the solvent are distilled off in vacuo at a bath temperature not exceeding 35°C. 50 to 70 ml of dry acetone are then added and also vacuum distilled. The residue is easily crystallized. It is collected, washed three times with small quantities of ethanol - 10 ml each - and air-dried. 12.2 g of N_1-(2'-furanidyl)-5-fluorouracil are obtained in the form of white crystalline solids; melting point 160°C to 162°C. Additional treatment of the mother liquor yields 3.0 g more of the product. Yield: 75% of theory, based on the starting 5-fluorouracilmercury.

After recrystallization from ethanol, 14.3 g of N_1-(2'-furanidyl)-5-fluorouracilare obtained, MP 164°C to 165°C.

References

Merck Index 8963
Kleeman and Engel p. 855
OCDS Vol. 3 p. 155 (1984)
I.N. p. 923
Townsend, L.B., Earl, R.A. and Manning, S.J.; US Patent 3,960,864; June 1, 1976; assigned to The University of Utah
Giller, S.A., Zhuk, R.A., Lidak, M.J. and Zidermane, A.A.; US Patent 3,635,946; Jan, 18, 1972
Suzuki, N., Kobayashi, Y., Hiyoshi, Y., Takagi, S., Sone, T., Wakabayashi, M. and Sowa, T.; US Patent 4,107,162; August 15, 1978; assigned to Asahi Kasei Kogyo K.K. (Japan)

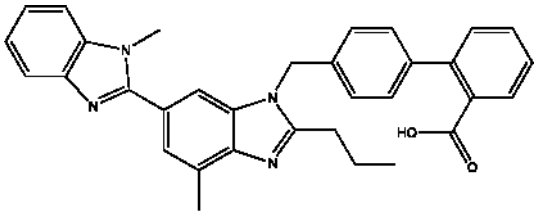
TELMISARTAN

Therapeutic Function: Antihypertensive

Chemical Name: 4'-((4-Methyl-6-(1-methyl-2-benzimidazolyl)-2-propyl-1-benzimidazolyl)methyl)-2-biphenylcarboxylic acid

Common Name: Telmisartan

Structural Formula:



Chemical Abstracts Registry No.: 144701-48-4

Trade Name	Manufacturer	Country	Year Introduced
Micardis	Boehringer Ingelheim Pharma KG	Germany	-
Pritor	Glaxo Wellcome S.P.A.	Italy	-
Telma	Healtheon (A Div. of Glenmark)	India	-
Telma 40	Glenmark	-	-
Telmisartan	Boehringer Ingelheim Pharma KG	Germany	-

Raw Materials

Butyric acid chloride
Sodium hydroxide
Sulfuric acid
Polyphosphoric acid
Acetic acid
Trifluoroacetic acid
Phosphorus oxychloride
2-Methylaminoaniline-dihydrochloride
Potassium t-butoxide
Methyl 3,4-diaminobenzoate dihydrochloride
t-Butyl 4'-bromomethyl-biphenyl-2-carboxylate

Manufacturing Process

A solution of 23.9 g (100 mMol) of methyl 3,4-diaminobenzoate dihydrochloride and 11.7 g (110 mMol) of butyric acid chloride in 100 ml of phosphorus oxychloride is refluxed for 2 h. Then about 80 ml of phosphorus oxychloride are distilled off and the residue is mixed with about 150 ml of water. The oily crude product precipitated is extracted three times with 50 ml of ethyl acetate and after evaporation purified by column chromatography (600 g of silica gel; eluant:methylene chloride/methanol (30:1)). Yield of methyl-2-n-propyl-benzimidazole-5-carboxylate: 15.0 g of oil (69%).

A solution of 15.0 g (73 mmol) of methyl 2-n-propyl-benzimidazole-5-carboxylate and 8 g (200 mMol) of sodium hydroxide in 200 ml of water and 400 ml of ethanol is refluxed for 2 h. Then the alcohol is distilled off, the aqueous solution is acidified with dilute sulphuric acid (pH 4-5) and evaporated using a rotary evaporator. The product crystallising out is suction

filtered, washed with 50 ml of acetone and 50 ml of diethylether and dried. Yield of 2-n-propyl-benzimidazole-5-carboxylic acid-hemisulphate: 9.1 g (61%), melting point: >220°C.

A solution of 6.7 g (25 mMol) of 2-n-propyl-benzimidazole-5-carboxylic acid-hemisulphate and 4.9 g (25 mMol) of 2-methylaminoaniline dihydrochloride in 200 g of polyphosphoric acid is stirred for 5 h at 150°C, then poured onto 600 ml of water and made alkaline with concentrated ammonia whilst cooling with ice. The resulting solution is extracted three times with 200 ml of ethyl acetate, the crude product thus obtained is purified by column chromatography (300 g of silica gel; eluant:methylene chloride/methanol = 15:1). Yield of 2-n-propy1-5-(1-methylbenzimidazol-2-yl)-benzimidazole: 2.8 g of oil (39%).

A solution of 2.0 g (6.9 mMol) of 2-n-propyl-5-(1-methylbenzimidazol-2-yl)-benzimidazole and 0.91 g (7.5 mmol) of potassium tert-butoxide in 50 ml of dimethylsulfoxide is stirred for 90 min at room temperature, then 2.6 g (7.5 mMol) of tert-butyl 4'-bromomethyl-biphenyl-2-carboxylate are added and the mixture is stirred for a further 15 h at room temperature. The mixture is then poured onto 300 ml of water and extracted three times with 50 ml of ethyl acetate. The crude product obtained after evaporation of the organic phase is purified by column chromatography (300 g silica gel; eluant:methylene chloride/methanol = 30:1). In this way, 2.7 g (70%) of an isomer mixture are obtained (by NMR spectroscopy), contains about 1.18 g of tert-butyl-4'-[(2-n-propyl-5-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]biphenyl-2-carboxylate and about 1.52 g of tert-butyl 4'-[(2-n-propyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]biphenyl-2-carboxylate).

2.70 g of the isomer mixture obtained above are dissolved in 100 ml of methylene chloride, mixed with 40 ml of trifluoroacetic acid and stirred for 4 h at room temperature. The mixture is then evaporated to dryness in vacuo, the residue is dissolved in 100 ml of 2 N sodium hydroxide solution, the solution is washed with 50 ml of diethylether and the product mixture is precipitated by acidifying the aqueous phase with acetic acid. By column chromatography (400 g of silica gel, eluant:methylene chloride/methanol = 15:1) of the solid thus obtained 0.9 g (74%) of 4'-[[2-n-propyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate, melting point 217°-218°C.

References

Narr B. et al.; US Patent No. 5,587,393; Dec. 24, 1996; Assigned: Dr. Karl Thomae GmbH, Biberach an der Riss, Germany

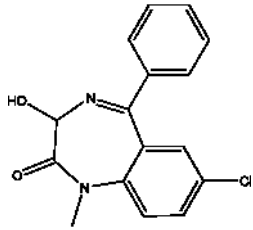
TEMAZEPAM

Therapeutic Function: Tranquilizer

Chemical Name: 7-Chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 846-50-4

Trade Name	Manufacturer	Country	Year Introduced
Levanxol	Carlo Erba	Italy	1970
Euhypnos	Montedison	UK	1977
Normison	Wyeth	UK	1977
Restoril	Sandoz	US	1981
Planum	Carlo Erba	W. Germany	1981
Normison	Wyeth Byla	France	1981
Euhypnos	Farmitalia	France	1981
Normison	Wyeth	Switz.	1983
Planum	Carlo Erba	Switz.	1983
Mabertin	Sidus	Argentina	-
Maeva	Ravizza	Italy	-
Signopam	Polfa	Poland	-

Raw Materials

3-Acetoxy-7-chloro-1-methyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one
Sodium hydroxide

Manufacturing Process

According to British Patent 1,022,645 3.4 g of 3-acetoxy-7-chloro-1-methyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one suspended in 80 ml alcohol was treated with 6 ml of 4 N NaOH. After complete solution had taken place, a solid precipitated; this solid was redissolved by the addition of 80 ml of water. The solution was acidified with acetic acid to give white crystals which were recrystallized from alcohol to yield 7-chloro-3-hydroxy-5-phenyl-1-methyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one, MP 119° to 121°C.

References

Merck Index 8976
Kleeman and Engel p. 856
PDR p. 1591
OCDS Vol. 2 p. 402 (1980)
DOT 6 (6) 224 (1970) & 9 (6) 238 (1973)
I.N. p. 923
REM p. 1064

American Home Products Corporation; British Patent 1,022,642; March 16, 1966
American Home Products Corporation; British Patent 1,022,645; March 16, 1966
Bell, S.C.; British Patent 1,057,492; February 1, 1967; assigned to American Home Products Corporation

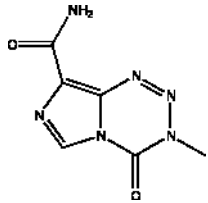
TEMOZOLOMIDE

Therapeutic Function: Antineoplastic

Chemical Name: Imidazo(5,1-d)(1,2,3,5)tetrazine-8-carboxamide, 3,4-dihydro-3-methyl-4-oxo-

Common Name: Methazolastone; Temozolomide

Structural Formula:



Chemical Abstracts Registry No.: 85622-93-1

Trade Name	Manufacturer	Country	Year Introduced
Temodal	Schering	-	-
Temodar	Schering	-	-

Raw Materials

Nitrous acid
1H-Imidazole-4-carboxilic acid amide
Methylisocyanate

Manufacturing Process

Reaction of 1H-imidazole-4-carboxilic acid amide with nitrous acid leads to the diazonium salt (5-diazenyl-1-H-imidazole-4-carboxilic acid amide). Condensation of the diazonium salt with methylisocyanate leads to initial formation of unstable urea which cyclizes under the reaction condition to give 3,4-dihydro-3-methyl-4-oxoimidazo(5,1-d)-1,2,3,5-tetrazine-8-carboxamide (temozolomide).

References

Merck Index, Monograph number: 9289, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Stevens M.F.G. et al.; J. Med. Chem., 1984, 27, 196

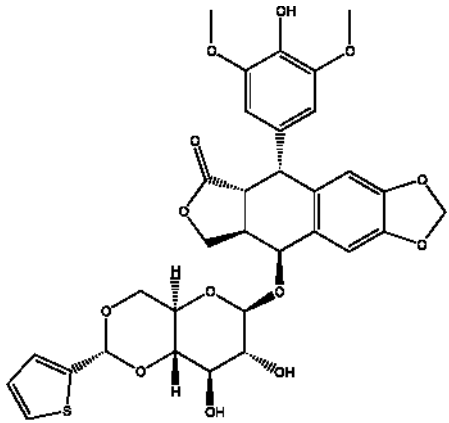
TENIPOSIDE

Therapeutic Function: Antineoplastic

Chemical Name: 4'-Demethylepipodophyllotoxin-β-D-thenylidene glucoside

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 29767-20-2

Trade Name	Manufacturer	Country	Year Introduced
Vehem	Sandoz	France	1976
Vumon	Bristol	W. Germany	1980
Vumon	Bristol	Switz.	1980
Vumon	Bristol	Italy	1982

Raw Materials

Thiophene-2-aldehyde
4'-Demethylepipodophyllotoxin-β-D-glucoside

Manufacturing Process

10 ml of pure thiophene-2-aldehyde and 0.25 g of anhydrous zinc chloride are

added to 0.5 g of dried 4'-demethylepipodophyllotoxin-β-D-glucoside and the mixture is shaken on a machine at 20°C in the absence of moisture, whereupon a clear solution is gradually obtained. The course of condensation is checked by thin layer chromatography. After a reaction period of 3 to 4 hours the solution is diluted with chloroform and shaken out with water. The chloroform phase is washed twice more with a small amount of water and then dried over sodium sulfate and concentrated by evaporation. Excess thiophene-2-aldehyde is removed by dissolving the resulting residue in a small amount of acetone and reprecipitation is effected by adding pentane.

Reprecipitation from acetone/pentane is repeatedly effected until the condensation product sults in flaky form. Further purification is effected in that the crude product is chromatographed on silica gel. The fractions which are uniform in accordance with thin layer chromatography are combined and yield crystals from absolute alcohol. Pure 4'-demethylepipodophyllotoxin-β-D-thenylidene glucoside has a melting point of 242°C to 246°C (last residue up to 255°C).

References

Merck Index 8978
Kleeman and Engel p. 857
DOT 12 (11) 465 (1976) & 16 (5) 170 (1980)
I.N. p. 924
REM p. 1156
Keller-Juslen, C., Kuhn, M., Renz, J. and von Wartburg, A.; US Patent 3,524,844; Aug. 18, 1970; assigned to Sandoz, Ltd. (Switz.)

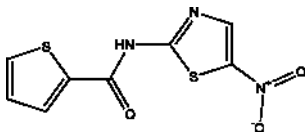
TENONITROZOLE

Therapeutic Function: Antiprotozoal

Chemical Name: 2-Thiophenecarboxamide, N-(5-nitro-2-thiazolyl)-

Common Name: Tenonitrozole; Thenitrazolum

Structural Formula:



Chemical Abstracts Registry No.: 3810-35-3

Trade Name	Manufacturer	Country	Year Introduced
Tenonitrozole	Innotech	-	-
Atrican	Innotech	-	-
Tenonitrozole	ZYF Pharm Chemical	-	-

Raw Materials

2-Amino-5-nitrothiazole
2-Thienoylchloride
Potassium hydroxide

Manufacturing Process

To a solution of 1 kg (7 moles) of 2-amino-5-nitrothiazole in 5 L of pyridine (dried with potassium hydroxide) was added dropwise for 2-3 hours 8.5 moles of 2-thienoylchloride. N-(5-Nitro-2-thiazolyl)-2-thiophenecarboxamide was prepared as a yellow crystals with melting point 255-256°C.

References

Henri M., Rene Chantereau, Brevet special de Medicament 835,121; August 5, 1960; Assigned to l'Imperie Nationale, Paris

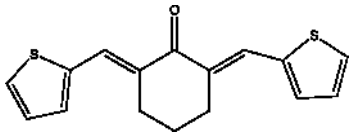
TENYLIDONE

Therapeutic Function: Hepatoprotectant

Chemical Name: 2,6-Bis(2-thenylidene)cyclohexanone

Common Name: Tenylidone; Vanitile

Structural Formula:



Chemical Abstracts Registry No.: 893-01-6

Trade Name	Manufacturer	Country	Year Introduced
Tenylidone	JINGTIAN PORTLINK CO., LTD.	-	-

Raw Materials

Cyclohexanone
2-Formylthiophene

Manufacturing Process

2,6-Bis(2-thenylidene)cyclohexanone was obtained by condensation of 1 mol cyclohexanone with 2 mol 2-formylthiophene.

References

Roland M., Blaise R., Brevet Special de Medicament FR 64M; JUL 22, 1960

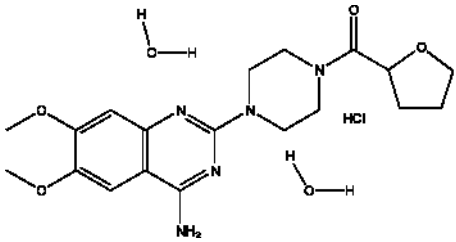
TERAZOSIN HYDROCHLORIDE DIHYDRATE

Therapeutic Function: Antihypertensive

Chemical Name: Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-((tetrahydro-2-furanyl)carbonyl)-, monohydrochloride dihydrate

Common Name: Terazosin hydrochloride dihydrate

Structural Formula:



Chemical Abstracts Registry No.: 70024-40-7

Trade Name	Manufacturer	Country	Year Introduced
Hytrin	Abbott Laboratories	India	-
Terapress	Intas Pharmaceuticals Pvt. Ltd.	India	-
Terazosin Hydrochloride	China Pharm Chemical Co., Ltd.	China	-

Raw Materials

4-Amino-2-chloro-6,7-dimethoxyquinazoline
N-(2-Tetrahydrofuroyl)piperazine

Manufacturing Process

To a solution of n-butanol (316 ml), water (24 ml) and N-(2-tetrahydrofuroyl)piperazine (20 g) were added, while stirring, 4-amino-2-chloro-6,7-dimethoxyquinazoline (22.2 g). The reaction mixture was heated to reflux and the reflux was maintained for about 9 h. Then the reaction mixture was cooled to room temperature and stirred at this temperature for about 10-12 h. The crystals were collected by filtration, washed with n-BuOH and dried in vacuo at 40-50°C to yield 40.1 g (94%) of the 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(tetrahydrofuroyl)piperazine hydrochloride dihydrate

(Terazosin HCl dihydrate).

References

Schwartz E. et al; US Patent No. 6,248,888 B1; June 19, 2001; Assigned: Teva Pharmaceutical Industries Ltd., Petah Tigva (IL)

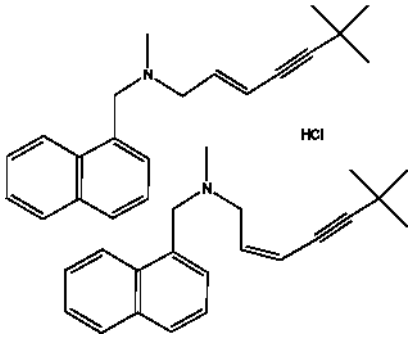
TERBINAFINE HYDROCHLORIDE

Therapeutic Function: Antifungal

Chemical Name: 1-Naphthalenemethanamine, N-(6,6-dimethyl-2-hepten-4-ynyl)-N-methyl-, (E/Z)-, (2:5), hydrochloride

Common Name: Terbinafine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 78628-80-5; 91161-71-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Lamisil	Novartis Pharmaceuticals UK	UK	-
Lamisil	Medley/EMS	-	-
Lamisil	Sandoz-Wander	-	-
Lamisil	Genpharm Inc.	-	-
Lamisil Dermagel	Novartis Pharma	Switz.	-

Raw Materials

Sodium hydroxide
Epichlorohydrin
Butyl lithium
Triethylamine
N-Methyl-1-naphthalenemethylamine hydrochloride
Thionyl chloride
3,3-Dimethylbutyne
Boron trifluoride diethyl etherate
Methanesulfonyl chloride

Manufacturing Process

To an ice-cooled solution of N-methyl-1-naphthalenemethylamine hydrochloride (2.1 g) in methanol (40 ml) and water (10 ml) was added sodium hydroxide powder (2 g) followed by dropwise addition of epichlorohydrin (8 ml). The mixture was heated at 60°C for 3 h, then cooled to room temperature. Volatile materials were removed in vacuo and the residue was taken up in ethyl acetate and washed with water. The organic phase was collected, dried over sodium sulfate, filtered and evaporated to dryness. The crude mixture was purified by flash chromatrography on silica gel (grade 9385, Merck, 230-400 mesh, 60 A) using a solvent gradient of a mixture of hexane and ethyl acetate (95:5, 90:10 and 85:15) as eluent, affording the N-methyl-N-naphthylmethyl-2,3-epoxypropane (1.85 g, 81.5%) as an oil.

To a solution of 3,3-dimethylbutyne (2.95 ml) in dry THF (50 ml) at -78°C was added a 2.5 M solution of n-BuLi in hexane (10 ml) dropwise. The mixture was allowed to warm to room temperature over 15 min and stirred at that temparature for a further 15 min, then was cooled back to -78°C and BF_3OEt_2 (3 ml) was added dropwise. The mixture was stirred for 15 min and 1.8 g of N-methyl-N-naphthylmethyl-2,3-epoxypropane, dissolved in THF (10 ml), was added dropwise. After stirring at -78°C for 2 h, saturated sodium bicarbonate solution (15 ml) was added, and the reaction mixture was allowed to warm to room temperature. The mixture was extracted with ethyl acetate (2 times 25 ml), and the combined organic fractions was dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatrography on silica gel (grade 9385, Merck, 230-400 mesh, 60 a) using a mixture of hexane and ethyl acetate (85:15) as eluent, thereby affording the N-methyl-N-(1-naphthylmethyl)-2-hydroxy-heptan-4-ynyl-1-amine as an oil (1.95 g, 79%).

To an ice-cooled solution of N-methyl-N-(1-naphthylmethyl)-2-hydroxy-heptan-4-ynyl-1-amine (155 mg) in THF (10 ml) was added Et_3N (0.35 ml) followed by methanesulfonyl chloride (0.075 ml). The resulting mixture was stirred at 0°C for 3 h, then filtered. The filtrate was concentrated in vacuo, dissolved in toluene (10 ml) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.37 ml) was added. The resulting mixture was heated at 80°C for 4 h, cooled to room temperature then poured onto a silica gel column and eluted with hexane (100%) followed by a mixture of hexane and ethyl acetate (95:5). Thus, a mixture of E- and Z-isomers of N-methyl-N-(1-naphthylmethyl)-6,6-dimethylhept-2-en-4-ynyl)-1-amine were obtained in a ratio of 2:5 (95 mg, 66%).

In practice it is usually used as hydrochloride salt.

References

Karimian K. et al., US Patent No. 5,817,875; Oct. 6, 1998

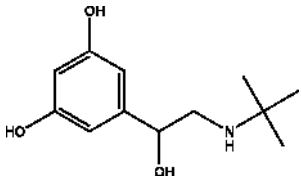
TERBUTALINE

Therapeutic Function: Bronchodilator

Chemical Name: 1-(3',5'-Dihydroxyphenyl)-2-(t-butylamino)-ethanol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 23031-25-6; 23031-32-5 (Sulfate)

Trade Name	Manufacturer	Country	Year Introduced
Bricanyl	Pharma-Stern	W. Germany	1971
Bricanyl	Astra	UK	1971
Bricanyl	Lematte/Boinot	France	1973
Bricanyl	Astra	US	1974
Bricanyl	Fujisawa	Japan	1974
Brethine	Ciba Geigy	US	1975
Terbasmin	Farmitalia	Italy	1976
Arubendol	Ankerwerk	E. Germany	-
Brethaire	Ciba Geigy	US	-
Bricalin	Teva	Israel	-
Brican	Draco	Sweden	-
Bristurin	Bristol	Japan	-
Filair	Riker	UK	-

Raw Materials

Benzyl-t-butylamine
3,5-Dibenzyloxy-ϖ-bromoacetophenone
Hydrogen

Manufacturing Process

To a solution of 32 g of benzyl-t-butylamine in 300 ml of absolute ethanol at reflux temperature was added 32 g of 3,5-dibenzyloxy-ϖ-bromoacetophenone in 10 ml of dry benzene. The mixture was refluxed for 20 hours and then evaporated. When absolute ether was added to the residue, benzyl-t-butylamine hydrobromide was precipitated. The precipitated compound was filtered off and to the filtrate was added an excess of 2 N sulfuric acid. This caused precipitation of the hydrogen sulfate of 3,5-dibenzyloxy-ϖ-(benzyl-t-butylamino)-acetophenone which was recrystallized from acetone/ether. If the

product is crystallized from different organic solvents, the melting point will vary with the type and amount of solvent of crystallization, but the product can be used directly for hydrogenation.

15 g of 3,5-dibenzyloxy-ϖ-(benzyl-t-butylamino)-acetophenone hydrogen sulfate in 200 ml of glacial acetic acid were hydrogenated in a Parr pressure reaction apparatus in the presence of 1.5 g of 10% palladium charcoal at 50°C and 5 atmospheres pressure. The reaction time was 5 hours. The catalyst was filtered off, the filtrate was evaporated to dryness and the hydrogen sulfate of 1-(3',5'-dihydroxyphenyl)-2-(t-butylamino)-ethanol was received. This compound is hygroscopic, but it can be transformed into a nonhygroscopic sulfate in the following manner.

The hydrogen sulfate was dissolved in water and the pH of the solution was adjusted to 5.6 (pH-meter) with 0.1 N sodium hydroxide solution. The water solution was evaporated to dryness and the residue dried with absolute ethanol/benzene and once more evaporated to dryness. The remaining crystal mixture was extracted in a Soxhlet extraction apparatus with absolute methanol. From the methanol phase the sulfate of 1-(3',5'-dihydroxyphenyl)-2-(t-butylamino)-ethanol crystallized. Melting point 246°C to 248°C.

References

Merck Index 8986
Kleeman and Engel p. 858
PDR pp. 889, 987
I.N. p. 925
REM p. 890
Wetterlin, K.Z.L. and Svensson, L.A.; US Patent 3,937,838; February 10, 1976; assigned to A.B. Draco (Sweden)

TERCONAZOLE

Therapeutic Function: Antifungal

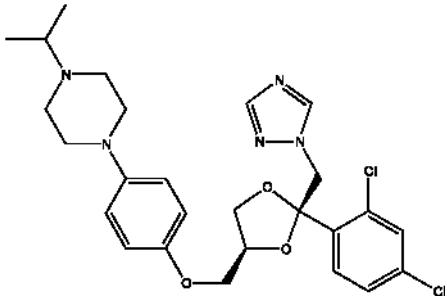
Chemical Name: Piperazine, 1-(4-((2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl)methoxy)phenyl)-4-(1-methylethyl)-, cis-

Common Name: Terconazole; Triaconazole

Chemical Abstracts Registry No.: 67915-31-5

Trade Name	Manufacturer	Country	Year Introduced
Terazol	Johnson and Johnson Pharmaceutical Research and Development, LLC	-	-
Terazol	Janssen-Ortho Inc.	Belgium	-

Structural Formula:



Raw Materials

1H-1,2,4-Triazole
Potassium carbonate
Sodium hydride
Methanesulfonyl chloride
Sodium methanolate
1-(4-Hydroxyphenyl)-4-(1-methylethyl)piperazine
cis-2-(Bromomethyl)-2-(2,4-dichlorophenyl)-l,3-dioxolan-4-ylmethyl benzoate

Manufacturing Process

A mixture of 1.6 parts of 1H-1,2,4-triazole, 54 parts of N.N-dimethylformamide and 45 parts of benzene is stirred and refluxed for 2 h. After cooling, 0.78 parts of sodium hydride dispersion 78% are added and the whole is stirred for 30 min at room temperature. Then there are added 8.9 parts of cis-2-(bromomethyl)-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-ylmethyl benzoate and stirring is continued overnight at 150°C. The reaction mixture is cooled and poured onto water. The product is extracted three times with benzene. The combined extracts are washed twice with water, dried, filtered and evaporated, yielding 8.5 parts of cis-[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol- 1-ylmethyl)-1,3-dioxolan-4-ylmethyl]benzoate as a residue.

A mixture of 289 parts of cis-[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-ylmethyl]benzoate, 200 parts of sodium hydroxide solution 50%, 1500 parts of 1,4-dioxane and 300 parts of water is stirred and refiuxed for 2 h. The reaction mixture is cooled and poured onto water. The product is extracted with dichloromethane. The extract is washed with water, dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The first fraction is collected and the eluent is evaporated, yielding 89 parts cis-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolane-4-methanol; melting point 138.2°C.

A mixture of 30.6 parts of cis-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-l,3-dioxolane-4-methanol and 75 parts of pyridine is stirred at room temperature and there are added dropwise 17.2 parts of methanesulfonyl chloride. Upon completion, stirring is continued overnight at room temperature. The reaction mixture is poured onto ice-water and the product is extracted twice with dichloromethane. The combined extracts are washed

twice with a diluted hydrochloric acid solution and twice with water, dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The first fraction is collected and the eluent is evaporated, yielding 21 parts of cis-[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-ylmethyl]methanesulfonate; melting point 98°C.

A mixture of 1-(4-hydroxyphenyl)-4-(1-methylethyl)piperazine, cis-[2-(2,4-dichloro-phenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-ylmethyl]methanesulfonate, potassium carbonate and N,N-dimethylformamide is stirred and heated overnight at 120°C. The reaction mixture is cooled and poured onto water. The product is extracted twice with dichloromethane. The combined extracts are washed twice with a potassium carbonate solution, dried, filtered and evaporated. The residue is taken up in methanol and a sodium methanolate solution 30% are added. The whole is stirred and refluxed for 1 h. The mixture is poured onto water and the layers are separated. The organic phase is dried, filtered and evaporated. The cis-1-(4-((2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl)methoxy)phenyl)-4-(1-methylethyl)piperazine was obtained, melting point 116.3°C.

References

Heeres J. et al.; US Patent No. 4,144,346; March 13, 1979; Assigned: Janssen Pharmaceutica N.V., Beerse, Belgium

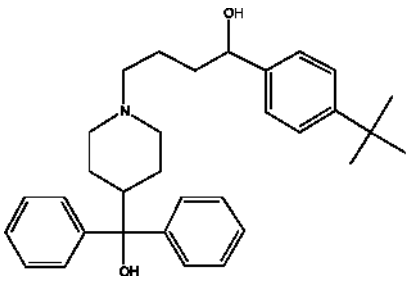
TERFENADINE

Therapeutic Function: Antihistaminic, Bronchodilator

Chemical Name: 1-Piperidinebutanol, α-(4-(1,1-dimethylethyl)phenyl)-4-(hydroxydiphenylmethyl)-

Common Name: Terfenadine

Structural Formula:



Chemical Abstracts Registry No.: 50679-08-8

Trade Name	Manufacturer	Country	Year Introduced
Histafen	Berk	-	-
Seldane	Omega Labs.	-	-
Seldane	Hoechst Marion Roussel	Canada	-
Terfenadine	Zenith Labs.	-	-
Terfenadine	Gruppo Lepetit S.p.A.	Italy	-

Raw Materials

Potassium hydrocarbonate
Potassium iodide
Sodium methoxide
Potassium borohydride
4'-tert-Butyl-4-chlorobutyrophenone
α,α-Diphenyl-4-piperidinemethanol

Manufacturing Process

A mixture of 107 g (0.4 mole) of α,α-diphenyl-4-piperidinemethanol, 105 g (0.44 mole) of 4'-tert-butyl-4-chlorobutyrophenone, 70 g (0.7 mole) of potassium bicarbonate, and a small amount of potassium iodide in 600 ml of toluene was refluxed and stirred for 2.5 days then filtered. The filtrate was treated with charcoal, filtered through celite then treated with ethereal HCl. The resulting solid was recrystallized from methanol and isopropyl alcohol to give the 4'-tert-butyl-4-[4-(α-hydroxy-α-phenylbenzyl)piperidino]-butyrophenone hydrochloride, melting point 234°-235°C.

To a mixture of 4.2 g (0.0083 mole) of 4'-tert-butyl-4-[4-(α-hydroxy-α-phenylbenzyl)piperidino]-butyrophenone hydrochloride and 0.54 g (0.01 mole) of sodium methoxide in 25 ml of methanol is added 2.16 g (0.04 mole) of potassium borohydride. The reaction mixture is stirred overnight, diluted with water and the methanol removed under reduced pressure. The remaining material is extracted with chloroform, washed with water, dried over magnesium sulfate and filtered. The filtrate is concentrated, and the residue is recrystallized from acetone-water to give 4-[α-(p-tert-butylphenyl)-α-hydroxybenzyl]-α-phenyl-1-piperidinebutanol, melting point 161°-163°C.

References

Carr A.A., Kinsolving C.R.; US Patent No. 3,941,795; March 2, 1976; Assigned: Richardson-Merrell Inc., Wilton, Conn
Carr A.A., Kinsolving C.R.; US Patent No. 3,806,526; April 23, 1974; Assigned: Richardson-Merrell Inc., New York, N.Y.

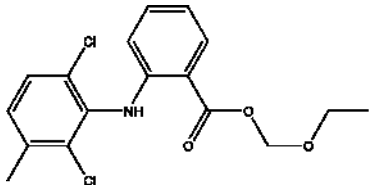
TEROFENAMATE

Therapeutic Function: Antiinflammatory, Analgesic

Chemical Name: 2-[(2,6-Dichloro-3-methylphenyl)amino]benzoic acid ethoxymethyl ester

Common Name: Etoclofene

Structural Formula:



Chemical Abstracts Registry No.: 29098-15-5

Trade Name	Manufacturer	Country	Year Introduced
Etofen Ilfi	Lusofarmaco	Italy	1980

Raw Materials

N-2,6-Dichloro-m-tolylanthranilic acid
Chloromethyl ethyl ether

Manufacturing Process

10 g sodium salt of N-2,6-dichloro-m-tolylanthranilic acid, 3 ml chloromethyl ethyl ether and 80 ml dry acetone were refluxed for 12 hours on waterbath under stirring. The solid was filtered off, and the solution evaporated to dryness. The residue was dissolved in chloroform, washed with sodium carbonate solution, then with water until neutral. After drying on sodium sulfate, the solution was evaporated to dryness. The obtained product was recrystallized from 95% ethanol. Melting point 73°C to 74°C.

References

Merck Index 8992
DFU 1 (8) 421 (1976)
I.N. p. 927
Manghisi, E.; US Patent 3,642,864; February 15, 1972; assigned to Istituto Luso Farmaco D'Italia S.R.L. (Italy)

TESTOLACTONE

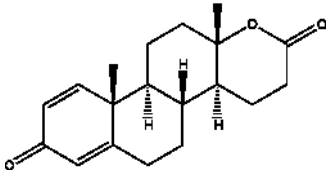
Therapeutic Function: Cancer chemotherapy

Chemical Name: D-Homo-17-α-oxaandrosta-1,4-diene-3,17-dione

Common Name: 1-Dehydrotestololactone

Chemical Abstracts Registry No.: 968-93-4

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Fludestrin	Heyden	W. Germany	1968
Teslac	Squibb	US	1969

Raw Materials

Bacterium Cylindrocarpon radicola
Corn steep liquor
Brown sugar

Manufacturing Process

(a) Fermentation: A medium of the following composition is prepared: 3.0 grams cornsteep liquor solids; 3.0 grams $NH_4H_2PO_4$; 2.5 grams $CaCO_3$; 2.2 grams soybean oil; 0.5 gram progesterone and distilled water to make 1 liter. The medium is adjusted to pH 7.00.1. Then, 100 ml portions of the medium are distributed in 500 ml Erlenmeyer flasks and the flasks plugged with cotton and sterilized in the usual manner (i.e., by autoclaving for 30 minutes at 120°C). When cool, each of the flasks is inoculated with 5 to 10% of a vegetative inoculum of Cylindrocarpon radicola [the vegetative inoculum being grown from stock cultures (lyophilized vial or agar slant) for 48 to 72 hours in a medium of the following composition: 15 grams cornsteep liquor; 10 grams brown sugar; 6 grams $NaNO_3$; 0.001 gram $ZnSO_4$; 1.5 grams KH_2PO_4;0.5 gram $MgSO_47H_2O$; 5 grams $CaCO_3$; 2 grams lard oil; and distilled water to make 1 liter].

The flasks are then placed on a reciprocating shaker (120 one and one-half inch cycles per minute) and mechanically shaken at 25°C for 3 days. The contents of the flasks are then pooled and, after the pH of the culture is adjusted to about 40.2 with sulfuric acid, filtered through Seitz filter pads to separate the mycelium from the fermented medium.

(b) Extraction: 40 liters of the culture filtrate obtained in (a) is extracted with 40 liters chloroform in an extractor (e.g., Podbelniak, US Patent 2,530,886, or improvements thereon) and the filtered chloroform extract is evaporated to dryness in vacuo. The residue (11.1 grams) is taken up in 200 ml of 80% aqueous methanol, and the resulting solution is extracted four times with 100 ml portions of hexane. The 80% aqueous methanol solution is then concentrated in vacuo until crystals appear; and, after cooling at 0°C for several (usually about 3 to 4) hours, the crystals formed are recovered by filtration. About 2.9 grams 1-dehydrotestololactone (MP 217° to 217.5°C) are thus obtained. Concentration of the mother liquors yields additionally about 6.0 grams of the lactone. Recrystallization from acetone yields a purified 1-

dehydrotestololactone having a melting point of 218° to 219°C.

References

Merck Index 8999
Kleeman and Engel p. 860
PDR p. 1768
OCDS Vol. 2 p. 160 (1980)
I.N. p. 928
REM p. 1000
Fried, J. and Thoma, R.W.; US Patent 2,744,120; May 1, 1956; assigned to Olin Mathieson Chemical Corporation

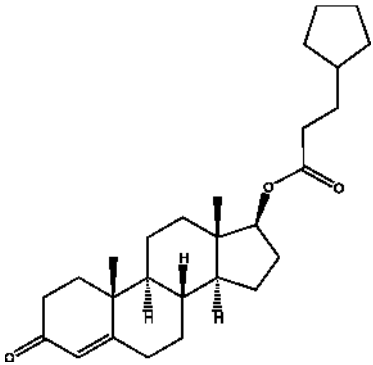
TESTOSTERONE CYPIONATE

Therapeutic Function: Androgen

Chemical Name: 17β-(3-Cyclopentyl-1-oxopropoxy)androst-4-en-3-one

Common Name: Depo-testosterone

Structural Formula:



Chemical Abstracts Registry No.: 58-20-8

Trade Name	Manufacturer	Country	Year Introduced
Depo-Testosterone	Upjohn	US	1951
T-Ionate P.A.	Tutag	US	1970
Andro-Cyp	Keene	US	-
Andronate	Pasadena	US	-
Ciclosterone	Farmigea	Italy	-
Depostomead	Spencer-Mead	US	-
Depotest	Blaine	US	-
Dep-Test	Sig	US	-
Dep-Testosterone	Rocky Mtn.	US	-

Trade Name	Manufacturer	Country	Year Introduced
Durandro	Ascher	US	-
Jectatest	Reid-Provident	US	-
Malogen Cyp	O'Neal, Jones and Feldman	US	-
Pertestis Dep.	Orma	Italy	-
Testomed P.A.	Medics	US	-
Testorit-Dep	Gallo	Italy	-

Raw Materials

β-Cyclopentylpropionic acid
Testosterone 3-enol-ethyl ether
Acetic anhydride
Hydrogen chloride

Manufacturing Process

1 g of crude 3-enol-ethyl ether of testosterone dissolved in 3 cc of pyridine is treated with 2 cc of β-cyclopentylpropionic anhydride (obtained from the β-cyclopentylpropionic acid and acetic anhydride: boiling point 180°C/2 mm Hg). After standing at room temperature overnight the mixture is diluted with water and extracted with ether, the ethereal layer, washed with water to neutrality and dried, is evaporated by vacuum. The oily residue is taken up in petroleum ether and filtered through a layer of aluminum oxide, which is afterwards washed with a further amount of petroleum ether. The solution so filtered and purified is evaporated to dryness; the crystalline residue is recrystallized from a small amount of methanol containing a trace of pyridine: about 1 g of 3-enol-ethyl-ether of the β-cyclopentyl propionate of testosterone, melting point 86°C to 88°C, is so obtained (by further recrystallization melting point 90°C to 91°C). This product (that may be employed either in the crystalline state, or in the oily one, that is, before the purification by filtration through aluminum oxide) by treatment with a small amount of hydrochloric acid in acetone solution yields the β-cyclopentyl propionate of testosterone, melting point 99°C to 101°C (recrystallized from methanol).

References

Merck Index 9002
Kleeman and Engel p. 861
PDR pp. 950, 1033, 1841
OCDS Vol. 1 p. 172 (1977)
I.N. p. 929
REM p. 1001
Ercoli, A. and de Ruggieri, P.; US Patent 2,742,485; April 17, 1956; assigned to Francesco Vismara Societa per Azioni & A. Ercoli (Italy)

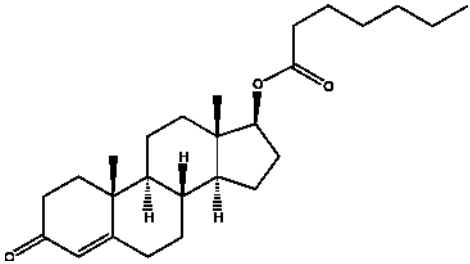
TESTOSTERONE ENANTHATE

Therapeutic Function: Androgen

Chemical Name: 17β-[(1-Oxoheptyl)oxy]androst-4-en-3-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 315-37-7

Trade Name	Manufacturer	Country	Year Introduced
Delatestryl	Squibb	US	1954
Reposo-TMD	Canfield	US	1961
Testate	Savage	US	1970
Testostroval PA	Tutag	US	1970
Androtardyl	S.E.P.P.S.	France	-
Andryl	Keene	US	-
Arderone	Buring-Arden	US	-
Atlatest	I.C.I.	US	-
Deladumon	Squibb	US	-
Delatest	Dunhall	US	-
Dura-Testate	Ries	US	-
Duratesterone	Myers-Carter	US	-
Enarmon	Teikoku Zoki	Japan	-
Everone	Hyrex	US	-
Malogen LA	Fellows-Testagar	US	-
Malogex	Stickley	Canada	-
Primoteston	Schering	W. Germany	-
Reprosteron	Spencer-Mead	US	-
Repro Testro Med	Medics	US	-
Retandros	Rocky Mtn.	US	-
Span-Test	Scrip	US	-
Tesone	Sig	US	-
Testanate	Kenyon	US	-
Testinon	Mochida	Japan	-
Testisan Depo	I.E. Kimya Evi	Turkey	-
Testo-Enant	Geymonat Sud	Italy	-
Testone	Ortega	US	-
Testrin	Pasadena	US	-
Testoviron	Schering	W. Germany	-
Testrone	N. Amer. Pharm.	US	-

Raw Materials

Oenanthic acid
Testosterone

Manufacturing Process

A mixture of testosterone, pyridine and oenanthic acid anhydride is heated for 1 1/2 hours to 125°C. The cooled reaction mixture is decomposed with water while stirring and cooling. After prolonged standing at a temperature below room temperature, the whole is extracted with ether and the ethereal solution is washed consecutively with dilute sulfuric acid, water, 5% sodium hydroxide solution, and again with water. The crude ester remaining on evaporation of the dried ether solution, after recrystallization from pentane, melts at 36° to 37.5°C.

References

Merck Index 9003
Kleeman and Engel p. 862
PDR pp. 1033, 1604
I.N. p. 929
REM p. 1001
Junkmann, K., Kathol, J. and Richter, H.; US Patent 2,840,508; June 24, 1958; assigned to Schering AG, Germany

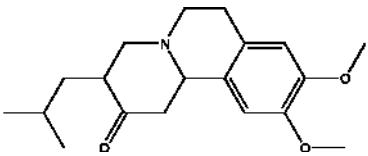
TETRABENAZINE

Therapeutic Function: Tranquilizer

Chemical Name: 1,3,4,6,7,11b-Hexahydro-9,10-dimethoxy-3-(2-methylpropyl)-2H-benzo[a]quinolizin-2-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 58-46-8

Trade Name	Manufacturer	Country	Year Introduced
Nitoman	Roche	UK	1960

Raw Materials

Paraformaldehyde	Isobutyl malonic acid dimethyl ester
Sodium	Hydrogen chloride
Ethanol	1-Carbethoxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline

Manufacturing Process

280 grams of 1-carbethoxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, 150 grams of mono-isobutylmalonic acid dimethyl ester and 35 grams of paraformaldehyde were refluxed for 24 hours in 1,000 ml of methanol. Upon cooling, 1-carbethoxymethyl-2-(2,2-dicarbomethoxy-4-methyl-n-pentyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline crystallized; MP after recrystallization from methanol, 94° to 96°C. The latter was subjected to Dieckmann cyclization, hydrolysis and decarboxylation in the following manner.

28 grams of sodium was dissolved in 650 ml of absolute ethanol, the solution was concentrated to dryness, and the residue was mixed with 3,600 ml of toluene and 451 grams of the intermediate prepared above. The mixture was heated, and the methanol formed by condensation was distilled off until the boiling point of toluene was reached. The mixture was thereupon refluxed for 2 hours, and then it was concentrated to dryness. The residue was dissolved in 5,200 ml of 3 N hydrochloric acid and heated for 14 hours at 120°C, thereby effecting hydrolysis and decarboxylation. The mixture was cooled, washed with diethyl ether, decolorized with carbon, made alkaline and taken up in diethyl ether. The process yields 2-oxo-3-isobutyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b-benzo[a]quinolizine; MP after recrystallization from diisopropyl ether, 126° to 128°C.

References

Merck Index 9009
OCDS Vol. 1 p. 350 (1977)
I.N. p. 931
Brossi, A., Schnider, O. and Walter, M.; US Patent 2,830,993; April 15, 1958; assigned to Hoffmann-La Roche, Inc.

TETRACAINE HYDROCHLORIDE

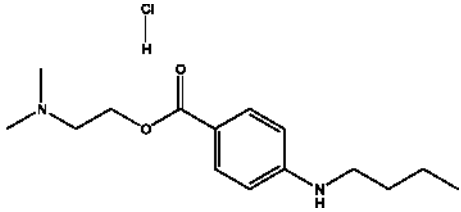
Therapeutic Function: Local anesthetic

Chemical Name: Benzoic acid, 4-(butylamino)-, 2-(dimethylamino)ethyl ester monohydrochloride

Common Name: Tetracaine hydrochloride; Amethocaine hydrochloride; Dicaine

Chemical Abstracts Registry No.: 136-47-0

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Anestesia topica	Miro	-	-
Anestol	Continental	-	-
Butylcain	Tanabe	-	-
Medicain	Grunau	-	-
Schleimhautanaestheticum	Tief	-	-
Supracaine	Hoechst-Canada	-	-

Raw Materials

n-Butyl bromide
4-Aminobenzoic acid sodium salt
Hydrochloric acid
Hydrochloride of β-dimethylaminoethanol

Manufacturing Process

4-Butylaminobenzoic acid is produced by boiling an aqueous solution of the sodium salt of 4-aminobenzoic acid with n-butyl-bromide. It forms a colorless crystalline powder melting at 153-154°C.

Equimolecular quantities of 4-butylaminobenzoic acid and the hydrochloride of β-dimethylaminoethanol are suspended in 10 times their joint weight of toluene. The mixture is saturated with hydrochloric acid gas and heated in an oil bath at about 150°C while a current of hydrochloric acid, gas is slowly passed through the mixture so that toluene slowly distils. Along with toluene the water produced by the esterification distils. After heating for about 10 hours the mixture is cooled and water is added until the salt is dissolved. The layer of toluene is separated and the ester base precipitated from the aqueous solution by means of a solution of sodium carbonate. By dissolving the base in ether, drying the ether solution separated over potassium carbonate and adding alcoholic hydrochloric acid, to the solution until it is neutral to litmus, the monohydrochloride is obtained in the form of a colorless crystalline powder which, when recrystallized from alcohol, melts at 147-148°C.

The 4-butylaminobenzoic acid β-di-methylaminoethylester monohydrochloride is a colorless crystalline powder, which is easily soluble in water. The solution may be sterilized by boiling without decomposition having to be feared. The base can be precipitated from the aqueous solution of the salt; it is at first in the form of an oil but soon solidifies, forms colorless crystals and melts at 43°C. The picrate melts at 120°C. When treated with oxalic acid, the base

forms a neutral oxalate which is easily soluble in water and an acid oxalate which is very difficultly soluble in cold water.

In practice it is usually used as hydrochloride salt.

References

OTTO EISLEB; US Patent No. 1,889,645; Nov. 29, 1932; Assigned to WINTHEOP CHEMICAL COMPANY, IETC., OF NEW YORK, N. Y., A CORPORATION OF NEW YORK

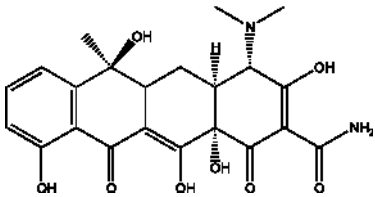
TETRACYCLINE

Therapeutic Function: Antibacterial

Chemical Name: 4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide

Common Name: Deschlorobiomycin; Omegamycin

Structural Formula:



Chemical Abstracts Registry No.: 60-54-8

Trade Name	Manufacturer	Country	Year Introduced
Tetracyn	Pfizer	US	1953
Achromycin	Lederle	US	1953
Polycycline	Bristol	US	1954
Panmycin	Upjohn	US	1955
Cancycline	Canfield	US	1964
Abricycline	Farmakhim	Bulgaria	-
Biotetra	I.E. Kimya Evi	Turkey	-
Copharlan	Cophar	Switz.	-
Economycin	D.D.S.A.	UK	-
Mervacycline	Byk	Netherlands	-
Mysteclin	Squibb	US	-
Pediatetracycline	Theranol	France	-
Pervasol	Poen	Argentina	-

Trade Name	Manufacturer	Country	Year Introduced
Sanbiotetra	Santos	Spain	-
SK-Tetracycline	SKF	US	-
Sumycin	Squibb	US	-
Teclinazets	Miluy	Spain	-
Tetra-Co	Coastal	US	-
Tetramig	Inava	France	-
Tetra-Proter	Proter	Italy	-

Raw Materials

Chlortetracycline
Hydrogen
Bacterium Streptomyces aureofaciens

Manufacturing Process

Tetracycline is usually prepared by the catalytic dechlorination of chlortetracycline as described in US Patents 2,699,054 and 3,005,023, or obtained directly by fermentation of Streptomyces aureofaciens or Streptomyces viridifaciens according to US Patents 2,712,517, 2,734,018, 2,886,595 and 3,019,173. The purification of tetracycline produced by either route is described in US Patent 3,301,899.

The production of tetracycline by catalytic dechlorination is described in US Patent 2,699,054 as follows: Pure chlortetracycline (4.8 grams) was suspended in 100 ml of methanol and sufficient anhydrous dioxane was added to completely dissolve the product. To the solution was added 0.5 gram of 5% palladium-on-charcoal catalyst. The mixture was placed in a conventional hydrogenation apparatus and subjected to a pressure of 50 psi of hydrogen while being agitated.

After the initial drop in pressure due to the absorption of gas by the catalyst and the solvent, there was a steady drop in pressure due to the hydrogenation of the antibiotic. After approximately 1 mol of hydrogen had been absorbed, no further reaction was observed. This occurred after about 2 hours. The catalyst was filtered and washed with boiling methanol and boiling dioxane. The solution gave a positive test for chloride ion when treated with silver nitrate solution. It also possessed a strongly acidic reaction demonstrating the release of the nonionic chlorine in the form of hydrogen chloride. A bioassay of the crude product in solution indicated a potency of approximately 580 μg/mg with oxytetracycline as the standard at a potency of 1,000 μg/mg. The solution was concentrated under vacuum at room temperature and the residual liquid was dried from the frozen state under vacuum. 3.1 grams of bright yellow amorphous tetracycline hydrochloride was obtained.

This product may be converted to tetracycline per se by redissolving it in water, carefully neutralizing it to pH 4.5 with dilute sodium hydroxide, and recovering the product by drying the solution.

References

Merck Index 9021
Kleeman and Engel p. 864
PDR pp.996, 1391, 1723, 1752, 1767
OCDS Vol. 1 p. 212 (1977)
I.N. p. 932
REM p. 1207
Conover, L.H.; US Patent 2,699,054; January 11, 1955
Gourevitch, A. and Lein, J.; US Patent 2,712,517; July 5, 1955; assigned to Bristol Laboratories Inc.
Minieri, P.P., Sokol, H. and Firman, M.C.; US Patent 2,734,018; February 7, 1956; assigned to American Cyanamid Company
Heinemann, B. and Hooper, I.R.; US Patent 2,886,595; May 12, 1959; assigned to Bristol Laboratories Inc.
Miller, P.A.; US Patent 3,005,023; October 17, 1961; assigned to American Cyanamid Company
Arishima, M. and Sekizawa, Y.; US Patent 3,019,173; January 30, 1962; assigned to American Cyanamid Company
Kaplan, M.A. and Granatek, A.P.; US Patent 3,301,899; January 31, 1967; assigned to Bristol-Myers Company

TETRACYCLINE PHOSPHATE COMPLEX

Therapeutic Function: Antibacterial

Chemical Name: Tetracycline phosphate complex

Common Name: -

Structural Formula: See tetracicline for the basic formula

Chemical Abstracts Registry No.: 1336-20-5

Trade Name	Manufacturer	Country	Year Introduced
Tetrex	Bristol	US	1956
Sumycin	Squibb	US	1957
Panmycin Phos	Upjohn	US	1957
Austrastaph	C.S.L.	Australia	-
Binicap	S.A.M.	Italy	-
Biocheclina	Wolner	Spain	-
Bristaciclina Retard	Antibioticos	Spain	-
Conciclina	Lusofarmaco	Italy	-
Devacyclin	Deva	Turkey	-
Fusfosiklin	T.E.M.S.	Turkey	-
Hexacycline	Diamant	France	-
Tetraksilin	Atabay	Turkey	-
Tetralet	Fako	Turkey	-
Tetramin	Efeyn	Spain	-

Trade Name	Manufacturer	Country	Year Introduced
Tetrex	Bristol	US	1956
Sumycin	Squibb	US	1957
Panmycin Phos	Upjohn	US	1957
Austrastaph	C.S.L.	Australia	-
Binicap	S.A.M.	Italy	-
Biocheclina	Wolner	Spain	-
Bristaciclina Retard	Antibioticos	Spain	-
Conciclina	Lusofarmaco	Italy	-
Devacyclin	Deva	Turkey	-
Fusfosiklin	T.E.M.S.	Turkey	-
Hexacycline	Diamant	France	-
Tetraksilin	Atabay	Turkey	-
Tetralet	Fako	Turkey	-
Tetramin	Efeyn	Spain	-

Raw Materials

Tetracycline
Phosphorus pentoxide

Manufacturing Process

In a 500-ml round-bottomed flask equipped with stirrer, condenser and thermometer was placed 7.1 grams (0.05 mol) P_2O_5 which was immediately covered with 100 ml of chloroform. To the mixture was added with stirring 0.9 ml (0.05 mol) of distilled water. In a few minutes, a lower oily layer appeared, which was believed to be freshly formed metaphosphoric acid resulting from the action of the P_2O_5 with an equimolar amount of water. To this mixture was added 100 ml of methanol and on continued stirring, the lower oily layer disappeared in the methanol forming a complete pale yellowish-green colored solution.

An additional 50 ml of methanol was added to the flask and then 22.2 grams (0.05 mol) of tetracycline, neutral form, was added portionwise intermittently with another 50 ml of methanol. A clear solution was maintained throughout the addition of the tetracycline. After addition of all of the tetracycline, the solution was a deep orange color and the temperature in the reaction flask was 35°C.

One hour after addition of the tetracycline, the clear reaction solution was poured into 1,500 ml of chloroform. A yellow product separated and was collected on a coarse sintered glass filter and air dried. The tetracycline-metaphosphoric acid complex weighed about 10 grams, contained 7.34% of phosphorus and had a bioassay of 634 gammas per milligram. Solubility in water is 750 mg/ml.

References

Merck Index 9021
I.N. p. 933

REM p. 1208
Sieger, G.M. Jr. and Weidenheimer, J.F.; US Patent 3,053,892; September 11, 1962; assigned to American Cyanamid Company

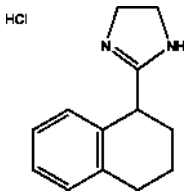
TETRAHYDROZOLINE HYDROCHLORIDE

Therapeutic Function: Nasal decongestant, Pharmaceutic aid

Chemical Name: 4,5-Dihydro-2-(1,2,3,4-tetrahydro-1-naphthalenyl)-1H-imidazole hydrochloride

Common Name: Tetryzoline HCl

Structural Formula:



Chemical Abstracts Registry No.: 522-48-5; 84-22-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Tyzine	Pfizer	US	1954
Visine	Leeming	US	1958
Constrilia	P.O.S.	France	1979
Azolin	Fischer	Israel	-
Burnil	Kurtsan	Turkey	-
Collyrium	Wyeth	US	-
Ischemol	Farmila	Italy	-
Murine	Ross	US	-
Narbel	Chugai	Japan	-
Nasin	Abic	Israel	-
Oftan-Starine	Star	Finland	-
Rhinopront	Mack	W. Germany	-
Stilla	Abic	Israel	-
Tinarhinin	VEB Berlin Chemie	E. Germany	-
Typinal	Ikapharm	Israel	-
Yxin	Pfizer	W. Germany	-

Raw Materials

1,2,3,4-Tetrahydro-α-naphthoic acid
Ethylenediamine
Hydrogen chloride

Manufacturing Process

A mixture of 540 grams (9.0 mols) of ethylenediamine, 270 grams (1.53 mols) of 1,2,3,4tetrahydro-α-naphthoic acid, and 360 ml (4.32 mols) of concentrated hydrochloric acid was introduced into a two-liter, three-necked flask fitted with a thermometer, stirrer, and distillation takeoff. The mixture was distilled under a pressure of about 20 mm of mercury absolute until the temperature rose to 210°C. Thereafter, heating was continued under atmospheric pressure and when the temperature reached about 260°C, an exothermic reaction was initiated. The heat was then adjusted to maintain a reaction temperature of 275° to 280°C for 45 minutes and the mixture thereafter cooled to room temperature.

900 ml of 4 N hydrochloric acid was added and the aqueous layer stirred with warming until a clear, brown solution resulted. This brown solution was made strongly alkaline with sodium hydroxide. The oil that separated solidified and was collected on a filter leaving filtrate A. The solid was dissolved in 370 ml of alcohol with warming, and the solution was treated with 130 ml of concentrated hydrochloric acid with stirring and cooling. This acidified mixture was diluted with 300 ml of ether and chilled. The solid salt was collected and dried and the filtrate concentrated to approximately 300 ml, diluted with 300 ml of ether and the salt which separated collected and dried.

Filtrate A was extracted with ether, dried, acidified with alcoholic hydrogen chloride, and the salt which separated was collected and dried. There was thus obtained, when all the salt had been combined, 250 grams (69.3% of the theoretical yield) of 2-(1,2,3,4-tetrahydro-1-naphthyl)imidazoline hydrochloride, melting at 256° to 257°C.

References

Merck Index 9042
Kleeman and Engel p. 867
PDR pp.974, 1555, 1945
OCDS Vol. 1 p. 242 (1977)
I.N. p. 936
REM p. 890
Synerholm, M.E., Jules, L.H. and Sahyun, M.; US Patent 2,731,471; January 17, 1956; assigned to Sahyun Laboratories
Gardocki, J.F., Hutcheon, D.E., Lanbach, G.D. and P'an, S.Y.; US Patent 2,842,478; July 8, 1958; assigned to Chas. Pfizer & Co., Inc.

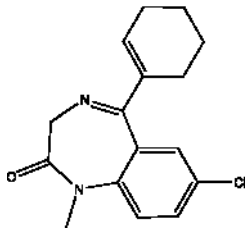
TETRAZEPAM

Therapeutic Function: Muscle relaxant

Chemical Name: 7-Chloro-5-(1-cyclohexen-1-yl)-1,3-dihydro-1-methyl-2H-1,4-benzodiazepin-2-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 10379-14-3

Trade Name	Manufacturer	Country	Year Introduced
Myolastan	Clin-Comar-Byla	France	1969
Musaril	Mack-Midy	W. Germany	1980

Raw Materials

Sodium hypochlorite — Lithium carbonate
Sodium methylate — Methyl iodide
7-Chloro-5-cyclohexyl-2-oxo-2,3-dihydro-1H-benzo[f]diazepine-1,4

Manufacturing Process

1,7-Dichloro-5-Cyclohexyl-2-Oxo-2,3-Dihydro-1H-Benzo[f]Diazepine-1,4: (a) Process Using Sodium Hypochlorite - 40 ml of a solution of sodium hypochlorite of 14.5 British chlorometric degrees are added to a suspension of 5.4 grams of 7-chloro-5-cyclohexyl-2-oxo-2,3-dihydro-1H-benzo[f]diazepine-1,4 in 80 ml of methylene chloride. The mixture is stirred at room temperature for 15 minutes; the solid dissolves rapidly. The organic layer is decanted, washed with water, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure without exceeding a temperature of 30°C. The residue is taken up in a little diisopropyl ether and the crystals which form are dried. They are recrystallized as rapidly as possible from ethyl acetate. Colorless crystals are obtained (3.9 grams; yield, 85%); MP = 163°C, with decomposition.

(b) Process Using Tertiary-Butyl Hypochlorite - 1.2 grams of tertiary-butyl hypochlorite are added to a suspension of 2.7 grams of 7-chloro-5-cyclohexyl-2-oxo-2,3-dihydro-1H-benzo[f]diazepine-1,4 in 20 ml of methylene chloride and the mixture is stirred and at the same time cooled in a water bath for 30 minutes. The solid dissolves in about 15 minutes. The product is evaporated to dryness under reduced pressure at a temperature below 40°C. The residue is taken up in diisopropyl ether and the crystals which separate are dried. Colorless crystals are obtained (2.8 grams; yield, 98%); MP = 161° to 162°C, with decomposition, according to US Patent 3,551,412.

7-Chloro-5-(1'-Chlorocyclohexyl)-2-Oxo-2,3-Dihydro-1H-Benzo[f]Diazepine-1,4: A solution of 117 grams of the compound prepared above in 450 ml ethyl acetate is heated under reflux until a precipitate begins to form. From then onwards reflux is continued until a negative reaction is obtained when the reaction mixture is tested with a solution of sodium iodide in acetone. The

reaction mixture is left to cool and the solid which separates is dried. Colorless crystals are obtained (76 grams), MP = 194° to 195°C, with decomposition. A second portion (14 grams) is isolated by concentrating the mother liquor, MPk = 194° to 195°C, with decomposition. The total yield is 77%. The melting point is raised to 196° to 197°C by recrystallization from ethyl acetate.

7-Chloro-5-(1'-Cyclohexenyl)-2-Oxo-2,3-Dihydro-1H-Benzo[f]Diazepine-1,4: 68 grams of 7-chloro-5-(1'-chlorocyclohexyl)-2-oxo-2,3-dihydro-1H-benzo[f]diazepine-1,4, 34 grams of lithium carbonate and 17 grams of lithium bromide and 340 ml of anhydrous dimethylformamide are placed in a three-necked flask equipped with a mechanical stirrer, immersion thermometer and a reflux condenser connected with a bubble counter.

The reaction mixture is gradually heated, with stirring, until evolution of carbon dioxide commences (about 100°C) and the temperature is maintained thereat until the reaction ceases. The temperature is then raised to 110°C and held thereat for 15 minutes.

The reaction mixture is allowed to cool and the mineral salts separated and dried. The solvent is evaporated under reduced pressure and the residue dissolved in water. It is allowed to crystallize, dehydrated, dried and then recrystallized from ethyl acetate. The product is yellowish crystals (47.5 grams; yield, 80%); MP = 207° to 208°C.

7-Chloro-5-(1'-Cyclohexenyl)-1-Methyl-2-Oxo-2,3-Dihydro-1H-Benzo[f]Diazepine-1,4: 9.7 grams of sodium methylate are added to a solution of 16.5 grams of 7-chloro-5-(1'-cyclohexenyl)-2-oxo-2,3-dihydro-1H-benzo[f]diazepine-1,4 dissolved in 120 ml of dry dimethylformamide and the mixture stirred for one-half hour. The reaction mixture is cooled in a water bath and a solution of 33.8 grams of methyl iodide dissolved in 35 ml of anhydrous dimethylformamide is then slowly added with stirring. The solution becomes dark brown in color and a precipitate forms. It is stirred for 2 hours, then diluted with a large volume of water and extracted with ethyl acetate. The ethyl acetate solution is washed with water, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. The residue is crystallized from a small volume of ethyl acetate. Brownish yellow crystals are obtained (9 grams; yield, 52%), MP = 144°C.

References

Merck Index 9065
Kleeman and Engel p. 865
DOT 6 (4) 148 (1970)
I.N. p. 936
Berger, L. and Sternbach, L.H.; US Patent 3,268,586; August 23, 1966; assigned to Hoffmann-La Roche Inc.
Schmitt, J.; US Patent 3,426,014; February 4, 1969; assigned to Etablissements Clin-Byla, France
Schmitt, J.; US Patent 3,551,412; December 29, 1970; assigned to Etablissements Clin-Byla, France

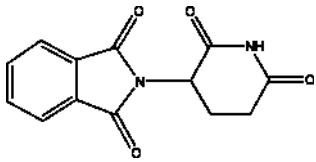
THALIDOMIDE

Therapeutic Function: Sedative, Hypnotic, Antiarthritic

Chemical Name: Phthalimide, N-(2,6-dioxo-3-piperidyl)-

Common Name: Thalidomide

Structural Formula:



Chemical Abstracts Registry No.: 50-35-1; 14088-68-7

Trade Name	Manufacturer	Country	Year Introduced
Contergan	Grunenthal	Germany	-
Imidan	Gowan	-	-
Isomin	Sumit Kapoor	India	-
Kevadon	Merrell	-	-
Neurodyn	Astra	-	-
Synercid	Celgene Corporation	USA	-
Talizer	Laboratorios Serral	Mexico	-
Thalomid	Celgene Corporation	USA	-

Raw Materials

N-Phthalyl glutaminic acid anhydride
Urea

Manufacturing Process

26 g of N-phthalyl glutaminic acid anhydride are melted with 12 g of urea in an oil bath at 170-180°C until the reaction is completed, which takes about 20 min. The reaction takes place with violent evolution of carbon dioxide and ammonia. After cooling, the reaction product is recrystallised by fractionation from 95% alcohol, and the first fraction may contain phthalic acid derivatives. The required product N-(2,6-dioxo-3-piperidyl)-phthalimide melts at 269-271°C. The yield is about 65-70% of the theoretical.

References

Keller H., Kunz W.; US Patent No. 2,830,991; April 15, 1958; Assigned: Chemie Grunenthal G. m. b. H., Stolberg, Rhineland, Germany

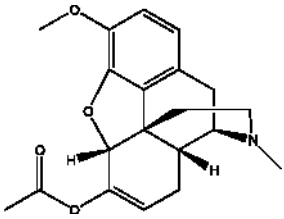
THEBACON

Therapeutic Function: Narcotic analgesic, Antitussive

Chemical Name: Morphinan-6-ol, 6,7-didehydro-4,5-epoxy-3-methoxy-17-methyl-, acetate (ester), (5α)-

Common Name: Acethydrocodone; Tebakon

Structural Formula:



Chemical Abstracts Registry No.: 466-90-0

Trade Name	Manufacturer	Country	Year Introduced
Acedicone	Boehringer Ingelheim S.A.	-	-

Raw Materials

Dihydrocodeinone
Acetic anhydride
Acetic acid

Manufacturing Process

7.7 g of dihydrocodeinone are heated with 40 ml of acetic anhydride for 2.5 hours under a reflux condenser, and the acetic anhydride and glacial acetic acid are then distilled off in vacuo. The oily residue is dissolved in water. In order to remove the last residues from the acetic anhydride it is extracted with ether. The new base is then precipitated with ammonia and crystallizes out immediately on addition of a small quantity of ether. The chemical analysis of the substance obtained corresponds to the values calculated for monoacetyl dihydrocodeinone.

References

CLEMENS SCHOPF; US Patent No. 1,731,152; Oct. 8, 1929; ASSIGNED to THE FIRM C. H. BOEHRINGER SOHN, OF NIEDER-INGELHEIM-ON-THE-RHINE, GERMANY, A SOCIETY OP GERMANY

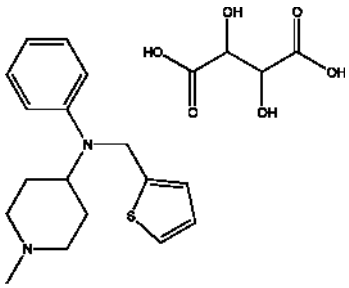
THENALIDINE TARTRATE

Therapeutic Function: Antihistaminic, Antipruritic

Chemical Name: 4-Piperidinamine, 1-methyl-N-phenyl-N-(2-thienylmethyl)-, tartrate (1:1)

Common Name: Thenalidine tartrate; Thenophenopiperidine tartrate

Structural Formula:



Chemical Abstracts Registry No.: 2784-55-6

Trade Name	Manufacturer	Country	Year Introduced
Thenalidine tartarte	Sandoz (Novartis)	-	-

Raw Materials

1-Methyl-4-amino-N'-phenylpiperidine
Sodium amide
2-Thenyl chloride
Ammonium chloride

Manufacturing Process

12 parts by weight of 1-methyl-4-amino-N'-phenyl-piperidine are dissolved in the five- to six-fold quantity of absolute xylene and then, while refluxing and stirring the resultant solution, 42.92 parts by weight of sodamide (10% excess) are added in the course of 2 to 3 hours. Then, without interrupting the heating, 144.5 parts by weight of freshly distilled 2-thenyl chloride, dissolved in the two-fold quantity of absolute xylene, are added dropwise in the course of 1.5 hours, the mixture being there upon heated for 40 to 42 hours at an oil-bath temperature of 170°C. After the mixture has cooled, any sodium amide which is present is decomposed with 10 to 20 parts by weight of NH_4Cl, xylene is added, and the mixture shaken out with about 600 parts by volume of water. The aqueous extract is clarified by filtration and then shaken out with benzene. The xylene and; benzene extracts are concentrated by evaporation under reduced pressure. Any remaining unreacted 2-thenyl chloride removed at 110°C/11 mm. The residue from the evaporation then distilled at a pressure of 0.1 mm. Unreacted 1-methyl-4-amino-N'-phenylpiperidine distils over first at 110-120°C, followed by impure 1-methyl-

4-amino-N'-phenyl-N'-(2-thenyl)-piperidine at 180-190°C.

In order to purify the latter compound, the crude base is dissolved in the six-fold quantity of absolute alcohol. A five-fold quantity of an absolute alcoholic solution of oxalic acid containing the stoichiometric quantity of oxalic acid (+ 10% excess) to form the monooxalate, is their added. A considerable evolution of heat taking place. Upon cooling of the reaction mixture; the monooxalate crystallizes out slowly, in an 80% yield. For purification purposes, the thus-obtained monooxalate is recrystallized from the 17-fold quantity (by volume) of absolute alcohol, with addition of animal charcoal, followed by recrystaillization from the 16-fold quantity (by volume) of a mixture of alcohol and benzene (1:1). The purified monooxalate melts at 160-162°C (decomposition).

To obtain the pure base, the oxalate is dissolved at 40°C in the twenty-fold quantity (by volume) of water and, while cooling with ice-water, the solution is rendered alkaline with 3-normal aqueous NaOH solution. The base, which at first separates in the form of a milky precipitate, crystallizes in the course of several hours and is then recrystallized from the 12-fold quantity (by volume) of an alcohol-water mixture (7.5:4.5). The purified base melts at 95-97°C.

In practice it is usually used as tartrate salt.

References

US Patent No. 2,717,251; Arthur Stoll, Arlesheim, near Basel, and Jean-Pierre 5 Bourquin, Basel, Switzerland, Assignors to Sandoz A. G., Basel, Switzerland

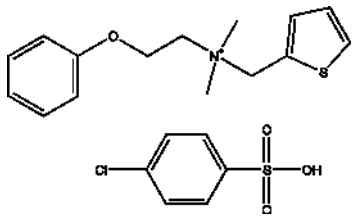
THENIUM CLOSYLATE

Therapeutic Function: Anthelmintic

Chemical Name: Ammonium, dimethyl(2-phenoxyethyl)-2-thenyl-, salt with p-chlorobenzenesulfonic acid (1:1)

Common Name: Thenium closilate; Thenium closylate

Structural Formula:



Chemical Abstracts Registry No.: 4304-40-9

Trade Name	Manufacturer	Country	Year Introduced
Thenium closylate	ZYF Pharm Chemical	-	-
Canopar	Schering-Plough Animal Health Corp.	-	-

Raw Materials

2-Chlormethylthiophene
1-Dimethylamino-2-phenoxyethane
p-Chlorobenzenesulfonic acid

Manufacturing Process

2-Chlormethylthiophene (6.6 g) was added to a solution of 1-dimethylamino-2-phenoxyethane (8.2 g) in acetone (45 ml). On standing for 30 min an oil separeted. The resulting suspension was heated to reflux for a further 30 min and cooled. On standing, the separated oil partially crystallized. The supernatant liquors were decanted and the residue was recrystallized by dissolution in warm isopropanol and careful precipitation with ethyl acetate or ether to give colourless needles N,N-dimethyl-N-2-phenoxyethyl-N-2'-thenylammonium chloride monohydrate, M.P. 85-86°C.

A solution of free base of the last compound and p-chlorobenzenesulfonic acid (molar ratio 1:1) were reacted together in boiling acetone. After 30 min the solution was cooled and ethyl acetate added to precipitate a colourless solid of N,N-dimethyl-N-(2-phenoxyethyl)-N-(2-thenyl)ammonium 4-chlorbenzolsulfonate.

References

COPP FREDERICK CHARLES; GB Patent No. 864,885; Dec. 15, 1958; Assigned to WELLCOME FOUNDATION LIMITED, London

THENYLDIAMINE

Therapeutic Function: Antihistaminic

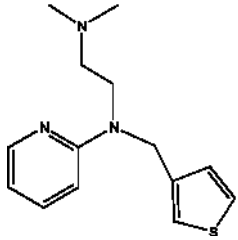
Chemical Name: Pyridine, 2-(N-(2-(dimethylamino)ethyl)-3-thenylamino)-

Common Name: Dethylandiamine; Thenyldiamine

Chemical Abstracts Registry No.: 91-79-2

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

Structural Formula:



Raw Materials

Sodium amide
2-(Dimethylamino)ethylaminopyridine
3-Thenyl bromide

Manufacturing Process

To a suspension of 3.12 g of sodium amide in 50 ml dry toluene was added dropwise 12 g of 2-(dimethylamino)ethylaminopyridine. The mixture was refluxed for 2 hours, cooled to 50°C, and 21 g 3-thenyl bromide was added dropwise. When reaction subsided, the brownish-orange mixture was refluxed for 0.5 hour, cooled, and poured into 150 ml of water. The toluene layer was separated, extracted with 5% hydrochloric acid. This extract was saturated with potassium carbonate. The free base was extracted with ether, dried and fractionated. Yield of N,N-dimethyl-N'-2-pyridinyl-N'-(3-thienylmethyl)-1,2-ethanediamine 31%, boiling point 169-172°C/1 mm.

106 g of the free base was dissolved in 500 ml of isopropyl alcohol and 34 ml concentrated hydrochloric acid was added. After shaking, the reaction mixture was allowed to added. After through cooling in an ice-methanol mixture, the salt was collected and washed on the filter with low boiling petroleum ether, Melting point of N,N-dimethyl-N'-2-pyridinyl-N'-(3-thienylmethyl)-1,2-ethanediamine hydrochloride 169.5-170°C.

References

Campaigne E., LeSuer W.M.; J. Amer.Chem.Soc. 1949, 71, 333

THEODRENALINE

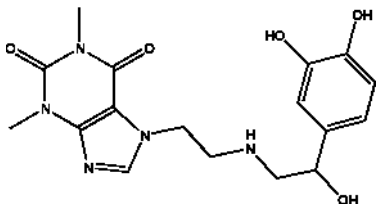
Therapeutic Function: Analeptic

Chemical Name: Theophylline, 7-(2-((β,3,4-trihydroxyphenethyl) amino)ethyl)-

Common Name: Noradrenalinaethyltheophyllin; Theodrenaline

Chemical Abstracts Registry No.: 13460-98-5

Structural Formula:



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

Raw Materials

ω-Chloroacetopyrocatechol
Hydrochloric acid
Platinum oxide
7-(2-Aminoethyl)theophylline
Hydrogen

Manufacturing Process

A solution of 27 g of ω-chloroacetopyrocatechol in 150 ml of ethyl alcohol is added dropwise within 2 hours into a stirred and refluxed solution of 81 g of 7-(β-aminoethyl)theophylline in 200 ml of a 60% aqueous ethyl alcohol. Following this, boiling is continued for another 3.5 hours while passing through nitrogen, and the precipitated product is separated by suction filtration, washed with water and dried. The product is suspended in alcohol, admixed with alcoholic hydrochloric acid while heating until an acid reaction is observed and subjected to suction filtration after cooling. Obtained in this manner are 37 g of 7-[β-(β'-3,4-dihydroxyphenyl-β'-oxoethylamino)ethyl]theophylline hydrochloride having a melting point of 246-249°C. To obtain an analytically pure product, the hydrochloride is dissolved in water and precipitated with acetone.

7.1 g of 7-[β-(β'-3,4-dihydroxyphenyl-β'-oxoethylamino)ethyl]theophylline hydrochloride are dissolved in 500 ml of distilled water and hydrogenated at 48°C in the presence of 1 g of platinum oxide. When no further hydrogen is absorbed after about 5 hours, the mixture is evaporated to dryness in vacuo. Purification is effected by taking up in methyl alcohol and mixing with ethyl acetate. 7-[β-(β'-3,4-dihydroxyphenyl-β'-hydroxyethylamino)ethyl]theophylline hydrochloride which has crystallized after several days is separated by suction filtration and dried in a desiccator. A product having a melting point of 176-178°C is obtained in amount of 6.1 g.

References

Erwin Kohlstaedt, Karl Heinz Klingler, US Patent No. 3,112,313; Nov. 26,1963; Assigned to Cneni-iewerk Homburg Zweigniederiassung der Deutschen Gold- und Silber-Scheideanstalt vorm. Roessler, Frankfurt am Main, Germany

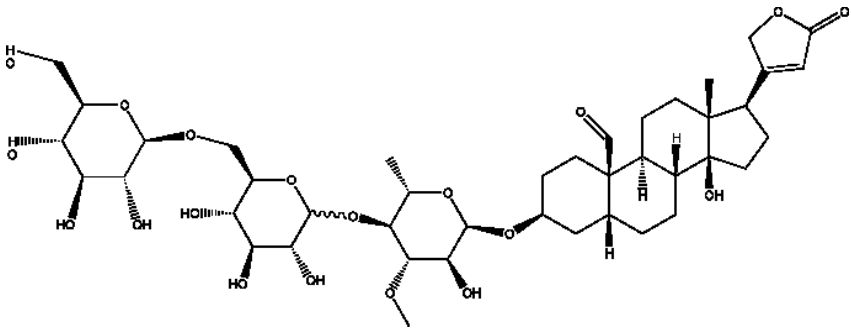
THEVETIN A

Therapeutic Function: Cardiotonic

Chemical Name: Card-20(22)-enolide, 3-((O-β-D-glucopyranosyl-(1-6)-O-D-glucopyranosyl-(1-4)-6-deoxy-3-O-methyl-α-L-glucopyranosyl)oxy)-14-hydroxy-19-oxo-, (3β,5β)-

Common Name: Tevosid; Thevetin A

Structural Formula:



Chemical Abstracts Registry No.: 37933-66-7

Trade Name	Manufacturer	Country	Year Introduced
Thevetin A	SigmaAldrich	-	-

Raw Materials

Ethanol
Thevetins A and B mixture
Sodium bisulfite
n-Butanol

Manufacturing Process

A mixture of Thevetins A and B was prepared by extraction from seeds of Thevetia neriifolia.

100 g of this mixture are dissolved in 1500 ml of aqueous ethanol at 96°C. Then 50 ml of a 30% solution of sodium bisulfite is added. The solution is left for about 1 hour and is then diluted with 3 L of water. The resulting solution is extracted 3 times in reflux extraction apparatus with 4 L of n-butanol as the extraction solvent. Thevetin A passes into said n-butanol which is then washed with distilled water and evaporated to dryness. The crude thevetin A is recrystallized in absolute ethanol (100 ml) and precipitating with 10 volumes of isopropyl oxide. The residual thevetin B of the bisulfite solution also may be prepared.

References

Delalande M., Baisse J.; US Patent No. 3,030,355; Apr. 17, 1962

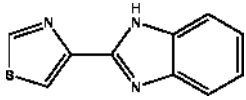
THIABENDAZOLE

Therapeutic Function: Anthelmintic

Chemical Name: 2-(4-Thiazolyl)-1H-benzimidazole

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 148-79-8

Trade Name	Manufacturer	Country	Year Introduced
Mintezol	MSD	US	1967
Mintezol	MSD	UK	1968
Mintezol	MSD-Chibret	France	1969
Minzolum	Sharp and Dohme	W. Germany	1970

Raw Materials

Thionyl chloride
Zinc
Hydrogen chloride
Thiazole-4-carboxylic acid
o-Nitroaniline

Manufacturing Process

6.5 grams of thiazole-4-carboxylic acid is stirred with 5.9 grams of thionyl chloride in 20 ml xylene for 10 hours at room temperature to form 4-thiazolyl acid chloride. 1.3 grams of 4-thiazolyl acid chloride and 1.3 grams of o-nitroaniline are then stirred together in 3.5 ml of pyridine at room temperature for about 12 hours. At the end of this time, the mixture is quenched in ice water and the solid nitroanilide recovered by filtration and washed with dilute sodium carbonate solution. The solid is suspended in 15 ml of glacial acetic acid, and 8 ml of 6 N hydrochloric acid added to the suspension. 6 grams of zinc dust is added in small portions to the acetic mixture. After the zinc addition is complete, and the reaction is essentially finished (by visual observation), the reaction mixture is filtered and the filtrate neutralized with concentrated ammonium hydroxide to precipitate 2-(4'-thiazolyl)-benzimidazole. The product is purified by recrystallization from ethyl acetate, according to US Patent 3,274,207.

References

Merck Index 9126
PDR p. 1200
OCDS Vol. 1 p. 325 (1977)
DOT 7 (5) 195 (1971)
REM p. 1237
Sarett, L.H. and Brown, H.D.; US Patent 3,017,415; January 16, 1962; assigned to Merck & Co., Inc.
Kaufman, A. and Wildman, G.T.; US Patent 3,262,939; July 26, 1966; assigned to Merck & Co., Inc.
Kollonitsch, J.; US Patent 3,274,207; September 20, 1966; assigned to Merck & Co., Inc.
Jones, R.E. and Gal, G.; US Patent 3,274,208; September 20, 1966; assigned to Merck & Co., Inc.

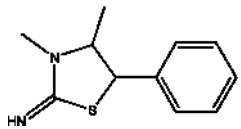
THIADRINE

Therapeutic Function: Anti-asthmatic, Antitussive

Chemical Name: 2-Imino-3,4-dimethyl-5-phenylthiazolidine

Common Name: Thiadrine; Priatan

Structural Formula:



Chemical Abstracts Registry No.: 14007-67-1

Trade Name	Manufacturer	Country	Year Introduced
Thiadrine	Sandoz A.G.	-	-

Raw Materials

Ammonium thiocyanate
Carbonate potassium or sodium
Hydrochloric acid
Racemic 1-phenyl-1-chloro-2-methylaminopropane hydrochloride

Manufacturing Process

1.5 kg of racemic 1-phenyl-1-chloro-2-methylaminopropane hydrochloride are suspended in 6 L of ethyl alcohol together with 1.15 kg of ammonium thiocyanate and 25 g of dry carbonate potassium or sodium and the reaction mixture is heated at a reflux condenser for 2 hours. The reaction product

having cooled down the precipitate which has formed and is composed of 3,4-dimethyl-5-phenyl-2-iminothiazolidine thiocyanate and ammonium chloride is extracted with water in order to remove the ammonium chloride. The remaining salt of the thiazolidine is recrystallized from hot water. The thiocyanate of the base melts in the pure state at 190-192°C. The yield amounts to about 80% of the theoretical yield.

The free base is precipitated by adding an alkali to the aqueous solution of the dimethylphenyliminothiazolidine thiocyanate. The free base is an oil which can be converted into its hydrochloride by dissolving the oil in ethyl alcohol, drying the solution and treating it with hydrochloric acid dissolved in ethyl alcohol. The hydrochloride has the melting point of 222-224°C.

References

Jucker E., Ehnoether A., Lindenmann A.; US Patent No. 2,558,068; Sept. 1959; Assigned to Sandoz A.G., Basel, Switzerland

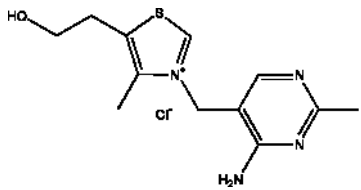
THIAMINE CHLORIDE

Therapeutic Function: Enzyme cofactor vitamin, Antineuritic

Chemical Name: Thiazolium, 3-((4-amino-2-methyl-5-pyrimidinyl)methyl)-5-(2-hydroxyethyl)-4-methyl- chloride

Common Name: Aneurine; B1-Vitamin; Oryzanin; Thiamine chloride; Torulin

Structural Formula:



Chemical Abstracts Registry No.: 59-43-8

Trade Name	Manufacturer	Country	Year Introduced
Thiamine chloride	Sopharma	-	-
Vitamin B1	GreatVista Chemicals	-	-
Thiamilate	Tyson Neutraceuticals	-	-
Bethamine	Ampharco Inc.	-	-
B1 Caps	Twinlab Corporation	-	-

Raw Materials

3-Ethoxypropionitrile Diethoxymethoxy-ethane

Acetamidine	Hydrobromic acid
Silver chloride	5-(2-Hydroxyethyl)-4-methylthiazole
Malononitrile	Hydrogen peroxide

Manufacturing Process

2 Methods of preparation of thiamine:

1. 3-Ethoxypropionitrile reacted with diethoxymethoxy-ethane and 3-ethoxy-2-methoxymethylenpropionitrile was obtained.

Then to the 3-ethoxy-2-methoxymethylenpropionitrile acetamidine was added and reaction mixture was stirred to give 4-amino-5-ethoxy-methyl-2-methylpyrimidine.

The 4-amino-5-ethoxy-methyl-2-methylpyrimidine was treated by hydrobromic acid to afford 4-amino-5-bromomethyl-2-methylpyrimidine hydrobromide.

The 4-amino-5-bromomethyl-2-methylpyrimidine hydrobromide reacted with 5-(2-hydroxyethyl)-4-methylthiazole in the presence of hydrobromic acid and as the result thiaminbromide was produced. For changing of the thiaminbromide to the thiamincloride the thiaminbromide was treated by AgCl.

2. To diethoxymethoxy-ethane malononitrile was added and ethoxymethylen-malononitrile was obtained. The ethoxymethylen-malononitrile reacted with acetamidine as a result 4-amino-5-cyano-2-methylpyrimidine was produced, which was reduced by H_2/Raney-Ni to 4-amino-5-aminomethyl-2-methylpyrimidine.

To the 4-amino-5-aminomethyl-2-methylpyrimidine 1-acetoxy-3-chloropentan-4-one was added in the presence CS_2 and NH_3, and reaction mixture was stirred, then to this mixture hydrochloric acid was added and thiamin (base) was obtained.

To thiamin (base) H_2O_2 and hydrocloricum acid are added, in the result reaction the thiamine chloride was obtained.

References

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

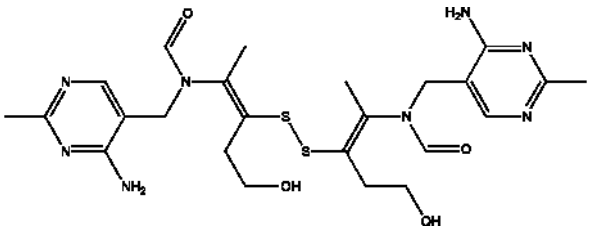
THIAMINE DISULFIDE

Therapeutic Function: Enzyme cofactor vitamin

Chemical Name: N,N'-[Dithiobis[2-(2-hydroxyethyl)-1-methylvinylene]]bis[N-[(4-amino-2-methyl-5-pyrimidinyl)methyl]formamide]

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 67-16-3

Trade Name	Manufacturer	Country	Year Introduced
Arcalion	Servier	France	1974

Raw Materials

Thiamine
Potassium ferricyanide

Manufacturing Process

20 parts by weight of thiamin are dissolved in 25 parts of water, a cold solution of 5 parts by weight of caustic soda in 25 parts of water added and the mixture oxidized with a solution of 2.4 parts by weight of caustic soda and 20 parts by weight of potassium ferric cyanide in 80 parts of water while stirring in the cold. The liquid is then evaporated to dryness and the resulting oxidation product extracted with warm butyl alcohol.

The butyl-alcoholic solution is evaporated in vacuo and the residue dissolved with gentle heating in 25 parts by volume of methyl alcohol. 100 parts by volume of acetone are added, the solution filtered and further quantities of acetone added, whereupon crystallization sets in. Yield: 12.2 parts by weight of the pure product, having the melting point 177° to 179°C.

References

Merck Index 9130
I.N. p. 941
Warnat, K.; US Patent 2,458,453; January 4, 1949; assigned to Hoffmann-La Roche Inc.

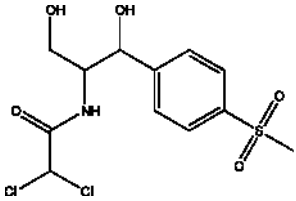
THIAMPHENICOL

Therapeutic Function: Antibacterial

Chemical Name: D-Threo-2,2-dichloro-N-[β-hydroxy-α-(hydroxymethyl)-p-methylsulfonylphenethyl]-acetamide

Common Name: Dextrosulphenidol; Thiophenicol

Structural Formula:



Chemical Abstracts Registry No.: 15318-45-3

Trade Name	Manufacturer	Country	Year Introduced
Thiophenicol	Clin Midy	France	1967
Chlomic J	Kowa Shinyaku	Japan	-
Descocin	Kanto	Japan	-
Efnicol	Nichiiko	Japan	-
Ericol	S.S. Pharm	Japan	-
Glitisol Orale	Zambon	Italy	-
Hyrazin	Kowa	Japan	-
Igralin	Zeria	Japan	-
Macphenicol	Nakataki	Japan	-
Masatirin	Maruko	Japan	-
Namicain	Nippon Kayaku, Co.	Japan	-
Neomyson	Eisai	Japan	-
Racenicol	Kissei Pharmaceutical Co., Ltd.	Japan	-
Rigelon	Dojin	Japan	-
Rincrol	Tanabe	Japan	-
Roseramin	Takata	Japan	-
Synticol	Nisshin	Japan	-
Thiamcetin	Mochida	Japan	-
Thiamcol	Morishita	Japan	-
Thiamyson	Ohta	Japan	-
Thiancol	Kakenyaku Kako	Japan	-
Thiofact	Showa	Japan	-
Thionicol	Mohan	Japan	-
Thiotal	Sumitomo	Japan	-
Tiozon	Mitsui	Japan	-
Unaseran-D	Isei	Japan	-
Urfamycine	Zambon	Italy	-
Urophenyl	Sanwa	Japan	-

Raw Materials

2-Acetylamino-1-(4-methylmercaptophenyl)-1,3-propanediol

Hydrogen chloride
Ethyl dichloroacetate
Peracetic acid

Manufacturing Process

A mixture of 50 parts by weight of racemic 2-acetylamino-1-(4-methylmercaptophenyl)-1,3-propanediol, 100 parts by weight of concentrated hydrochloric acid, and 500 parts by weight of water was warmed on a steam bath for thirty minutes. The resulting solution was cooled to about 40°C and was then made strongly alkaline by addition of 35% aqueous sodium hydroxide solution. The alkaline solution was then refrigerated. The white solid which separated from the cooled solution was collected on a filter. There was thus obtained 27 parts by weight of 2-amino-1-(4-methylmercaptophenyl)-1,3-propanediol. This product melted at 130.7°C to 131.9°C after recrystallization from methanol.

This compound was converted to the tartrate and the optical isomers were resolved.

A mixture of 1.1 g of 2-amino-1-(4-methylmercaptophenyl)-1,3-propanediol, obtained as described above and 1.6 ml of ethyl dichloroacetate was heated on a steam bath for three hours. The resulting viscous yellow oil was dissolved in 25 ml of ethylene chloride and filtered hot with charcoal, and the filtrate was allowed to cool to about 25°C. From the filtrate there separated 0.92 g of tiny white leaflets which were collected on a filter. Recrystallization of this product, which was a dextro-rotary form of 2-dichloroacetylamino-1-(4-methylmercaptophenyl)-1,3-propanediol from nitroethane yielded the pure product, which melted at 111.6°C to 112.6°C.

7 g of the 2-dichloroacetylamino-1-(4-methylmercaptophenyl)-1,3-propanediol obtained as described above was dissolved in 30 ml of acetone. To this solution there was added dropwise with stirring 10 ml of 40% peracetic acid. The temperature during the reaction was maintained at 39°C to 45°C by cooling the reaction vessel. After stirring the mixture for two hours, it was diluted with 100 ml of water and the solution allowed to stand over the weekend in the refrigerator. The solid which separated from solution was collected on a filter, washed several times with ice water, and dried overnight at 70°C.

References

Merck Index 9140
Kleeman and Engel p. 874
OCDS Vol. 2 p. 45 (1980)
I.N. p. 942
Suter, C.M.; US Patent 2,759,976: August 21, 1956; assigned to Sterling Drug, Inc.
Parke, Davis and Co.; British Patent 770,277; March 20, 1957

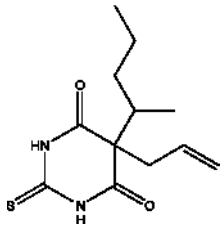
THIAMYLAL

Therapeutic Function: Anesthetic

Chemical Name: Dihydro-5-(1-methylbutyl)-5-(2-propenyl)-2-thioxo-4,6(1H,5H)-pyrimidinedione

Common Name: Thioseconal

Structural Formula:



Chemical Abstracts Registry No.: 77-27-0

Trade Name	Manufacturer	Country	Year Introduced
Surital	Parke Davis	US	1951
Citosol	Kyorin	Japan	-
Isozol	Yoshitomi	Japan	-

Raw Materials

Sodium
Diethyl allyl-(1-methylbutyl)malonate
Methanol
Thiourea

Manufacturing Process

In 450 cc of methanol is added 47 grams of sodium metal and the mixture allowed to completely react to form a methanol solution of sodium methoxide. The methanol solution of sodium methoxide is then cooled to 60°C and 68 grams of thiourea which has been thoroughly dried is added with stirring until a uniform solution is formed. Thereafter, 157 grams of diethyl allyl-(1-methylbutyl)malonate is added to the solution of the sodio derivative of thiourea at a temperature of 55°C and the condensation reaction mixture maintained at the said temperature for 24 hours. Methyl alcohol is removed under vacuum during the course of the reaction while maintaining a temperature of 55°C.

The viscous reaction mixture is then poured into 1.5 liters of ice water and agitated to form a uniform solution. The solution is treated with activated carbon and filtered. Thereafter, 80% acetic acid is added until the filtered solution remains acidic to litmus. The precipitate formed is filtered and washed thoroughly with distilled water. The product is air-dried at a

temperature of 95° to 100°C for 48 hours to yield 133 grams of 5-allyl-5-(1-methylbutyl)-2-thiobarbituric acid having a melting point of 132° to 133°C and assaying at 99.5% pure, from US Patent 2,876,225.

References

Merck Index 9141
Kleeman and Engel p. 875
OCDS Vol. 1 p. 274 (1977)
I.N. p. 942
REM p. 1046
Volwiler, E.H. and Tabern, D.L.; US Patent 2,153,729; April 11, 1939; assigned to Abbott Laboratories
Donnison, G.H.; US Patent 2,876,225; March 3, 1959; assigned to Abbott Laboratories

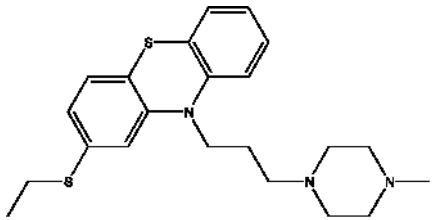
THIETHYLPERAZINE

Therapeutic Function: Antiemetic

Chemical Name: 2-(Ethylthio)-10-[3-(4-methyl-1-piperazinyl)propyl] phenothiazine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 1420-55-9; 52239-63-1 (Maleate)

Trade Name	Manufacturer	Country	Year Introduced
Torecan	Boehringer Ingelheim	US	1961
Torecan	Sandoz	Italy	1962
Torecan	Sandoz	France	1962
Torecan	Sandoz	UK	1962
Torecan	Sandoz	W. Germany	1964
Toresten	Sandoz-Sankyo	Japan	-

Raw Materials

Sodium amide 3-Ethylmercapto-phenothiazine
1-Methyl-4-(3'-chloropropyl-1')-piperazine

Manufacturing Process

26.1 parts of 3-ethylmercapto-phenothiazine (melting point 95°C to 97°C), 4.7 parts of finely pulverized sodium amide and 120 parts by volume of absolute xylene are heated to boiling for two hours, under reflux and while stirring the reaction mixture, at an oil-bath temperature of 180°C. Without interrupting the heating, a solution of 20.0 parts of 1-methyl-4-(3'-chloropropyl-1')-piperazine (boiling point 95°C to 97°C at a pressure of 10 mm Hg) in 20 parts by volume of xylene is added dropwise in the course of 1 1/2 hours. After heating 3 more hours, the reaction mixture is cooled and 10.0 parts of ammonium chloride added; the mixture is then shaken out three times, using 50 parts by volume of water each time. The xylene solution is extracted with 250 parts by volume of aqueous tartaric acid of 15% strength, after which the tartaric acid extract is washed with 80 parts by volume of benzene and then rendered phenolphthalein-alkaline by the addition of 60 parts by volume of concentrated aqueous caustic soda solution. The base which precipitates is taken up in a total of 150 parts by volume of benzene; the benzene layer is dried over potassium carbonate and is then evaporated under reduced pressure. The residue from the evaporation is distilled in a high vacuum. After separating a preliminary distillate which passes over up to 226°C under a pressure of 0.01 mm Hg the main fraction - 3-ethylmercapto-10-[3'-(1''-methyl-piperazyl-4'')-propyl-1']-phenothiazine - which distills at 226°C to 228°C under the last-mentioned pressure is collected. The analytically pure base boils at 227°C under a pressure of 0.01 mm Hg and melts at 62°C to 64°C.

Upon the addition of ethanolic HCl to a solution, cooled to 0°C, of 26.38 parts of the free base in 130 parts by volume of absolute ethanol, until a Congo-acid reaction is achieved, the crystalline dihydrochloride of 3-ethylmercapto-10-[3'-(1''-methyl-piperazyl-4'')-propyl-1']phenothiazine is precipitated. The analytically pure salt has a melting point of 214°C to 216°C (bubbles); it begins to sinter at 205°C. The dimaleate melts at 188°C to 190°C after sintering from 180°C (recrystallized from methanol).

References

Merck Index 9151
Kleeman and Engel p. 875
PDR p. 683
OCDS Vol. 1 p. 382 (1977)
DOT 9 (6) 228 (1973)
I.N. p. 943
REM p. 810
Renz, J., Bourquin, J.P., Gamboni, G. and Schwarb, G.; US Patent 3,336,197; August 15, 1967; assigned to Sandoz, Ltd. (Switz.)

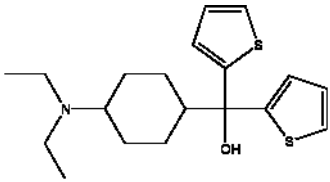
THIHEXINOL

Therapeutic Function: Anticholinergic

Chemical Name: α-[4-(Diethylamino)cyclohexyl]-α-2-thienyl-2-thiophene-methanol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 53626-54-3

Trade Name	Manufacturer	Country	Year Introduced
Sorboquel	Schering	US	1960
Entoquel	White	US	1961

Raw Materials

Formaldehyde
Magnesium
2-Bromothiophene
Ethyl-p-aminobenzoate
Hydrogen

Manufacturing Process

The requisite intermediate, ethyl 4-dimethylaminocyclohexylcarboxylate is prepared as follows: 33 g of ethyl p-aminobenzoate dissolved in 300 cc of absolute ethanol containing 16.8 cc of concentrated hydrochloric acid is hydrogenated at 50 pounds hydrogen pressure in the presence of 2 g of platinum oxide. The theoretical quantity of hydrogen is absorbed in several hours, the catalyst removed by filtration and the filtrate concentrated to dryness in vacuo. The residue is dissolved in water, made alkaline with ammonium hydroxide and extracted with chloroform. After removal of the solvent, the residual oil is distilled to yield ethyl 4-aminocyclohexylcarboxylate, boiling point 114°C to 117°C/10 mm.

A mixture of 49 g of this ester compound, 76 g of 98% formic acid and 68 ml of formalin solution is heated under reflux for 8 hours. The solvents are then removed in vacuo on the steam bath, the residue dissolved in water, made alkaline with ammonium hydroxide and extracted with chloroform. Removal of the solvent and distillation in vacuo yields ethyl 4-dimethylaminocyclohexylcarboxylate, boiling point 122°C to 125°C/10 mm.

To a solution of thienyl magnesium bromide prepared from 21.4 g of magnesium and 144 g of 2-bromothiophene are added 39.8 g of ethyl 4-dimethylaminocyclohexylcarboxylate. The mixture is allowed to warm to room temperature and stirred for an additional six hours. The reaction mixture is then decomposed with dilute ammonium chloride solution and extracted with ether. The combined ether extracts are extracted thoroughly with 10% hydrochloric acid and the acid solution made alkaline with ammonium

hydroxide. The aqueous solution is extracted with chloroform which is then washed with water, dried and evaporated to a residue in vacuo. Recrystallization of the residue from hexane yields α,α^1-dithienyl-4-dimethylaminocyclohexyl carbinol, melting point 156°C to 157°C after recrystallization from benzene.

References

Merck Index 9152
I.N. p. 943
Villani, F.J.; US Patent 2,764,519; September 25, 1956; assigned to Schering Corp.

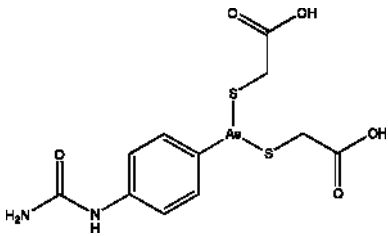
THIOCARBARSONE

Therapeutic Function: Antiamebic

Chemical Name: 2,2'-[[[4-[(Aminocarbonyl)amino]phenyl]arsinidene] bis(thio)]bis[acetic acid]

Common Name: Thio-carbamisin

Structural Formula:



Chemical Abstracts Registry No.: 120-02-5

Trade Name	Manufacturer	Country	Year Introduced
Thiocarbarsone	Lilly	US	1951

Raw Materials

Thioglycolic acid
Carbarsone oxide

Manufacturing Process

121 g of thioglycolic acid and 100 g of carbarsone oxide are reacted in a solution of 128 g of sodium bicarbonate in 2 liters of water.

The mixture is heated on a steam bath for 20 minutes. The reaction mixture

is then cooled and filtered to remove a small amount of insoluble material. The filtrate is diluted with about 600 cc of water and is acidified with concentrated hydrochloric acid.

On treating the reaction mixture with acid, di-(carboxymethylthio)-p-carbamidophenylarsine precipitates, and is separated by filtration and dried.

Di -(carboxymethylthio)-p-carbamidophenylarsine thus prepared was obtained as a white amorphous solid, soluble in dilute alkali. It contained about 19.85% of arsenic as compared with the calculated amount of 19.09%.

References

Merck Index 9162
I.N. p. 944
Rohrmann, E.; US Patent 2,516,831; July 25, 1950; assigned to Eli Lilly & Co.

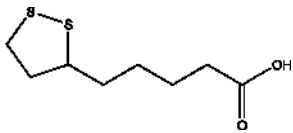
THIOCTIC ACID

Therapeutic Function: Growth factor, Lipotropic, Detoxicant

Chemical Name: 1,2-Dithiolane-3-pentanoic acid

Common Name: Acetate replacing factor; Acidum lipoicum; Acidum thiocticum; Lipoic acid; Pyruvate oxidation factor; Thioctic acid; Tioctic acid

Structural Formula:



Chemical Abstracts Registry No.: 1077-28-7

Trade Name	Manufacturer	Country	Year Introduced
Neurium	Hexal	-	-
Thioctic acid	Antibioticos S.p.A.	-	-
Thioctacid 300	ASTA Medica AG	-	-
Thiogamma	Worwag Pharma GmbH and Co	-	-

Raw Materials

Aluminum chloride
Ethylene
Potassium hydroxide
Hydrochloric acid
Ethyl 8-chloroformylvalerate
Thiolacetic acid
Ethyl-6,8-dibromooctanoate
Iodoform

Ethyl 6,8-diacetyl-mercaptooctanoate

Manufacturing Process

To a suspension of 106 g of anhydrous aluminum chloride in 450 ml of carbontetrachloride is added dropwise, with vigorous stirring, 70 g of ethyl 8-chloroformylvalerate (H. Bergs, C. Wittfeld and H. Frank, Ber., 67B, 1622 (1947)). The temperature is maintained at 25°C. The cooling bath is removed and ethylene is passed in for a period of 2 hours. The reaction mixture is poured onto cracked ice, the organic layer separated, and the aqueous layer extracted with 200 ml of chloroform. The combined organic extracts are dried over anhydrous sodium sulfate and the solvent removed in vacuo. The dark colored oil remaining, crude ethyl 8-chloro-6-oxooctanoate is distilled in vacuo through a 6 in. Vigreaux column. After small forerun, the main fraction, 48-54 g (72-80%), B.P. 112-114°C (2 mm.); n^{25}_{D}1-4485, is collected.

Redistilled thiolacetic acid (14.7 g) is cooled in an ice-bath and neutralized to the phenolphthalein end-point with a 10% solution of potassium hydroxide in ethanol (approximately 135 ml required). To this solution is added 29 g of ethyl-6,8-dibromooctanoate and the mixture is stirred and heated under reflux in an atmosphere of nitrogen for 5 hours. The reaction mixture, which contains ethyl 6,8-diacetyl-mercaptooctanoate, is cooled and 35 g of potassium hydroxide (85%) is added. The reaction mixture is stirred at room temperature in an atmosphere of nitrogen for 17 hours, then acidified (pH less than 1) with 6 N hydrochloric acid. Ethanol is removed in vacuo, sufficient water is added to dissolve the inorganic solids and the mixture is extracted with two 150 ml portions of chloroform. To the combined organic extracts, which contain 6,8-dimercaptooctanoic acid , is added 575 ml of chloroform and 210 ml of water. This mixture is stirred vigorously in an atmosphere of nitrogen While sufficient iodoform reagent (R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," 2nd. Ed., John Wiley and Sons, New York, N.Y., 1940, p. 53) is added dropwise during a 6 hour period to give a permanent brown color. Approximately 185 ml of iodoform reagent is required. The organic layer is separated, washed with 500 ml of 1% sodium thiosulfate solution, and then extracted with two 250 ml portions of 5% sodium bicarbonate solution. The aqueous extracts are acidified (pH less than 1) with 6 N hydrochloric acid and extarcted with two 125 ml portions of chloroform. The combined chloroform extracts are dried over anhydrous sodium sulfate and the solvent is then removed in vacuo. The yellow viscous oil remaining solidifies when cooled and scratched. This solid material is extracted with three 300 ml portions of boiling Skelly B solvent (essentially n-hexane). The combined extracts are seeded with crystalline DL-α-lipoic acid and allowed to stand at room temperature overnight and then in a refrigerator for several hours. Large yellow crystals separate, M.P. 60.5-61.5°C. The yield of product is 10.8-12.3 g (60-68%). 1,2-Dithiolane-3-pentanoic acid was recrystallized from Skelly B solvent, M.P. 61-62°C.

References

Lester J. Reed; US Patent No. 2,980,716; June 11, 1954; Assigned to Research Corporation, New York, N.Y., a corporation of New York

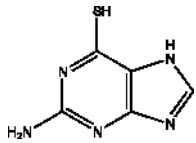
THIOGUANINE

Therapeutic Function: Cancer chemotherapy

Chemical Name: 2-Aminopurine-6-thiol

Common Name:-

Structural Formula:



Chemical Abstracts Registry No.: 154-42-7

Trade Name	Manufacturer	Country	Year Introduced
Thioguanine Tabloid	Burroughs-Wellcome	US	1966
Lanvis	Wellcome	UK	1972
Thioguanine Wellcome	Burroughs-Wellcome	Italy	1974
Thioguanin Wellcome	Burroughs-Wellcome	W. Germany	1975

Raw Materials

Guanine
Phosphorus pentasulfide

Manufacturing Process

A mixture of 2.7 grams of finely divided guanine, 10 grams of pulverized phosphorus pentasulfide, 10 ml of pyridine and 100 ml of tetralin was heated at 200°C with mechanical stirring for 5 hours. After cooling, the mixture was filtered and the insoluble residue treated with 150 ml of water and 50 ml of concentrated ammonium hydroxide. The ammoniacal solution was filtered, heated to boiling and acidified with acetic acid. Upon cooling, 2-amino-6-mercaptopurine precipitated as a dark yellow powder, according to US Patent 2,697,709.

References

Merck Index 9177
Kleeman and Engel p. 892
PDR p. 765
OCDS Vol. 2 p. 464 (1980)
I.N. p. 954
REM p. 1153

Hitchings, G.H. and Elion, G.B.; US Patent 2,697,709; December 21, 1954; assigned to Burroughs Wellcome & Co. (U.S.A.) Inc.
Hitchings, G.H. and Elion, G.B.; US Patent 2,800,473; July 23, 1957; assigned to Burroughs Wellcome & Co. (U.S.A.) Inc.
Hitchings, G.H. and Elion, G.B.; US Patent 2,884,667; May 5, 1959
Hitchings, G.H., Elion, G.B. and Mackay, L.E.; US Patent 3,019,224; January 30, 1962; assigned to Burroughs Wellcome & Co. (U.S.A.) Inc.
Hitchings, G.H., Elion, G.B. and Goodman, I.; US Patent 3,132,144; May 5, 1964; assigned to Burroughs Wellcome & Co. (U.S.A.) Inc.

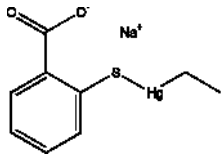
THIOMERSAL

Therapeutic Function: Antiseptic, Pharmaceutic aid

Chemical Name: Mercury, ethyl(2-mercaptobenzoato-S)-, sodium salt

Common Name: Mercurothiolate sodique; Sodium ethylmercurithiosalicylate; Thimerosal; Thiomerosol; Thiomersal; Thiomersalate

Structural Formula:



Chemical Abstracts Registry No.: 54-64-8

Trade Name	Manufacturer	Country	Year Introduced
Timeolate	Lifar	-	-
Mersol	Century	-	-
Vitaseptol	Novartis Pharma	-	-

Raw Materials

Methyl mercuric chloride
Sodium hydroxide
Thiosalicylic acid

Manufacturing Process

To a solution or suspension in alcohol of 0.1 mole of methyl mercuric chloride is added 0.1 mole of sodium hydroxide in water and 0.1 mole of thiosalicylic acid in ethanol. The product is poured into water, whereupon; the methyl mercurithiosalicylic acid is precipitated, since it is insoluble in water. This precipitate can be collected on a filter, and washed well with water to remove all the alcohol, salts, and free inorganic acids. The washed precipitate may then be dissolved in a water solution of sodium hydroxide, or, better, in a water solution of sodium bicarbonate. This produces the water-soluble salt of the methyl mercurithiosalicylic acid.

The methyl mercurithiosalicylic acid is a white solid which melts at about 171°C. It is soluble in alcohol and in ether. It is soluble in either sodium bicarbonate or sodium hydroxide solution, to form the corresponding salt; which is suitable for intravenous injection.

The alkali metal salts, such as the sodium and potassium salts, of this acid, are readily a soluble in water; so are its ammonium salts, and many (probably all) of its alkyl-ammonium salts; but the alkaline earth salts, such as the calcium salt, are insoluble in water.

References

Moris-Selik Khrash; US Patent No. 1,672,615; June 5, 1928; College Park, Maryland

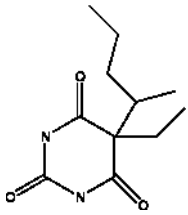
THIOPENTAL

Therapeutic Function: Narcotic analgesic, Anesthetic

Chemical Name: 4,6,(1H,5H)-Pyrimidinedione, 5-ethyldihydro-5-(1-methylbutyl)-2-thioxo-

Common Name: 5-Ethyl-5-(1-methylbutyl)-2-thiobarbituric acid; Thiomebumal

Structural Formula:



Chemical Abstracts Registry No.: 76-75-5

Trade Name	Manufacturer	Country	Year Introduced
Pentothal	Abbott	-	-
Pental	Ibrahim Ethem	-	-
Tiobarbital	Miro	-	-

Raw Materials

Sodium ethylate
Ethyl (1-methylbutyl)malonic ester
Thiourea
Ammonium hydroxide

Manufacturing Process

130 g of ethyl (1-methylbutyl) malonic ester is added to a concentrated solution of sodium ethylate prepared from 34 g of sodium in absolute alcohol; with stirring, 60 g of finely divided thiourea is added, and, the mixture refluxed for 10 hours. Most or all of the solvent is evaporated and the residual mass is dissolved in cold water. The barbituric acid derivative so formed is precipitated by the addition of dilute hydrochloric acid. It may be 1 purified by solution in dilute ammonium hydroxide solution and precipitated by carbon dioxide, followed by recrystallization from 95% alcohol. The ethyl (1-methylbutyl)thiobarbituric acid so obtained is a white crystalline solid, melting at 158-159°C and readily forming salts with alkalies.

References

Ernest H. Volwiler, Donalee L. Tabern; US Patent No. 2,153,729; Apr. 11, 1939; Assigned to Abbott Laboratories, North Chicago, EL, a corporation of Illinois

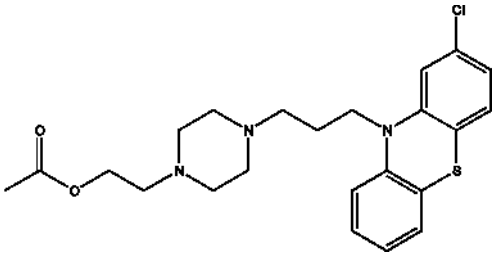
THIOPROPAZATE

Therapeutic Function: Antipsychotic

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

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 84-06-0; 146-28-1 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Dartal	Searle	US	1957
Dartalan	Searle	UK	-
Vesitan	Boehringer Mannheim	W. Germany	-

Raw Materials

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

Piperazine
β-Bromoethyl acetate

Manufacturing Process

A mixture of 155 parts of 2-chloro-10-(γ-chloropropyl)phenothiazine, 75 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 extracted with ether. This ether 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-piperazinopropyl)phenothiazine at about 214°C to 218°C.

A mixture of 50 parts of the distillate, 25.6 parts of β-bromoethyl acetate, 10.7 parts of potassium carbonate and 400 parts of toluene is stirred at reflux temperature for 16 hours. The mixture is heated with water. The organic layer is separated, washed with water and extracted with dilute hydrochloric acid. The resulting extract is washed with benzene, rendered alkaline and extracted with benzene. The resulting benzene solution is dried over anhydrous potassium carbonate, filtered and concentrated. The residue is dissolved in 300 parts of ethanol and treated with 2.2 equivalents of a 25% solution of anhydrous hydrochloric acid in 2-propanol. The resulting crystals are recrystallized from 400 parts of ethanol and 10 parts of water. The dihydrochloride of N-(β-acetoxyethyl)-N'-[γ-(2'-chloro-10'-phenothiazine)propyl]piperazine melts unsharply at about 200°C to 230°C.

References

Merck Index 9198
Kleeman and Engel p. 878
OCDS Vol. 1 p. 383 (1977)
I.N. p. 946
Cusic, J.W.; US Patent 2,766,235; October 9, 1956

THIOPROPERAZINE

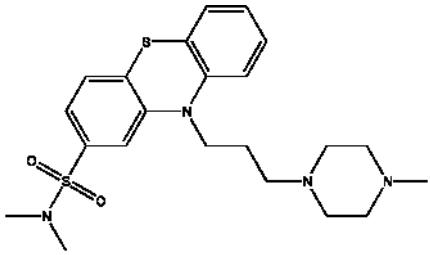
Therapeutic Function: Neuroleptic, Antiemetic

Chemical Name: N,N-Dimethyl-10-[3-(4-methyl-1-piperazinyl)propyl]-phenothiazine-2-sulfonamide

Common Name: Thioperazine

Chemical Abstracts Registry No.: 316-81-4

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Majeptil	Specia	France	1960
Cephalmin	Shionogi	Japan	-
Mayeptil	Rhodia Pharma	W. Germany	-
Vontil	S.K.F.	US	-

Raw Materials

3-Dimethylsulfamoylphenothiazine
3-(4-Methyl-1-piperazinyl)-1-chloropropane
Sodium amide

Manufacturing Process

A solution of 3-dimethylsulfamoylphenthiazine (5 g) in anhydrous xylene (100 cc) is heated under reflux for 1 hour with sodamide (0.67 g). 3-(4-methyl-1-piperazinyl)-1-chloropropane (3.2 g) in solution in anhydrous xylene (20 cc) is added and the mixture heated under reflux for 5 hours. After treatment of the reaction products, a crude oily base (2.5 g) is obtained after treatment. By the addition of a solution of fumaric acid in ethanol to an ethanolic solution of the base, 3-dimethylsulfamoyl-10-(3-41-methyl-11-piperazinylpropyl)-phenthiazinediacid fumarate (2.6 g) is obtained, melting point 182°C. The base recrystallized from ethyl acetate melts at about 140°C.

References

Merck Index 9199
Kleeman and Engel p. 879
I.N. p. 946
Soc. des Usines Chimiques Rhone-Poulenc; British Patent 814,512; June 3, 1959

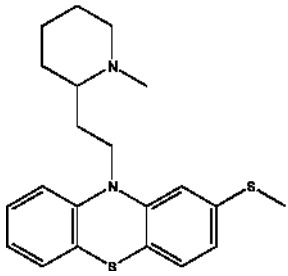
THIORIDAZINE

Therapeutic Function: Tranquilizer

Chemical Name: 10-[2-(1-Methyl-2-piperidyl)ethyl]-2-(methylthio) phenothiazine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 50-52-2; 130-61-0 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Mellaril	Sandoz	US	1959
Mellaril	Sandoz	France	1960
Baylaril	Bay	US	1983
Mellerette	Wander	Italy	-
Melleretten	Sandoz	W. Germany	-
Novoridazide	Novopharm	Canada	-
Orsanil	Orion	Finland	-
Ridazin	Taro	Israel	-
Stalleril	Pharmacal	Finland	-
Thioril	I.C.N.	Canada	-

Raw Materials

Sulfur	m-Methylmercaptoaniline
Iodine	2-(N-Methylpiperidyl-2')-1-chloroethane
Sodium amide	Potassium o-chlorobenzoate

Manufacturing Process

N-(m-methylmercapto-phenyl)-aniline (MP 59° to 61°C) is prepared by condensing m-methylmercapto-aniline (BP 163° to 165°C/16 mm Hg) with the potassium salt of o-chloro-benzoic acid and decarboxylating the resultant N-(m-methylmercapto-phenyl)-anthranilic acid (MP 139° to 141°C) by heating, and then distilling.

9.87 parts of N-(m-methylmercapto-phenyl)-aniline are heated with 2.93 parts of sulfur and 0.15 part of powdered iodine for 15 minutes in a bath at about 160°C. Upon termination of the ensuing evolution of hydrogen sulfide, animal charcoal is added to the reaction mixture and recrystallization carried out first from 40 parts by volume of chlorobenzene, and then from 25 to 30 parts by volume of benzene at the boiling temperature. The obtained citron-yellow 3-methylmercapto-phenothiazine has a MP of 138° to 140°C.

17.82 parts of 2-methylmercapto-phenothiazine, 3.4 parts of finely pulverized

sodamide and 80 parts by volume of absolute xylene are heated to boiling for two hours at a bath temperature of 180°C under a reflux condenser and while stirring the reaction mixture. Without interrupting the heating, a solution of 13.2 parts of 2-(N-methyl-piperidyl-2')-1chloro-ethane in 40 parts by volume of absolute xylene is then added dropwise in the course of 1 1/2 hours. After further heating for 3 hours, the reaction mixture is cooled and, after the addition of 5 parts of ammonium chloride, is shaken three times with water, using 25 parts by volume each time. The xylene solution is extracted once with 35 parts by volume of 3 normal acetic acid and then three times, each time with 15 parts by volume of the said acid, after which the acetic acid extract is washed with 60 parts by volume of ether and is then made phenolphthalein-alkaline by means of 25 parts by volume of concentrated aqueous caustic soda solution.

The precipitated oily base is taken up in a total of 100 parts by volume of benzene. The benzene layer, dried over potassium carbonate, is filtered and then evaporated under reduced pressure. The residue from the evaporation is distilled in a high vacuum; after separating a preliminary distillate which passes over up to 228°C under a pressure of 0.92 mm Hg, the principal fraction, 2-methylmercapto-10-[2'-(N-methyl-piperidyl-2'')-ethyl-1']phenothiazine, which distills over at 228° to 232°C under the last-mentioned pressure, is collected. The analytically pure base has a BP of 230°C/0.02 mm Hg.

References

Merck Index 9202
Kleeman and Engel p. 879
PDR pp. 1586, 1606
OCDS Vol. 1 p. 389 (1977)
DOT 9 (6) 227 (1973)
I.N. p. 946
REM p. 1090
Renz, J., Bourquin, J.P., Gamboni, G. and Schwarb, G.; US Patent 3,239,514; March 8, 1966; assigned to Sandoz Ltd., Switzerland

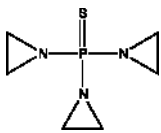
THIOTEPA

Therapeutic Function: Antineoplastic

Chemical Name: 1,1',1''-Phosphionothioylidynetrisaziridine

Common Name: Triethylenethiophosphoramide

Structural Formula:



Chemical Abstracts Registry No.: 52-24-4

Trade Name	Manufacturer	Country	Year Introduced
Thio-Tepa	Lederle	US	1959
Onca-Tiotepa	Simes	Italy	-
Tespamin	Somitomo	Japan	-

Raw Materials

Ethyleneimine
Thiophosphoryl chloride

Manufacturing Process

A solution of 30.3 parts of triethylamine and 12.9 parts of ethylenimine in 180 parts of dry benzene is treated with a solution of 16.9 parts of thiophosphoryl chloride in 90 parts of dry benzene at 5°C to 10°C. Triethylamine hydrochloride is filtered off. The benzene solvent is distilled from the filtrate under reduced pressure and the resulting crude product is recrystallized from petroleum ether. The N,N',N''-triethylenethiophosphoramide had a melting point of 51.5°C.

References

Merck Index 9484
Kleeman and Engel p. 880
PDR p. 1030
I.N. p. 946
REM p. 1156
Kun, E. and Seeger, D.R.; US Patent 2,670,347; February 23, 1954; assigned to American Cyanamid Co.

THIOTHIXENE

Therapeutic Function: Tranquilizer

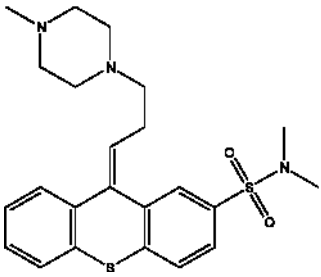
Chemical Name: (Z)-N,N-Dimethyl-9-[3-(4-methyl-1-piperazinyl) propylidene] thioxanthene-2-sulfonamide

Common Name: Tiotixen

Chemical Abstracts Registry No.: 3313-26-6

Trade Name	Manufacturer	Country	Year Introduced
Navane	Roerig	US	1967
Navane	Pfizer	UK	1967
Orbinamon	Pfizer	W. Germany	1968
Navane	Pfizer Taito	Japan	1970
Navane	Pfizer	Italy	1971

Structural Formula:



Raw Materials

Thioxanthene	Thionyl chloride
Butyl lithium	Paraformaldehyde
Sodium borohydride	Chlorosulfonic acid
Dimethylamine	Methyl acetate
1-Methylpiperazine	Phosphorus oxychloride

Manufacturing Process

Sodium Thioxanthene-2-Sulfonate: A solution of thioxanthene (32.2 grams, 0.160 mol) in 160 ml of chloroform was cooled to 0°C and chlorosulfonic acid (12.4 ml, 0.190 mol) added as rapidly as possible while maintaining the internal temperature below 10°C. After the addition was complete, the reaction mixture was allowed to approach room temperature during 30 minutes, then refluxed for an additional 20 minutes. The deep red solution was poured onto 100 grams of crushed ice and to convert the sulfonic acid to its sodium salt there was added 20 grams of sodium chloride. After filtering the slurry through a sintered glass funnel, the filter cake was washed with 50 ml of chloroform and 50 ml of 20% sodium chloride solution.

The crude sulfonate product was digested in 1,500 ml of boiling water, and filtered at the boiling point. Crystallization was allowed to proceed overnight at 4°C and after filtration and vacuum drying at 100°C, 33.3 grams (69%) of glistening, colorless plates were obtained.

2-Dimethylsulfamylthioxanthene: To a slurry of dry sodium thioxanthene-2-sulfonate (33.3 grams, 0.111 mol) in 50 ml of N,N-dimethylformamide was added thionyl chloride (14.3 grams, 0.122 mol) in divided portions. An exothermic reaction ensued with complete dissolution being effected in minutes. Treatment of the reaction mixture with crushed ice precipitated a gum which crystallized after a short period of stirring. The sulfonyl chloride was filtered, washed with water, and stirred with 100 ml of liquid dimethylamine. After allowing the mixture to evaporate to dryness, water was added and the sulfonamide filtered, washed with water, and dried in vacuo. The crude product (32.5 grams, 96%) obtained melts at 163.5° to 165°C. One crystallization from ethanol chloroform yielded an analytical sample, MP 164.5 to 166.5°C.

9-Acetyl-2-Dimethylsulfamylthioxanthene: A suspension of 2-dimethylsulfamylthioxanthene (12.22 grams, 0.04 mol) in 60 ml of

dimethoxymethane is cooled to 0°C and 17.2 ml of a 2.91 M solution of n-butyl lithium in heptane is added slowly in a nitrogen atmosphere while the temperature is maintained below 10°C. After an additional 10 minutes of stirring, the cooling bath is removed and a solution of 2.96 grams of methyl acetate in 20 ml of dimethoxyethane is added during 1/2 hour and then the mixture is stirred at 25°C for an additional 3 hours. The reaction mixture is then treated with 60 ml of ethyl acetate and with 60 ml of a 10% aqueous ammonium chloride solution. The layers are separated and the ethyl acetate layer is washed once with water (25 ml) and then the solvent is removed by distillation.

The product is purified by the method of Teitelbaum, J. Org. Chem., 23, 646 (1958). The gummy residue is treated with 7.8 grams of Girard's "T" reagent, a commercially available (carboxymethyl) trimethylammonium chloride hydrazide which can be prepared by the method described by Girard in Organic Syntheses, collective volume II, page 85 (1943). 0.2 grams of a methacrylic-carboxylic cation exchange resin of 20 to 50 mesh particle size, such as Amberlite IRC-50 (Rohm & Haas Co.) and 20 ml of ethanol. The mixture is refluxed for 1 hour, then is cooled to 25°C, is diluted with 80 ml of water and is filtered. The filtrate is stirred for 16 hours with 20 ml of aqueous formaldehyde and the product precipitates as a white solid, MP 118° to 123°C, net 5.6 grams, yield, 40% of the theoretical.

9-(3-Dimethylaminopropionyl)-2-Dimethylsulfamylthioxanthene: To a mixture of 9-acetyl-2-dimethylsulfamylthioxanthene (54.1 grams, 0.155 mol), 100 ml isopropanol, 10.6 grams paraformaldehyde and 16.4 grams (0.200 mol) dimethylamine hydrochloride, is added 1.0 milliliter of concentrated hydrochloric acid. The mixture is refluxed in a nitrogen atmosphere for 24 hours, then is concentrated to one-half volume by distillation of part of the solvent in vacuo. The concentrate is treated with 60 ml of ethyl acetate then the mixture is cooled to 5°C whereupon the crystalline product precipitates. This is removed by filtration and, after drying, weighs 47.8 grams, and melts at 177° to 181°C. After two crystallizations from isopropanol the product is obtained as the monohydrochloride addition salt, MP 187° to 189°C.

9-[3-(4-Methyl-1-Piperazinyl)-1-Hydroxypropyl]-2-Dimethylsulfamylthioxanthene: A mixture of 9-(3-dimethylaminopropionyl)-2-dimethylsulfamylthioxanthene hydrochloride (17 grams, 0.039 mol) and 20.0 grams (0.2 mol) 1-methylpiperazine in 40 ml of isopropanol is refluxed in a nitrogen atmosphere for 3 hours. 200 ml ethyl acetate is then added and the mixture is washed twice with 100 ml of water, the organic layer is separated and dried with anhydrous sodium sulfate, then the solvent is removed by distillation in vacuo. The 9-[3-(4-methyl-1-piperazinyl)propionyl]-2-dimethylsulfamylthioxanthene which remains as a residue is treated with a solution of 3.03 grams (0.08 mol) of sodium borohydride in 100 ml of ethanol. The mixture is refluxed under nitrogen for 3 hours, is cooled and is treated with an equal volume of water. The aminoalcohol is extracted 3 times with equal volumes of ethyl acetate. The organic layer is separated and is dried with anhydrous magnesium sulfate, then the solvent is removed by distillation leaving the product as a white, amorphous solid.

9-[3-(4-Methyl-1-Piperazinyl)-Propylidene]-2-Dimethylsulfamylthioxanthene: A solution of 12 grams of 9-[3-(4-methyl-1-piperazinyl)-1-hydroxypropyl]-2-dimethylsulfamylthioxanthene in 20 ml of pyridine is cooled to 0°C in an ice

bath and 18.4 ml of phosphorus oxychloride dissolved in 60 ml of pyridine is added dropwise. The mixture is allowed to warm to 25°C during 30 minutes, then is heated, immersed in an 80°C oil bath, for an additional 30 minutes. The dark brown reaction mixture is cooled to 25°C then is poured onto 50 grams of ice. After the ice has melted, the aqueous solution is saturated with potassium carbonate and the liberated oil is extracted with three 150 ml portions of ethyl acetate. The solvents are removed from the separated organic layer by distillation. The product, a light brown amorphous solid, remains as a residue from the distillation. The free base is dissolved in 50 ml of acetone, is treated with two stoichiometric equivalents of maleic acid in 50 ml of acetone and the white crystalline dimaleate salt is removed by filtration. There is obtained 12.3 grams, 47% yield, MP 158° to 160.5°C (after recrystallization from ethanol).

References

Kleeman and Engel p. 894
PDR p. 1528
OCDS Vol. 1 p.400 (1977) & 2,412 (1980)
DOT 4 (4) 163 (1968) & 9 (6) 229 (1973)
I.N. p. 955
REM p. 1091
Bloom, B.M. and Muren, J.F.; US Patent 3,310,553; March 21, 1967; assigned to Chas. Pfizer & Co., Inc.

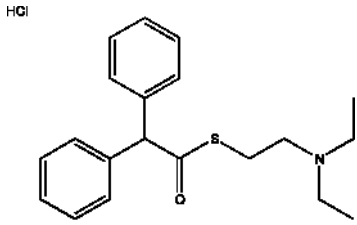
THIPHENAMIL HYDROCHLORIDE

Therapeutic Function: Spasmolytic

Chemical Name: α-Phenylbenzeneethanethioic acid S-[2-(diethylamino)ethyl] ester hydrochloride

Common Name: 2-Diethylaminoethyl diphenylthiolacetate hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 548-68-5; 82-99-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Trocinate	Poythress	US	1950

Raw Materials

2-Diethylaminoethanethiol
Diphenylacetyl chloride

Manufacturing Process

The following procedure is described in US Patent 2,510,773: To an ice-cold solution of 13.3 grams of 2-diethylaminoethanethiol in 100 cc of dry benzene is slowly added a solution of 23.05 grams of diphenylacetyl chloride in 200 cc of dry benzene. The mixture is stirred 2 hours, then heated to dissolve the fine white solid that is formed. Upon cooling 31.3 grams of 2-diethylaminoethyl diphenylthiolacetate hydrochloride precipitates. It recrystallizes from a mixture of benzene and petroleum ether (BP 60° to 70°C) as rosettes of tiny needles and melts at 129° to 130°C. From a mixture of absolute ethanol and ethyl acetate it recrystallizes as large, almost transparent prisms.

References

Merck Index 9215
REM p. 919
Richardson, A.G.; US Patent 2,390,555; December 11, 1945; assigned to William P. Poythress & Company, Inc.
Clinton, R.O.; US Patent 2,510,773; June 6, 1950; assigned to Sterling Drug Inc.

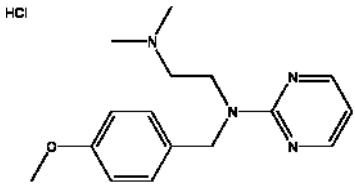
THONZYLAMINE HYDROCHLORIDE

Therapeutic Function: Antihistaminic

Chemical Name: N-[(4-Methoxyphenyl)methyl]-N,N'-dimethyl-N-2-pyrimidinyl-1,2-ethanediamine monohydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 63-56-9

Trade Name	Manufacturer	Country	Year Introduced
Neohetramine	Warner Lambert	US	1948
Anahist	Warner Lambert	US	1949
Tonamil	Ecobi	Italy	-

Raw Materials

2-(p-Methoxybenzyl)aminopyrimidine
Sodium amide
Dimethylaminoethyl chloride

Manufacturing Process

54 g of 2-(p-methoxybenzyl)aminopyrimidine and 12.0 g of sodamide were suspended in 250 cc of toluene and were refluxed for 31 hours. To the thus prepared sodium salt of 2-(p-methoxybenzyl)aminopyrimidine, 28.1 g of dimethylaminoethyl chloride were added and refluxed under continuous stirring for 26 hours. After cooling, the reaction mixture was extracted with dilute hydrochloric acid at about pH 5.0, removing the product thus formed containing only very little of the unreacted 2-(p-methoxybenzyl)aminopyrimidine. This solution was then made alkaline to liberate the free base of the product, which was extracted with ether. The ether solution was evaporated and the residue vacuum distilled. The product, 2-(p-methoxybenzyl-dimethylaminoethyl)aminopyrimidine forms an oily liquid, boiling point 185°C to 187°C at 2.2 mm.

References

Merck Index 9219
OCDS Vol. 1 p. 52 (1977)
I.N. p. 947
Friedman, H.L. and Tolstoouhov, A.V.; US Patent 2,465,865; March 29, 1949; assigned to Pyridium Corp.

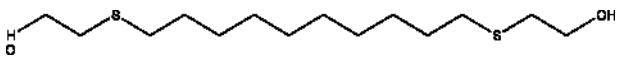
TIADENOL

Therapeutic Function: Antihyperlipidemic

Chemical Name: 2,2'-(Decamethylenedithio)diethanol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 6964-20-1

Trade Name	Manufacturer	Country	Year Introduced
Fonlipol	Lafon	France	1972
Tiaden	Malesci	Italy	1979
Braxan	Bago	Argentina	-
Delipid	Coop. Farm.	Italy	-
Eulip	Robin	Italy	-
Millaterol	Therapia	Spain	-
Tiaclar	C.I.	Italy	-
Tiodenol	Leti	Spain	-

Raw Materials

Thioethylene glycol
Decamethylene bromide

Manufacturing Process

Thioethylene glycol, $HSCH_2CH_2OH$ (prepared from ethylene oxide and hydrogen sulfide) is first reacted with sodium to give $HOCH_2CH_2SNa$.It is then reacted with decamethylene bromide, $Br(CH_2)_{10}Br$ to give tiadenol.

References

Merck Index 9263
Kleeman and Engel p. 881
DOT 8 (12) 454 (1972)
I.N. p. 948
Williams, J.L.R. and Cossar, B.C.; US Patent 3,021,215; February 13, 1962; assigned to Eastman Kodak Company

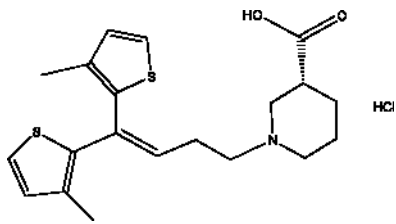
TIAGABINE HYDROCHLORIDE

Therapeutic Function: Antiepileptic

Chemical Name: 3-Piperidinecarboxylic acid, 1-(4,4-bis(3-methyl-2-thienyl)-3-butenyl)-, (R)-, hydrochloride

Common Name: Tiagabine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 145821-59-6; 115103-54-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Gabitril	Cephalon, Inc.	USA	-
Gabitril	David Bull Laboratories	-	-
Gabitril	Sanofi Synthelabo	-	-

Raw Materials

Butyl lithium
Ethyl 4-bromobutyrate
Potassium carbonate
Hydrochloric acid
3-Methyl-2-bromothiophene
Ethyl nipecotate
Nipecotic acid ethyl ester
Sodium hydroxide

Manufacturing Process

A solution of 34 ml of n-butyl lithium in 30 ml of anhydrous ether was cooled to -65°C under nitrogen and 5.3 ml of 3-methyl-2-bromothiophene in 10 ml anhydrous ether was added dropwise over a period of 10 min. The reaction mixture was stirred at -65°C for 1 h and 2.7 ml of ethyl 4-bromo-butyrate in 10 ml of anhydrous ether was added slowly. The reaction was stirred for 4 h while the temperature raised to -20°C, 20 ml water was added, and the mixture was stirred for 5 min after which the aqueous layer was removed. The ether layer was washed with 20 ml of water, and the combined aqueous phases were extracted with 50 ml of ether. The combined organic phases were dried over anhydrous sodium sulfate, which after evaporation yielded 9 g of 1-bromo-4,4-bis(3-methylthien-2-yl)but-3-ene as an oil.

This compound was without further purification used for coupling with ethyl nipecotate.

A suspension of 5.0 g of 1-bromo-4,4-bis(3-methylthien-2-yl)but-3-ene, 3.4 g of nipecotic acid ethyl ester and 3.3 g of potassium carbonate in 150 ml of dry acetone was kept under reflux for 15 h. The reaction mixture was evaporated and, after addition of 30 ml of water, the resulting solution was extracted twice with 50 ml of ethyl acetate. The ethyl acetate extracts were dried and evaporated leaving 7.3 g of an oil. By column chromatography on silica gel using methanol as eluent, N-(4,4-bis(3-methylthien-2-yl)but-3-enyl)nipecotic acid ethyl ester was isolated.

5.3 g of N-(4,4-bis(3-methylthien-2-yl)but-3-enyl)nipecotic acid ethyl ester was dissolved in 100 ml of ethanol and 200 ml of an 8 N sodium hydroxide solution was added. The mixture was heated at reflux for 1 h, cooled and acidified by adding 10% hydrochloric acid. The resulting solution was evaporated and 100 ml of water was added to the residue. The resulting acid solution was extracted with ethyl acetate and the dried extract was evaporated to give (R)-N-(4,4-bis(3-methylthien-2-yl)but-3-enyl)nipecotic acid hydrochloride, melting point 187°-189°C.

References

Gronvald F.C., Braestrup C.; US Patent No. 5,010,090; April 23, 1991; Assigned: Novo Nordisk A/S., Bagsvaerd, Denmark

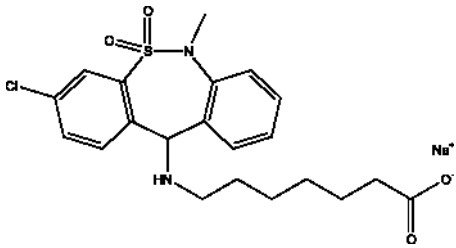
TIANEPTINE SODIUM

Therapeutic Function: Antidepressant

Chemical Name: Sodium 7-[8-chloro-10-dioxo-11-methyldibenzo[c,f] thiazepin-(1,2)-5-yl]-aminoheptanoate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 30123-17-2; 66981-73-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Stablon	Servier	France	1983

Raw Materials

Ethyl 7-aminoheptanoate
5,8-Dichloro-10-dioxo-11-methyldibenzo[c,f]thiazepine(1,2)
Sodium hydroxide

Manufacturing Process

A solution of 27.6 g (0.16 mol) of freshly distilled ethyl 7-aminoheptanoate in 40 ml of nitromethane was added all at once and with mechanical stirring to a suspension of 26.2 g (0.08 mol) of 5,8-dichloro-10-dioxo-11-methyldibenzo[c,f]thiazepine(1,2) in 120 ml of nitromethane. The whole was heated to 55°C for 30 minutes, the solvent was then evaporated in vacuo and the residue was taken up in water. The crude ester was extracted with ether. After evaporation of the ether 36 g of crude ester were obtained, and 30 g (0.065 mol) there of were treated under reflux with a solution of 2.8 g (0.07 mol) of sodium hydroxide in 35 ml of ethanol and 25 ml of water. After one hour's refluxing, the alcohol was evaporated in vacuo. The residue was taken up in 150 ml of water.

The mixture was twice extracted with 75 ml of chloroform and the aqueous phase was evaporated in vacuo. The sodium salt was then dissolved in 150 ml of chloroform, the solution was dried over sodium sulfate and the product precipitated with anhydrous ether.

The salt was filtered off, washed with ether and dried at 50°C. 13 g of sodium 7-[8-chloro-10-dioxo-11-methyldibenzo[c,f]thiazepin-(1,2)-aminoheptanoate,

melting with decomposition at about 180°C, were obtained.

References

Merck Index 9265
DFU 4 (7) 522 (1979) (As S-1574) & 6 (12) 797 (1981)
DOT 19 (6) 306 (1983)
Malen, C., Danree, B. and Poignant, J.C.; US Patents 3,758,528; September 11, 1973; and 3,821,249; June 28, 1974; both assigned to Societe et Nom Collectif Science Union et Cie, Societe Francaise de Recherche Medicale

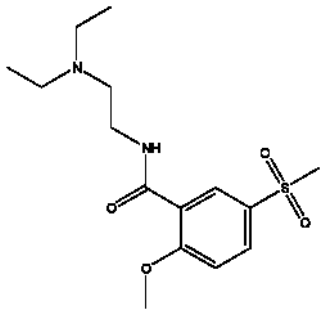
TIAPRIDE

Therapeutic Function: Antiemetic

Chemical Name: N-(Diethylaminoethyl)-2-methoxy-5-methylsulfonylbenzamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 51012-32-9; 51012-33-0 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Tiapridal	Delagrange	France	1977
Tiapridex	Schuerholz	W. Germany	1977
Sereprile	Vita	Italy	1977
Tiapridal	Pharmos	Switz.	1981
Italprid	Prophin	Italy	-
Neuropri	Italchemi	Italy	-

Raw Materials

2-Methoxy-5-methylsulfonylbenzoic acid

Isobutyl chloroformate
N,N-Diethylethylenediamine

Manufacturing Process

5 g of 2-methoxy-5-methylsulfonylbenzoic acid, 50 ml of dioxan, 3.02 ml of triethylamine and 3 g of isobutyl chloroformate were introduced into a 250 ml balloon flask at ambient temperature.

After the mixture had been stirred for 30 minutes, 3 g of N,N-diethylethylenediamine were added. The reaction mixture was stirred for 6 hours and the solvents were evaporated under vacuum.

The residue was dissolved in 50 ml of water and the solution was made alkaline with sodium hydroxide. The precipitate formed was filtered, washed and dried in a drying oven at 60°C. 6 g of N-(diethylaminoethyl)-2-methoxy-5-methylsulfonylbenzamide (melting point: 124°C to 125°C) was produced.

References

DFU 1 (2) 88 (1976)
Kleeman and Engel p. 881
DOT 13 (8) 340 (1977)
I.N. p. 949
Societe d'Etudes Scientifiques et Industrielles de l'Ile-de-France; British Patent 1,394,563; May 21, 1975

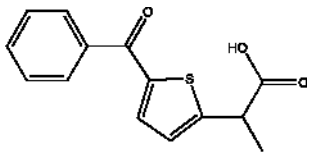
TIAPROFENIC ACID

Therapeutic Function: Antiinflammatory

Chemical Name: 5-Benzoyl-α-methyl-2-thiopheneacetic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 33005-95-7

Raw Materials

Thiophene-2α-methylacetic acid
Benzoyl chloride

Trade Name	Manufacturer	Country	Year Introduced
Surgam	Roussel	France	1975
Surgam	Roussel	W. Germany	1980
Surgam	Hoechst	Switz.	1982
Surgam	Roussel	UK	1982
Surgamic	Roussel-Iberica	Spain	-

Manufacturing Process

A mixture of 10.3 g of thiophene-2α-methylacetic acid [prepared by process of Bercot-Vatteroni, et al., Bull. Soc. Chim. (1961) pp. 1820-21], 11.10 g of benzoyl chloride and a suspension of 23.73 g of aluminum chloride in 110 cc of chloroform was allowed to stand for 15 minutes and was then poured into a mixture of ice and hydrochloric acid. The chloroform phase was extracted with a 10% aqueous potassium carbonate solution and the aqueous alkaline phase was acidified with N hydrochloric acid and was then extracted with ether. The ether was evaporated off and the residue was crystallized from carbon tetrachloride to obtain a 54% yield of 5-benzoyl-thiophene-2α-methylacetic acid melting at 83°C to 85°C. The product occurred in the form of colorless crystals soluble in dilute alkaline solutions, alcohol and ether and insoluble in water.

References

Merck Index 9266
Kleeman and Engel p. 882
DOT 12 (6) 238 (1976)
I.N. p. 38
Clemence, F. and Le Martret, O.; US Patent 4,159,986; July 3, 1979; assigned to Roussel Uclaf (France)

TIARAMIDE

Therapeutic Function: Antiinflammatory

Chemical Name: 4-[(5-Chloro-2-oxo-3(2H)-benzothiazolyl)acetyl]-1-piperazineethanol

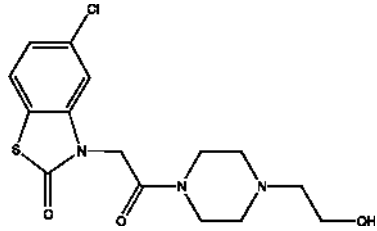
Common Name: -

Chemical Abstracts Registry No.: 32527-55-2; 35941-71-0 (Hydrochloride salt)

Raw Materials

Ethyl 5-chloro-2-oxobenzothiazoline acetate
1-(2-Hydroxyethyl)piperazine

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Solantal	Fujisawa	Japan	1975
Ventaval	Crinos	Italy	1981
Royzolon	Sawai	Japan	-

Manufacturing Process

A solution of ethyl 5-chloro-2-oxo-3-benzo-thiazolineacetate (4.0 grams) in 1-(2-hydroxyethyl)piperazine is heated at 100°C for 24 hours. After cooling, the resulting mixture is extracted with chloroform. The chloroform extract is washed with water and shaken with 10% hydrochloric acid. The hydrochloric acid layer is washed with chloroform, made alkaline with 10% sodium hydroxide solution and extracted with chloroform. The chloroform extract is washed with water, dried over magnesium sulfate and concentrated. The residual oil (5.5 grams) is allowed to stand to form crystals, which are recrystallized from a mixture of ethyl acetate (40 ml) and ethanol (15 ml) to give 3-[4-(2-hydroxyethyl)-1-piperazinylcarbonylmethyl]-5-chloro-2(3H)-benzothiazolinone (3.2 grams) as colorless crystals, MP 159° to 161°C.

The following is an alternate method of preparation: A mixture of 3-(1-piperazinyl)carbonylmethyl-5-chloro-2(3H)-benzothiazolinone (500 mg), anhydrous potassium carbonate (400 mg), 2-hydroxyethyl bromide (300 mg) and anhydrous ethanol (20 ml) is heated while refluxing for 5 hours. The reaction mixture is concentrated under reduced pressure. The residue is extracted with chloroform. The chloroform layer is dried over magnesium sulfate and concentrated. The residue is crystallized from a mixture of ethyl acetate and ethanol to give 3-[4-(2-hydroxyethyl]-1-piperazinylcarbonylmethyl]-5-chloro-2(3H)-benzothiazolinone (370 mg) as crystals, MP 159° to 160°C.

References

Merck Index 9268
Kleeman and Engel p. 882
DOT 9 (9) 390 (1973)
I.N. p. 949
Umio, S.; US Patent 3,661,921; May 9, 1972; assigned to Fujisawa Pharmaceutical Co., Ltd., Japan

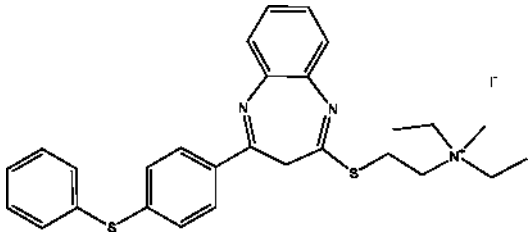
TIBEZONIUM IODIDE

Therapeutic Function: Antimicrobial

Chemical Name: 2β-N-Diethylaminoethylthio-4-p-phenylthiophenyl-3H-1,5-benzodiazepine iodomethylate

Common Name: Thiabenzazonium iodide

Structural Formula:



Chemical Abstracts Registry No.: 54663-47-7

Trade Name	Manufacturer	Country	Year Introduced
Antoral	Recordati	Italy	1977

Raw Materials

4-Acetyldiphenylsulfide
Methyl iodide
β-Dimethylaminoethyl chloride
o-Phenylenediamine
Carbon disulfide

Manufacturing Process

4-Acetyldiphenylsulfide is reacted with carbon disulfide in an initial step to give 4-phenylthiobenzoyl dithioacetic acid. That, in turn, is reacted with o-phenylenediamine.

A mixture of 3.6 g of the thus obtained 4-p-phenylthiophenyl-1,3-dihydro-2H-1,5-benzodiazepine-2-thione, 0.50 g of 50% sodium hydride in oil and 200 ml of benzene is refluxed for 30 minutes, then a solution of 2.02 g of β-diethylaminoethyl chloride in 5 ml of benzene are added dropwise over 5 minutes.

The mixture is refluxed for 10 hours. The mixture is then cooled and filtered to separate the sodium chloride. The filtrate is evaporated to dryness in vacuo. The oily residue is dissolved in petroleum ether and the solution is filtered with charcoal. The solvent is evaporated in vacuo. The oily residue is heated to 50°C in vacuo (0.01 mm Hg) to remove the excess of β-diethylaminoethyl chloride.

This treatment is continued until the β-diethylaminoethyl chloride disappears

(TLC). The oil is then dissolved in isopropanol and weakly acidified with HCl in propanol. The 2β-N-diethylaminoethylthio-4-p-phenylthiophenyl-3H-1,5-benzodiazepine HCl product crystallizes by addition of anhydrous ethyl ether to the solution. The crystals are filtered and recrystallized from ethyl acetate. Yield 3.65 g, melting point 150°C.

2.55 g of methyl iodide are added to a solution of 5.93 g of 2-β-N-diethylaminoethylthio-4-phenylthiophenyl-3H-1,5-benzodiazepine in 100 ml of isopropanol. The mixture is kept at 20°C to 30°C for 60 hours. The crystals are then filtered. Yield 6.2 g, melting point 161°C.

References

Merck Index 9269
DFU 3 (2) 152 (1978)
Kleeman and Engel p. 883
DOT 14 (6) 252 (1978)
I.N. p. 950
Nardi, D., Massarani, E. and Degen, L.; US Patent 3,933,793; January 20, 1976; assigned to Recordati S.A. Chemical and Pharmaceutical Co.

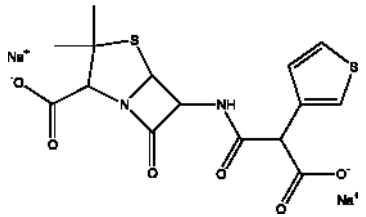
TICARCILLIN DISODIUM

Therapeutic Function: Antibiotic

Chemical Name: α-Carboxy-α-(3-thienyl)methyl penicillin disodium salt

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 4697-14-7; 3973-04-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Ticar	Beecham	US	1976
Aerugipen	Beecham-Wulfing	W. Germany	1977
Ticar	Beecham	UK	1979
Monapen	Fujisawa	Japan	1979
Ticarpenin	Beecham	Japan	1980
Ticalpenin	Beecham	Italy	1980
Ticar	Beecham	France	1981

Trade Name	Manufacturer	Country	Year Introduced
Neoanabactyl	Beecham	-	-
Ticillin	C.S.L.	Australia	-
Timentin	Beecham	US	-

Raw Materials

Hydrogen
Thionyl chloride
Sodium bicarbonate
Monobenzyl-3-thienylmalonate
6-Aminopenicillanic acid

Manufacturing Process

A mixture of monobenzyl-3-thienylmalonate (1.38 g, 5 mmol) and thionyl chloride (2.5 ml) was warmed at 50°C to 55°C for 1 hour, then at 60°C to 65°C for 10 minutes. The excess of thionyl chloride was removed in vacuo at not more than 30°C, the last traces being removed by codistillation with dry benzene (1 ml) under high vacuum, leaving monobenzyl3-thienylmalonyl chloride as a yellow oil.

The acid chloride obtained as described above was dissolved in dry acetone (10 ml) and added in a steady stream to a stirred solution of 6-aminopenicillanic acid (1.08 g, 5 mmol) in a mixture of N sodium bicarbonate (15 ml) and acetone (5 ml). After the initial reaction the reaction mixture was stirred at room temperature for 45 minutes, then washed with ether (3 x 25 ml). Acidification of the aqueous solution with N hydrochloric acid (11 ml) to pH 2 and extraction with ether (3 x 15 ml) gave an ethereal extract which was decolorized with a mixture of activated charcoal and magnesium sulfate for 5 minutes.

The resulting pale yellow ethereal solution was shaken with sufficient N sodium bicarbonate (4 ml) to give an aqueous extract of pH 7 to 7.5. This extract was concentrated to syrup at low temperature and pressure, then isopropanol was added with stirring until the mixture contained about 10% water.

Crystallization was initiated, and completed at about 0°C overnight, to give the sodium salt of α-(benzyloxycarbonyl)-3-thienylmethylpenicillin as white crystals in 50% weight yield. This product was estimated by colorimetric assay with hydroxylamine to contain 91% of the anhydrous sodium salt.

A solution of the sodium salt of α-(benzyloxycarbonyl)-3-thienylmethylpenicillin (2.13 g, 4.3 mmol) in water (30 ml) was added to a suspension of 5% palladium on calcium carbonate (10.65 g) in water (32 ml) which had been prehydrogenated for 1 hour.

The mixture was then hydrogenated at just above atmospheric pressure for 1 1/2 hours and filtered through a Dicalite bed. The clear filtrate was evaporated at low temperature and pressure, and the residue dried in vacuo over phosphorus pentoxide, to give 1.64 g of the salt of α-(3-thienyl)methylpenicillin as a white solid.

Colorimetric assay with hydroxylamine showed this salt to contain 94% of the

anhydrous penicillin. Paper chromatography showed complete reduction of the benzyl group.

References

Merck Index 9271
Kleeman and Engel p. 883
PDR pp. 663, 666
OCDS Vol. 2 p. 437 (1980)
DOT 10 (2) 55 (1974); 11 (11) 446 (1975) & 13 (9) 374 (1977)
I.N. p. 950
REM p. 1199
Beecham Group, Ltd.; British Patent 1,125,557; August 28, 1968
Brain, E.G. and Nayler, J.H.C.; US Patent 3,282,926; November 1, 1966; and US Patent 3,492,291; January 27, 1970; both assigned to Beecham Group, Ltd.

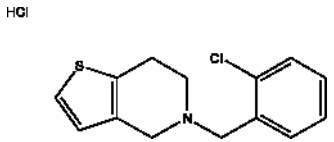
TICLOPIDINE HYDROCHLORIDE

Therapeutic Function: Platelet aggregation inhibitor

Chemical Name: 5-[(2-Chlorophenyl)methyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 53885-35-1; 55142-85-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Ticlid	Millot	France	1978
Tiklidan	Labaz	W. Germany	1980
Panaldin	Daiichi Seiyaku	Japan	1981
Tiklid	Midy	Italy	1981
Ticlodone	Crinos	Italy	1982
Caudaline	Exa	Argentina	-

Raw Materials

Thieno[3,2-c]pyridine
2-Chlorobenzyl chloride
Sodium borohydride
Hydrogen chloride

Manufacturing Process

A solution of thieno[3,2-c]pyridine (13.5 g; 0.1 mol) and 2-chlorobenzyl chloride (17.7 g) in acetonitrile (150 ml) is boiled during 4 hours.

After evaporation of the solvent, the solid residue consists of 5-(2-chlorobenzyl)-thieno[3,2-c]pyridinium chloride which melts at 166°C (derivative n° 30). This compound is taken up into a solution comprising ethanol (300 ml) and water (100 ml). Sodium borohydride ($NaBH_4$)(20 g) is added portionwise to the solution maintained at room temperature. The reaction medium is maintained under constant stirring during 12 hours and is then evaporated. The residue is taken up into water and made acidic with concentrated hydrochloric acid to destroy the excess reducing agent. The mixture is then made alkaline with ammonia and extracted with ether. The ether solution is washed with water, dried and evaporated. The oily residue is dissolved in isopropanol (50 ml) and hydrochloric acid in ethanol solution is then added thereto.

After filtration and recrystallization from ethanol, there are obtained 5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride crystals (yield: 60%) having a melting point (Koefler block) of 190°C.

References

Merck Index 9272
DFU 1 (4) 190 (1976)
Kleeman and Engel p. 884
OCDS Vol. 3 p. 228 (1984)
DOT 15 (8) 354 (1979)
I.N. p. 951
Castaigne, A.R.J.; US Patent 4,051,141; September 27, 1977; assigned to Centre d'Etudes Pour l'Industrie Pharmaceutique (France)

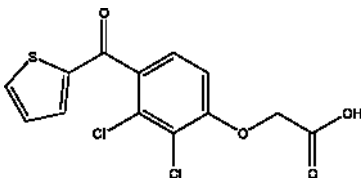
TICRYNAFEN

Therapeutic Function: Diuretic, Hypertensive

Chemical Name: [2,3-Dichloro-4-(2-thienylcarbonyl)phenoxy]acetic acid

Common Name: Thienylic acid

Structural Formula:



Chemical Abstracts Registry No.: 41080-04-9

Trade Name	Manufacturer	Country	Year Introduced
Diflurex	Anphar	France	1976
Diflurex	Ritter	Switz.	1978
Selacryn	SK Dauelsberg	W. Germany	1979
Selacryn	SKF	US	1979

Raw Materials

2,3-Dichloroanisole
Aluminum chloride
Ethyl chloroacetate
Thiophene-2-carboxylic acid chloride
Sulfuric acid
Sodium hydroxide

Manufacturing Process

(a) To a solution of 55 g of 2,3-dichloroanisole (0.31 mol), 91 g of thiophene-2-carboxylic acid chloride (0.62 mol) and 180 ml carbon disulfide; there was added little by little 82.7 g of anhydrous aluminum chloride, keeping the temperature at about 25°C. The reaction mixture was stirred at ambient temperature for five hours, left standing overnight and then heated for one hour at 55°C. The solution was cooled and hydrolyzed by 250 g of ice and 60 ml concentrated hydrochloric acid. The precipitate formed is treated with a 30% solution of caustic soda, then washed with water. After recrystallization in 95% ethanol, 88.6 g (yield 92%) of crystals are obtained melting at 108°C.

The process can also be carried out without solvent keeping the same proportions of reactants, or in methylene chloride by adding a slight excess of aluminum chloride powder to a solution of one mol of dichloroanisole and one mol of acid chloride.

(b) 88.6 g of the ketone just obtained (0.308 mol) were dissolved in 300 ml of benzene, 123.5 g of aluminum chloride was added in small doses, and the mixture was boiled under reflux for two hours.

The reaction mixture was hydrolyzed by 500 g ice; the precipitate extracted and taken up in a 10% aqueous caustic soda solution. The benzene phase obtained after hydrolysis is concentrated. The oil obtained is treated as above and the precipitate added to the other. The crystals were recrystallized in 50% ethanol, 60 g of product were obtained, melting at 142°C.

The reaction may also be effected with excellent yields in methylene chloride.

(c) A solution of sodium ethylate was prepared by dissolving 3.45 g of sodium (0.15 mol) in 300 ml absolute ethanol. There was then added 31 g of the preceding phenol (0.15 mol) then 25.8 g ethyl chloroacetate. The mixture was refluxed for 15 hours. Hot extraction was carried out to eliminate the sodium chloride.

The ester precipitated on cooling the filtrate. The product was recrystallized once in isopropanol to give 29.4 g of crystals melting at 58°C. The pure product melts at 63°C to 64°C.

The ester was dissolved in a solution of 500 ml 95% ethanol and 9 ml of 10 N caustic soda.

The mixture was boiled under reflux for 30 minutes. The precipitate of the sodium salt of the acid which forms in the cold was extracted and taken up in warm water. The free acid was then precipitated in mineral acid medium. After recrystallization in 50% ethanol, it melted at 148°C to 149°C.

References

Merck Index 9273
Kleeman and Engel p. 886
OCDS Vol. 2 p. 104 (1980)
DOT 12 (10) 413 (1976)
I.N. p. 38
Godfroid, J.J. and Thuillier, J.E.; US Patent 3,758,506; September 11, 1973; assigned to Centre Europeen de Recherches Pharmacologiques (C.E.R.P.H.A.) (France)

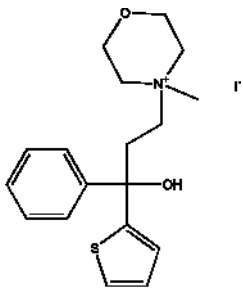
TIEMONIUM IODIDE

Therapeutic Function: Spasmolytic, Anticholinergic

Chemical Name: 4-[3-Hydroxy-3-phenyl-3-(2-thienyl)propyl]-4-methyl-morpholinium iodide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 144-12-7

Trade Name	Manufacturer	Country	Year Introduced
Visceralgine	Riom	France	1963
Viseralgina	S.I.T.	Italy	1965
Ottimal	Farnex	Italy	-

Raw Materials

Bromobenzene
Thienyl-morpholinoethyl ketone
Magnesium
Methyl iodide

Manufacturing Process

(a) N-(3-hydroxy-3-phenyl-3-α-thienyl-propyl) morpholine was first prepared: The following quantities of reactants were mixed in a 2-liter balloon flask having 3 tubes fitted respectively with a mercury-sealed agitator, a reflux condenser having a calcium chloride seal, and a dropping funnel:

Magnesium turnings 27 g (1.1 g at. wt)

Bromobenzene 181 g (1.15 mol)

Anhydrous ether 500 cc

(b) To the cold Grignard solution was added a solution containing:

Thienyl-morpholinoethyl ketone 180 g (0.8 mol)

Anhydrous ether 250 cc

The ketone, preferably prepared by a Grignard reaction, was added in such a way as to maintain the ether under constant reflux. When all of the solution had been added, the mixture was refluxed for a further hour. The mixture was then allowed to stand for 12 hours at ambient temperature, after which the reaction mass was extracted with ice and ammonium chloride in known manner.

(c) The ether solution was treated with 2 N hydrochloric acid solution and the amino-alcohol was obtained as the hydrochloride (yield approximately 60%); it was purified by recrystallization from methanol.

The resulting product was dissolved in water, made alkaline with dilute $NH_4OH$and was extracted with ether. After evaporation of the ether, the amino-alcohol was obtained as a base.

(d) To prepare the quaternary ammonium iodide, the amino-alcohol above was dissolved in a minimum amount of anhydrous ether and was treated with its own weight of methyl iodide. A well-crystallized product was obtained and was washed with anhydrous ether. (Melting point 189°C to 191°C).

References

Merck Index 9274
Kleeman and Engel p. 885
DOT 15 (9) 427 (1979)
I.N. p. 951

Laboratoires d'Analyses et de Recherches Biologiques Mauvernay C.E.R.F.A.; British Patent 953,386; March 25, 1964

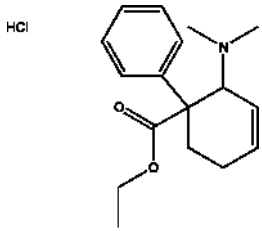
TILIDINE HYDROCHLORIDE

Therapeutic Function: Analgesic

Chemical Name: 2-(Dimethylamino)-1-phenyl-3-cyclohexene-1-carboxylic acid ethyl ester hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 27107-79-5; 20380-58-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Valoron	Goedecke	W. Germany	1970
Valoron	Isom	Italy	1983
Kitadol	Larma	Spain	-
Perdolat	Inca	Argentina	-
Tilitrate	Substancia	Spain	-

Raw Materials

Diethylamine
Crotonaldehyde
Atropic acid ethyl ester
Hydrogen chloride

Manufacturing Process

In a first step, dimethylamine is reacted with crotonaldehyde to give 1-(dimethylamino)-1,3-butadiene.

A solution of 194 grams (2 mols) of fresh-distilled 1-(dimethylamino)-1,3-butadiene is combined at room temperature in a 1 liter round-bottom flask with 352 grams (2 mols) atropic acid ethyl ester. After being stirred for about 10 minutes, the reaction mixture gradually becomes exothermic. By cooling with ice water, the contents of the flask are kept at a temperature of 40° to 60°C. After the reaction has ceased, the mixture is kept overnight (about 8 to

24 hours) at room temperature. The next day the viscous product is dissolved in 10 liters of ether and precipitated with ethereal hydrogen chloride forming the corresponding hydrochloride. By fractional crystallization from ethyl acetate/methyl ethyl ketone (10:1), an almost complete separation of the isomeric cis/trans isomers (I) and (II) is achieved. The separation can be carried out very easily due to the low solubility of the 1 1/2-hydrate of (I). Therefore, during the crystallization a sufficient quantity of water for the formation of the 1 1/2-hydrate of (I) is added to the mixture of solvents, whereby (I) readily precipitates.

Isomer (I): 4-phenyl-3-cis-dimethylamino-4-cis-carbethoxy-Δ^1-cyclohexenehydrochloride, [ethyl-cis-3-(dimethylamino)-4-phenyl-1-cyclohexene-4-carboxylate hydrochloride] , MP 84°C (the free base boils at 97.5° to 98°C at 0.01 mm pressure), 64.4% yield.

Isomer (II): 4-phenyl-3-trans-dimethylamino-4-trans-carbethoxy-Δ^1-cyclohexenehydrochloride, [ethyl-trans-3-(dimethylamino)-4-phenyl-1-cyclohexene-4-carboxylate hydrochloride], MP 159°C (the free base boils at 95.5° to 96°C at 0.01 mm pressure), 22.2% yield.

References

Merck Index 9280
Kleeman and Engel p. 887
DOT 7 (1) 33 (1971)
I.N. p. 952
Satzinger, G.; US Patent 3,557,127; January 19, 1971; assigned to Warner-Lambert Pharmaceutical Company

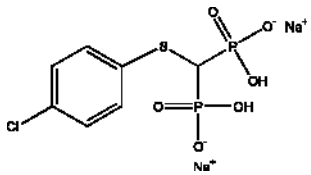
TILUDRONATE DISODIUM

Therapeutic Function: Bone calcium regulator

Chemical Name: Phosphonic acid, (((4-chlorophenyl)thio)methylene)bis-, disodium salt

Common Name: Tiludronate disodium

Structural Formula:



Chemical Abstracts Registry No.: 149845-07-8

Trade Name	Manufacturer	Country	Year Introduced
Scelid	Sanofi Pharmaceuticals Inc.	USA	-
Scelid	Sanofi-Synthelabo	France	-
Tiludronate Disodium	Sanofi Chimie	France	-
Tiludronate Disodium	Inter-Chemical (Chongqing) Co., Ltd.	China	-

Raw Materials

Sodium hydride
Tetraisopropyl methylene-diphosphonate
Hydrogen chloride
1-(4-Chlorphenyl) disulfide
Sodium hydroxide

Manufacturing Process

The 50% strength suspension of sodium hydride in oil is added, a little at a time to a solution of tetraisopropyl methylene-diphosphonate in dimethylformamide. After all has been added, the mixture is stirred, the 1-(4-chlorphenyl) disulfide is then added and the whole is heated at 25°C for 6 h. The mixture is evaporated to dryness in vacuo and residue is taken up in hexane. The solution is washed with water and dried. The solvent is evaporated to dryness and the residue is chromatographed on silica column, elution being carried out with a 98:2 (v/v) mixture of methylene chloride/methanol. The obtained 1-(4-chlorphenylthio)tetraisopropyl methylene-diphosphonate is then hydrolyzed with 12 N HCl for 18 h to give the 1-(4-chlorphenylthio)methylene-diphosphonic acid.

The 1-(4-chlorphenylthio)methylene-diphosphonic acid are dissolved in water, containing sodium hydroxide. The solution is filtered, the methanol are then added and the mixture is left to crystallize. The precipitate is filtered off and washed with methanol and dried at 80°C in vacuo and the disodium salt of 1-(4-chlorphenylthio)methylene-diphosphonic acid is thus obtained.

References

Breliere J.C, et al.; US Patent No. 4,876,248; Oct. 24, 1989; Assigned: Sanofi, Paris, France

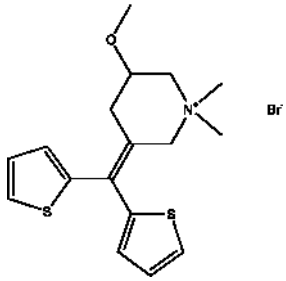
TIMEPIDIUM BROMIDE

Therapeutic Function: Anticholinergic

Chemical Name: 3-(Di-2-thienylmethylene)-5-methoxy-1,1-dimethylpiperidinium bromide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 35035-05-3

Trade Name	Manufacturer	Country	Year Introduced
Sesden	TANABE SEIYAKU	Japan	1976
Mepidum	Poli	Italy	-

Raw Materials

5-Hydroxynicotinic acid
Dimethyl sulfate
2-Thienyl bromide
Nickel Raney
Methyl bromide
Methanol
Hydrogen
Hydrogen chloride

Manufacturing Process

120 g of 5-hydroxynicotinic acid are dissolved in 1 liter of methanol. After saturating with dry-hydrogen chloride gas at 0°C, the solution is refluxed for 2 hours. Then, the solution is concentrated to dryness. The residue thus obtained is dissolved in water. The solution is neutralized with sodium bicarbonate. The precipitated crystals are collected by filtration, washed with water and then dried. 126 g of methyl 5-hydroxynicotinate are obtained. Yield: 93%. Melting point 184°C to 186°C.

460 g of methyl 5-hydroxynicotinate and 621 g of potassium carbonate are suspended in 200 ml of tetrahydrofuran-methanol (4:1). 1,134 g of dimethyl sulfate are added dropwise to the suspension in nitrogen atmosphere at room temperature. The mixture is stirred overnight at the same temperature and then filtered. The filtrate is concentrated to dryness. The residue thus obtained is mixed with 1.6 liters of methanol and 280 ml of Raney-nickel, and hydrogenated overnight in an autoclave at room temperature and at a pressure of 85 atmospheres. 200 g of Raney-nickel are added to the reaction mixture. The mixture is adjusted to pH 9.5 with triethylamine, and is further subjected to hydrogenation for 20 hours in an autoclave at 70°C and at a pressure of 100 atmospheres. Potassium carbonate and a small amount of ice are added to the reaction mixture to bring the pH to 11. The mixture is extracted with ether. After drying, the ether layer is filtered. The filtrate is

evaporated to remove ether. The residue thus obtained is distilled under reduced pressure. 450 g of methyl N-methyl-5-methoxynipecotinate are obtained. Yield: 80%. Boiling point 80°C to 81°C/0.5 mm Hg.

A solution of 18 g of 2-thienyl bromide in 30 ml of tetrahydrofuran is gradually added to a mixture of 2.6 g of magnesium and 80 ml of tetrahydrofuran under stirring at 50°C. The mixture is stirred for 5 hours at room temperature until the magnesium is entirely dissolved in the solution. 6.2 g of methyl N-methyl-5-methoxy-nipecotinate are added to the mixture. Then, the mixture is refluxed for 4 hours. After the reaction is completed, tetrahydrofuran is distilled off under reduced pressure. An aqueous ammonium chloride solution is added to the residue, and the solution is extracted with chloroform. The extract is dried and then evaporated to remove chloroform. The viscous oil thus obtained is recrystallized from a mixture of benzene and ether. 7 g of di-(2-thienyl)-(N-methyl-5-methoxy-3-piperidyl)-carbinol are obtained as crystals. Melting point 142°C to 146°C.

7 g of the product are dissolved in 150 ml of 10% hydrochloric acid, and the solution is heated at 80°C for 30 minutes. After the reaction is completed, the solution is basified with sodium hydroxide and then extracted with ether. The extract is washed with water, dried and evaporated to remove ether. 5 g of di-(2-thienyl)-(N-methyl-5-methoxy-3-piperidylidene)-methane are obtained as pale yellow oil.

365 mg of di-(2-thienyl)-(N-methyl-5-methoxy-3-piperidylidene)-methane are dissolved in 15 ml of ether. 1 ml of methyl bromide is added to the solution. Then, the solution is stirred overnight. The precipitated crystals are collected by filtration and recrystallized from a mixture of acetone and ether. 390 mg of di-(2-thienyl)-(N-methyl-5-methoxy-3-piperidylidene)-methane methyl bromide are obtained as colorless crystals. Melting point 198°C to 200°C.

References

Merck Index 9283
Kleeman and Engel p. 888
DOT 12 (12) 490 (1976)
I.N. p. 952
Kawazu, M., Kanno, T., Saito, S.and Tamaki, H.; US Patent 3,764,607; October 9, 1973; assigned to Tanabe Seiyaku Co., Ltd. (Japan)

TIMOLOL MALEATE

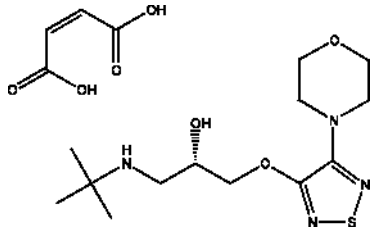
Therapeutic Function: Antiarrhythmic, Antiglaucoma

Chemical Name: S-(-)-(1-tert-Butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate

Common Name: -

Chemical Abstracts Registry No.: 26921-17-5; 26839-75-8 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Blocadren	MSD	UK	1974
Timacor	MSD	France	1976
Timserin	Sharp and Dohme	W. Germany	1976
Timoptic	MSD	US	1978
Timoptic	Chibret	Switz.	1978
Timoptol	MSD	UK	1979
Timoptol	Sharp and Dohme	W. Germany	1979
Blocadren	MSD	Italy	1980
Timoptic	MSD	Italy	1980
Timoptol	Merck-Banyu	Japan	1981
Blocadren	MSD	US	1981
Betim	Leo	Denmark	-
Cardina	Orion	Finland	-
Chibro-Timoptol	Chibret	France	-
Cusimolol	Cusi	Spain	-

Raw Materials

Bromoacetol
p-Toluenesulfonyl chloride
t-Butylamine
3-Morpholino-4-hydroxy-1,2,5-thiadiazole
Maleic acid
Sodium borohydride

Manufacturing Process

Step A: Preparation of 3-tert-Butylamino-2-Oxopropanol - To an aqueous solution of tert-butylamine (1 mol) at ambient temperature, there is added slowly and with vigorous stirring 2 mols bromoacetol. The reaction mixture is allowed to stand at ambient temperature for about 5 hours whereupon it is made basic by the addition of sodium hydroxide.

The reaction mixture then is extracted with ether, the excess amine is removed from the ethereal solution under reduced pressure and the ether then removed by evaporation to give 3-tert-butylamino-2-oxopropanol.

Step B: A solution of the 3-tert-butylamino-2-oxopropanol in a mixture of pyridine hydrochloride and pyridine is treated with p-toluenesulfonylchloride. The mixture is stirred for 1/2 hour at 25° to 30°C and then poured into cold

water. The solution is treated with potassium carbonate and the pyridine evaporated in vacuo at a temperature between 55° and 60°C. The aqueous residue is treated with potassium carbonate and the mixture extracted with methylene chloride. Evaporation of the dried extract provides 1-toluenesulfonyloxy-2-oxo-3-tert-butylaminopropane.

Step C: Preparation of 3-Morpholino-4-(3-tert-Butylamino-2-Oxopropoxy)-1,2,5-Thiadiazole - The 1-toluenesulfonyloxy-2-oxo-3-tert-butylaminopropane, prepared as described in Step B, (11 mols) is added to 0.80 N methanolic sodium methoxide (15 ml) at 0°C. The mixture is stirred for 15 minutes at 0° to 5°C, treated with 3-morpholino-4-hydroxy-1,2,5-thiadiazole (4.29 grams) and then refluxed for 16 hours. The solvent is evaporated in vacuo and the residue is treated with excess potassium carbonate to provide 3-morpholino-4-(3-butylamino-2-oxopropoxy)-1,2,5-thiadiazole.

Step D: Chemical Reduction Preparation of 3-Morpholino-4-(3-tert-Butylamino-2-Hydroxypropoxy)-1,2,5-Thiadiazole - The 3-morpholino-4-(3-tert-butylamino-2-oxopropoxy)-1,2,5-thiadiazole (0.01 mol) is dissolved in isopropanol (10 ml). To the solution is added sodium borohydride in portions until the initial evolution of heat and gas subsides. The excess sodium borohydride is destroyed by addition of concentrated hydrochloric acid until the mixture remains acidic. The precipitate of sodium chloride is removed, ether is added, and the solution is concentrated to crystallization. The solid material is removed by filtration and dried thus providing 3-morpholino-4-(3-tert-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole, MP 161° to 163°C (as hydrochloride).

Alternative Step D: Reduction with a Reductate - Sucrose (1 kg) is dissolved in water (9 liters) in a 20-liter bottle equipped with a gas trap. Baker's yeast (Saccharomyces cerevisiae, 1 kg) is made into a paste with water (1 liter) and added to the sucrose solution with stirring. After lively evolution of gas begins (within 1 to 3 hours), 3-morpholino-4-(3-tert-butylamino-2-oxopropoxy)-1,2,5-thiadiazole hydrogen maleate [1.35 mols, prepared by reaction of the 3-morpholino-4-(3-tert-butylamino-2-oxopropoxy)-1,2,5-thiadiazole with an equimolar quantity of maleic acid in tetrahydrofuran]. The mixture is allowed to stand until fermentation subsides, after which the bottle is kept in a 32°C incubator until all fermentation has ended (in approximately 1 to 3 days). The yeast is filtered off with addition of diatomaceous earth and the filtrate is evaporated to dryness to give S-3-morpholino-4β-tert-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole, MP 195° to 198°C (as hydrogen maleate), according to US Patent 3,619,370.

Step E: The base may be converted to the maleate by maleic acid.

References

Merck Index 9284
Kleeman and Engel p. 889
PDR pp. 1145, 1211, 1214
OCDS Vol. 2 p. 272 (1980)
DOT 10 (4) 145 (1974) & 16 (3) 92 (1980)
I.N. p. 953
REM p. 907

Weinstock, L.M., Tull, R.J. and Mulvey, M.D.; US Patent 3,619,370; November 9, 1971; assigned to Charles E. Frosst & Co.
Wasson, B.K.; US Patent 3,655,663; April 11, 1972
Weinstock, L.M., Tull, R.J. and Mulvey, D.M.; US Patent 3,657,237; April 18, 1972; assigned to Charles E. Frosst & Co.

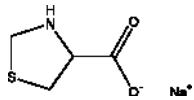
TIMONACIC SODIUM

Therapeutic Function: Hepatoprotectant, Choleretic

Chemical Name: 4-Thiazolidinecarboxylic acid sodium salt

Common Name: ATC

Structural Formula:



Chemical Abstracts Registry No.: 444-27-9 (Acid)

Trade Name	Manufacturer	Country	Year Introduced
Hepaldine	Riker	France	1964
Leberschutz	Karner	W. Germany	1977
Dexotepa	Ayerst	Italy	1979
Tiazolidin	U.C.M.-Difme	Italy	1980
Heparegene	Syntex-Pharm	Switz.	-
Thiobiline	Riker	France	-

Raw Materials

Cysteine
Formaldehyde
Sodium hydroxide

Manufacturing Process

Cysteine is first dissolved in distilled water which has been freed of oxygen by boiling. Formaldehyde of 30% (w/v) concentration is added while stirring and the temperature of the mixture rises, while the thiazolidine carboxylic acid begins crystallizing. The stirring is continued for 2 hours after which ethyl alcohol of 95% (w/v) concentration is added to induce further crystallization. The mixture is left to stand for 24 hours at 4°C. The mixture is then filtered with retention of a crude product, which is purified by recrystallization from boiling distilled water. The crystals are then dried at about 40°C. The free acid is then converted to the sodium salt with NaOH.

References

Merck Index 9285
DFU 5 (8) 415 (1980)
Kleeman and Engel p. 890
I.N. p. 953
Sogespar, S.A.; British Patent 1,041,787; September 7, 1966

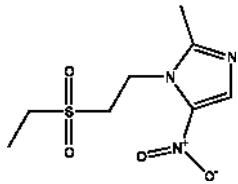
TINIDAZOLE

Therapeutic Function: Antitrichomonal (vaginal)

Chemical Name: 1-[2-(Ethylsulfonyl)ethyl]-2-methyl-5-nitroimidazole

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 19387-91-8

Trade Name	Manufacturer	Country	Year Introduced
Simplotan	Pfizer	W. Germany	1971
Fasigyne	Pfizer	France	1975
Fasigyn	Pfizer	Italy	1975
Fasigyn	Pfizer Taito	Japan	1981
Fasigyn	Pfizer Taito	UK	1982
Amplium	Farmasa	Brazil	-
Pletil	Andromaco	Brazil	-
Protocide	Unipharm	Israel	-
Sorquetan	Basotherm	W. Germany	-
Tinigyn	Leiras	Finland	-
Tricanix	Orion	Finland	-
Trichogin	Chiesi	Italy	-
Trimonase	Tosi	Italy	-

Raw Materials

Ethyl sulfonyl ethanol
p-Toluenesulfonyl chloride
2-Methyl-5-nitroimidazole

Manufacturing Process

The preparation of ethylsulfonylethyl-p-toluenesulfonate is carried out in the following manner: 69.0 grams (0.5 mol) ethylsulfonylethanol dissolved in 150 ml pyridine is cooled to 0°C with stirring and while maintaining the temperature between 0° to 10°C, 95 grams (0.5 mol) p-toluenesulfonyl chloride is added in portions over a 10 minute period. After this time, 250 ml water is added slowly and the mixture extracted with chloroform, the organic phase washed first with 2 N HCl, then with water, separated and dried. The product which crystallizes on cooling is filtered and dried to give 77.5% yield of this intermediate.

A mixture of 12.7 grams (0.1 mol) of 2-methyl-5-nitroimidazole and 58.4 grams (0.2 mol) ethylsulfonylethyl-p-toluenesulfonate is heated with stirring, under nitrogen, at 145° to 150°C for about 4 hours. After this time, the reaction mixture is extracted with 500 ml hot water, the aqueous portion adjusted with 10% Na_2CO_3 to a pH of 9 and extracted with chloroform (3 times with 150 ml portions). The separated organic phase is washed with water, dried with Na_2SO_4 and evaporated to dryness. The crude tinidazole product is then crystallized from benzene to give 4.36 grams of product having a MP of 127° to 128°C.

References

Merck Index 9287
Kleeman and Engel p. 890
DOT 7 (5) 193 (1971) and 8 (2) 73 (1972)
I.N. p. 953
REM p. 1224
Butler, K.; US Patent 3,376,311; April 2, 1968; assigned to Chas. Pfizer and Co., Inc.

TINORIDINE

Therapeutic Function: Antiinflammatory

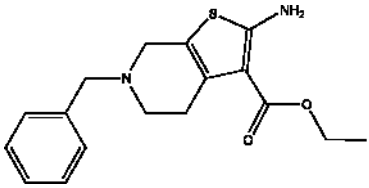
Chemical Name: 2-Amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylic acid ethyl ester

Common Name: -

Chemical Abstracts Registry No.: 24237-54-5; 23237-55-6 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Nonflamin	Yoshitomi	Japan	1971
Dimaten	Promeco	Argentina	-

Structural Formula:



Raw Materials

Sulfur
1-Benzyl-4-piperidone
Morpholine
Ethyl cyanoacetate

Manufacturing Process

A solution of 1-benzyl-4-piperidone, ethyl cyanoacetate, powdery sulfur and morpholine in ethanol is heated moderately under reflux for about 20 minutes to dissolve the powdery sulfur. The mixture is heated under reflux for one further hour to complete the reaction. On standing at room temperature, the mixture yields a precipitate. The precipitate is collected by filtration, washed well with methanol and recrystallized from methanol to give 2-amino-6-benzyl-3-ethoxycarbonyl-4,5,6,7-tetrahydrothieno(2,3-c)-pyridine as almost colorless needles melting at 112° to 113°C.

References

Merck Index 9289
Kleeman and Engel p. 891
DOT 7 (6) 224 (1971)
I.N. p. 954
Nakanishi, M., Tahara, T., Imamura, H. and Maruyama, Y.; US Patent 3,563,997; Feb. 16, 1971; assigned to Yoshitomi Pharmaceutical Industries, Ltd., Japan

TIOCARLIDE

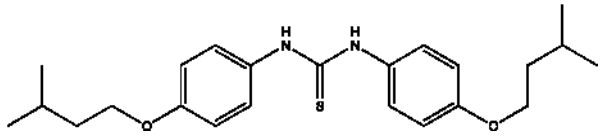
Therapeutic Function: Antitubercular

Chemical Name: N,N'-[4-(3-Methylbutoxy)phenyl]thiourea

Common Name: Thiocarlide

Chemical Abstracts Registry No.: 910-86-1

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Tiocarlide	Ciba	W. Germany	1963
Tiocarlide	Ciba	Italy	1964
Tiocarlide	Ciba	France	1965
Isoxyl	Continental Pharma	UK	1969
Amixyl	Inibsa	Portugal	-
Disoxyl	Ferrosan	Denmark	-

Raw Materials

Isoamyloxyaniline
Carbon disulfide

Manufacturing Process

100 parts by weight of p-isoamyloxyaniline are refluxed for 6 hours with 34 parts by volume of carbon disulfide, 300 parts by volume of ethanol and 5 parts by weight of potassium ethyl xanthate. The reaction mixture is then cooled and the formed 1,3-bis-(p-isoamyloxyphenyl)-2-thiourea is filtered off, washed with a small amount of ethanol and water, and recrystallized from ethanol. The thus-obtained product melts at 134°C to 145°C.

References

Merck Index 9292
Kleeman and Engel p. 891
I.N. p. 954
Huebner, C.F. and Scholz, C.R.; US Patent 2,703,815; March 8, 1955; assigned to Ciba Pharmaceutical Products, Inc.

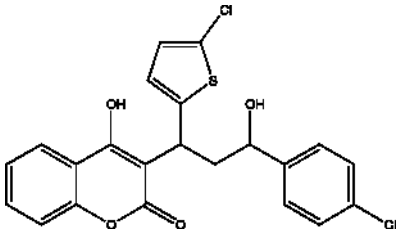
TIOCLOMAROL

Therapeutic Function: Anticoagulant

Chemical Name: 3-[3-(4-Chlorophenyl)-1-(5-chloro-2-thienyl)-3-hydroxypropyl]-4-hydroxy-2H-1-benzopyran-2-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 22619-35-8

Trade Name	Manufacturer	Country	Year Introduced
Apegmone	Oberval	France	1978

Raw Materials

p-Chloroacetophenone
4-Hydroxycoumarin
5-Chlorothiophene-2-aldehyde
Aluminum isopropylate

Manufacturing Process

(a) 1-para-chlorophenyl-3-(5'-chloro-2'-thienyl)-2-propen-1-one - (a) This new compound was prepared in the following manner:

4.4 g of NaOH, in solution in 40 ml of water and 20 ml of ethanol, are cooled to 120°C, and then there are successively added at this temperature 13.2 g (0.086 mol) of para-chloroacetophenone and 12.6 g of 5-chlorothiophene-2-aldehyde. The solution is left standing for 3 hours while stirring at ambient temperature and the precipitate which has formed is centrifuged off, whereafter it is washed with water and recrystallized from alcohol. Yield: 18.4 g, i.e., 75.7% of product, melting at 134°C.

(b) The ketone prepared according to a is condensed at the rate of 14.15 g (0.05 mol) with 8.9 g (0.055 mol) of 4-hydroxycoumarin in 80 ml of water in the presence of 42 mg of hexamethyleneimine. Heating takes place for 4 hours under reflux and, after recrystallization, first of all from a mixture of acetone and water and then from benzene, there are obtained: 12.6 g of 3-(4'-hydroxy-3'-coumarinyl)-3-(5''-chloro-2''-thienyl)-parachloropropiophenone, melting at 162°C (sealed tube).

(b) 4.45 g (0.01 mol) of 3-(4'-hydroxy-3'-coumarinyl)-3-(5''-chloro-2''-thienyl)-parachloropropiophenone, in solution in 75 ml of isopropanol, are reduced with 6.12 g (0.03 mol) of aluminum isopropylate, introduced while stirring and in small quantities at ambient temperature.

The solution is refluxed for one hour and after cooling it is poured into 250 ml of ice and 15 ml of concentrated HCl. On standing, a white precipitate is obtained, which is centrifuged, washed with water, taken up in methanol and

filtered.

5 volumes of water are added to this solution, and it is allowed to crystallize at ambient temperature.

The product is analytically pure and shows a pasty fusion at 104°C (sealed tube). Yield: 89%.

References

Merck Index 9293
Kleeman and Engel p. 892
DOT 14 (8) 383 (1978)
I.N. p. 954
Boschetti, E., Molho, D.and Fontaine, L.; US Patent 3,574,234; April 6, 1971; assigned to Lyonnaise Industrielle Pharmaceutique (LIPHA) (France)

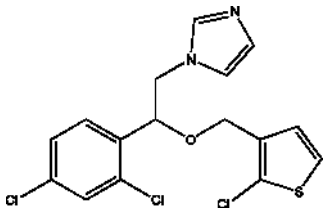
TIOCONAZOLE

Therapeutic Function: Antifungal

Chemical Name: 1-[2-[(2-Chloro-3-thienyl)methoxy]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 65899-73-2

Trade Name	Manufacturer	Country	Year Introduced
Fungata	Pfizer	W. Germany	1981
Trosyd	Pfizer	Switz.	1983
Trosyd	Pfizer	US	1983

Raw Materials

1-(2,4-Dichlorophenyl)-2-(1-imidazolyl)ethanol
Sodium hydride

2-Chloro-3-chloromethylthiophene

Manufacturing Process

A solution of 1-(2,4-dichlorophenyl)-2-(1-imidazolyl)ethanol (1.5 g, 5.8 mmol) dissolved in dry tetrahydrofuran (10 ml) was added to a stirred suspension of sodium hydride (0.39 g, as 80% dispersion in oil, 16 mmol) in dry tetrahydrofuran (10 ml) and warmed to 70°C for 90 minutes.

The mixture was cooled in ice and a solution of 2-chloro-3-chloromethylthiophene (8.8 mmol) in dry tetrahydrofuran was added. The mixture was heated at 70°C for 3 hours and allowed to stir at room temperature overnight. The solvent was removed under vacuum and the residue stirred with dry ether (200 ml). The ether solution was filtered through Celite and saturated with hydrogen chloride gas to precipitate an oil which was solidified by trituration with ether and ethyl acetate. The solid product was collected and recrystallized from a mixture of acetone and diisopropyl ether to give the product, melting point 168°C to 170°C.

References

Merck Index 9294
DFU 5 (10) 509 (1980)
DOT 19 (8) 341 (1983)
I.N. p. 954
REM p. 1231
Gymer, G.E.; US Patent 4,062,966; December 13, 1977; assigned to Pfizer, Inc.

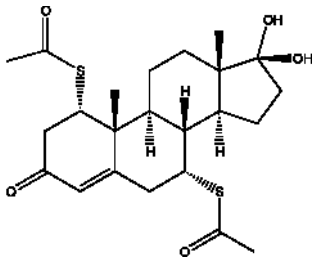
TIOMESTERONE

Therapeutic Function: Anabolic

Chemical Name: Androst-4-en-3-one, 17β-hydroxy-1α,7α-dimercapto-17-methyl-, 1,7-diacetate

Common Name: Protabol; Thiomestrone; Tiomestrone

Structural Formula:



Chemical Abstracts Registry No.: 2205-73-4

Trade Name	Manufacturer	Country	Year Introduced
Tiomesterone	Yick-Vik Chemicals and Pharmaceticals (H.K.) Ltd.	-	-

Raw Materials

17α-Methyl-1,4,6-androstatriene-17β-ol-3-one
Thioacetic acid

Manufacturing Process

4 g 17α-methyl-1,4,6-androstatriene-17β-ol-3-one are boiled in 12 ml thioacetic acid under reflux for 1.5 hours. This reaction mixture is thereafter concentrated in vacuum to dryness and the 1α,7α -diacetylthio-17β-hydroxy-17-methylandrost-4-en-3-one is crystallized from the residue after treatment with methanol; melting point 202-204°C; $[\alpha]_D$ = -74.6° (dioxane); λ_{max} 237.5 nm.

References

Bruekner K., Irmscher K., Gillsen J.; US Patent No. 3,087,942; April 30, 1963; Assigned to Merck Aktiengesellschaft , Darmstadt, Germany

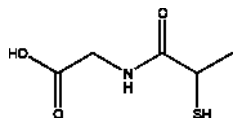
TIOPRONIN

Therapeutic Function: Antidote (heavy metal)

Chemical Name: N-(2-Mercapto-1-oxopropyl)glycine

Common Name: Mercamidum

Structural Formula:



Chemical Abstracts Registry No.: 1953-02-2

Trade Name	Manufacturer	Country	Year Introduced
Thiosol	Coop. Farm.	Italy	1969
Mercaptopropionylglycin	Fresenius	W. Germany	1976
Mucolysin	Proter	Italy	1976
Mucolysin	Interdecta	Switz.	1982

Trade Name	Manufacturer	Country	Year Introduced
Capen	Phoenix	Argentina	-
Epatiol	Medici	Italy	-
Sutilan	Cusi	Spain	-
Thiola	Santen	Japan	-
Vincol	Reig Jofre	Spain	-

Raw Materials

Thionyl chloride	α-Mercaptopropionic acid
Sodium	Benzyl chloride
Glycine	Ammonia

Manufacturing Process

α-Benzylmercaptopropionic acid (melting point 76°C to 78°C; 100 g) prepared by condensation of α-mercaptopropionic acid with benzyl chloride is allowed to stand overnight with 80 g of thionyl chloride. After removal of excess thionyl chloride distillation in vacuo gives 70 g of α-benzylmercaptopropionic acid chloride of boiling point 138°C to 139°C/7 to 8 mm Hg.

Then, 25 g of glycine is dissolved in 165 ml of 2 N sodium hydroxide solution and 70 g of α-benzylmercaptopropionic acid chloride and 100 ml of 2 N sodium hydroxide solution are dropped thereinto simultaneously at 3°C to 5°C. The solution is then stirred at room temperature for 3 to 4 hours to complete the reaction, the reaction solution is washed with ether, the aqueous layer is acidified with hydrochloric acid, and the resulting crystals are collected by filtration. These are recrystallized from a mixture of methanol and ethyl acetate to give 60 g of α-benzylmercaptopropionylglycine of melting point 133°C to 134°C.

This α-benzylmercaptopropionylglycine (60 g) is dissolved in 400 ml of liquid ammonia, kept at about -50°C, and 12 g of sodium metal is gradually added thereto. After the reaction, excess ammonia is removed therefrom, the residue is dissolved in water, washed with ether and the residual aqueous layer is adjusted to pH 1 with hydrochloric acid and concentrated in vacuo in a stream of hydrogen sulfide. The crystalline residue is dried and recrystallized from ethyl acetate to give 25 g of α-mercaptopropionylglycine of melting point 95°C to 97°C.

References

Merck Index 9296
Kleeman and Engel p. 893
DOT 14 (1) 38 (1978)
I.N. p. 955
Mita, I., Toshioka, N. and Yamamoto, S.; US Patent 3,246,025; April 12, 1966; assigned to Santen Pharmaceutical Co. (Japan)

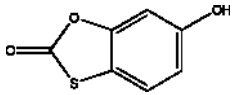
TIOXOLONE

Therapeutic Function: Antiseborreic, Antifungal, Keratolytic

Chemical Name: 6-Hydroxy-1,3-benzoxathiol-2-one

Common Name: Thioxolone; Thixolone; Tioxolone

Structural Formula:



Chemical Abstracts Registry No.: 4991-65-5

Trade Name	Manufacturer	Country	Year Introduced
Acnosan	Unia	-	-

Raw Materials

Potassium thiocyanate
Resorcinol
Copper sulfate

Manufacturing Process

40 g potassium thiocyanate in 50 ml of water are added, while stirring at room temperature, to a solution of 11 g of resorcinol and 50 g of crystallized copper sulfate in 250 ml of water. The black cupric thiocyanate formed becomes colorless after a short time, which indicates that the introduction of thiocyanogen is terminated. The cuprous thiocyanate is removed by filtering with suction and then washed with water; the filtrate is mixed with 50 ml of a 2 N sodium carbonate solution, whereby the imino-thiocarbonate of resorcinol separates in the form of a colorless crystalline body. The yield amounts to 16 g. The new compound which melts at 149°C dissolves very easily in many organic solvents and in mineral acids.

A 10% solution of the imino-thiocarbonate of resorcinol in 10% hydrochloric acid is heated for 15 min on the steam bath. The 6-hydroxy-1,3-benzoxathiol-2-one (thiocarbonate free from) nitrogen separates, on cooling, in the form of fine crystals melting at 158°C.

References

Georg Werner; US Patent No. 2,332,418; Oct. 19, 1943; Assigned to Winthrop Chemical Company, Inc., New York, N. Y., a corporation of New York

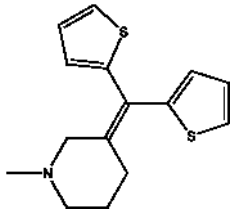
TIPEPIDINE

Therapeutic Function: Antitussive, Expectorant

Chemical Name: Piperidine, 3-(di-2-thienylmethylene)-1-methyl-

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 5169-78-8

Trade Name	Manufacturer	Country	Year Introduced
Sotal	G. Ramon	-	-

Raw Materials

Ethyl nicotinate
Hydrogen
Nickel
Dimethyl sulfate

Manufacturing Process

From ethyl 1-methylpiperidine-3-carboxylate (which was prepared by hydrogenation of ethyl nicotinate with Ni-catalyst and then by methylation by action dimethyl sulfate) and 2-thienyl magnesium bromide was synthesized 1,1-di(thiophen-2-yl)-2-(3'-N-methylpiperidine), 3-(di-2-thienylmethylene)-1-methylpiperidine was obtained by dehydration of 1,1-di(thiophen-2-yl)-2-(3'-N-methylpiperidine) by action of base.

References

GB Patent No. 924,544; Dec. 7, 1961; Assigned to Tanabe Seiyaku Co., LTD, Japanese Co.

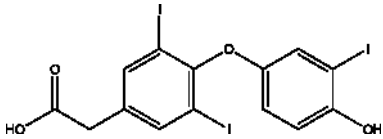
TIRATRICOL

Therapeutic Function: Thyroid hormone

Chemical Name: [4-(4-Hydroxy-3-iodophenoxy)-3,5-diiodophenyl]acetic acid

Common Name: Triiodothyroacetic acid

Structural Formula:



Chemical Abstracts Registry No.: 51-24-1

Trade Name	Manufacturer	Country	Year Introduced
Triacana	Ana	Italy	1972

Raw Materials

Ethyl-3,5-diiodo-4-(4'-hydroxyphenoxy)phenyl acetate
Hydroiodic acid
Iodine

Manufacturing Process

Preparation of 3:5-diiodo-4-(4'-hydroxyphenoxy)phenylacetic acid (diacid): A solution of ethyl 3:5-diiodo-4-(4'-methoxyphenoxy)phenyl acetate (9.5 g) in acetic acid (60 ml) was heated under reflux with hydroiodic acid (SG 1.7, 50 ml) and red phosphorus (0.5 g) for 1 hour. The hot solution was filtered and the filtrate concentrated at 50°C and 15 mm of mercury to above 20 ml. The residue was treated with water (70 ml) containing a little sodium thiosulfate to decolorize the product. The solid was collected by filtration and purified by the method of Harington and Pitt-Rivers [Biochem. J. (1952), Vol. 50, page 438]. Yield 8.36 g (95%). After crystallization from 70% (v/v) acetic acid it melted at 219°C.

A solution of 438 mg of diac in methanol (20 ml) and ammonia solution (SG 0.88; 20 ml) was iodinated at 0°C with 1.8 ml 1 N iodine solution. The product was isolated in almost theoretical yield in a manner similar to that described for tetrac. After crystallization from 50% (v/v) methanol, triac was obtained as colorless needles which melted over the range 65°C to 90°C according to the rate of heating. The molten form resolidified at about 110°C and finally melted at 180°C to 181°C without decomposition. The compound, dried at 25°C/3 mm over silica gel, contains methanol of crystallization.

References

Merck Index 9299
I.N. p. 956
Wilkinson, J.H.; British Patent 805,761; December 10, 1958; assigned to National Research Development Corp. (UK)

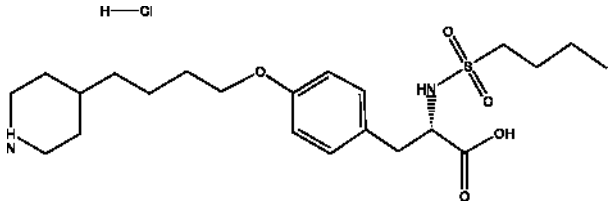
TIROFIBAN HYDROCHLORIDE

Therapeutic Function: Fibrinogen receptor antagonist

Chemical Name: L-Tyrosine, N-(butylsulfonyl)-O-(4-(4-piperidinyl)butyl)-monohydrochloride

Common Name: Aggrastat; Tirofiban hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 144494-65-5 (Base); 142373-60-2

Trade Name	Manufacturer	Country	Year Introduced
Aggrastat	Merck and Co., Inc.	-	-
Aggrastat	GUILFORD PHARMS	-	-

Raw Materials

Tyrosine
4-Picoline
Butyl lithium
Palladium on charcoal
Bis-trimethylsilyl trifluoraceramide
Butylsulfonyl chloride
1-Bromo-3-chloropropane

Manufacturing Process

The synthesis of tirofiban starts by reaction of tyrosine with bis-trimethylsilyl trifluoraceramide to give a derivative in which both functions -OH and COOH- are protected. Treatment of this intermediate with butylsulfonyl chloride gives the corresponding sulfonamide derivative; the quite labile silyl groups are then removed under mildly acidic conditions to give N-butylsulfonyl-tyrosine. In a parallel scheme, 4-picoline is converted to its anion by means of butyl lithium; this gives 4-(4-chlorobutyl)-pyridine on alkylation with 1-bromo-3-chloropropane. The reaction of this compound with N-butylsulfonyl-tyrosine in presence of NaOH gives the ether 2-butylsulfonyaminol-3-[4-pyridin-4-yl-butoxy-phenyl]propionic acid. Hydrogenation over palladium on charcoal then reduce the pyridine ring to a piperidine to afford the fibrinogen receptor antagonist tirofiban.

References

Merck Index, Monograph number: 9605, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.

Chung J.Y.L. et al.; Tetrahedron, 1993, 49, 5767
Lednicer D., The Organic chemistry of drugs synthesis, v .6, p. 21 1999, J. Wiley and Sons, Inc.

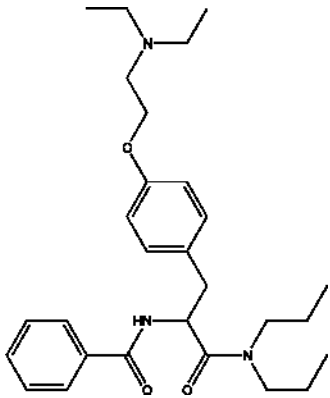
TIROPRAMIDE

Therapeutic Function: Smooth muscle relaxant

Chemical Name: α-(Benzoylamino)-4-[2-(diethylamino)ethoxy]-N,N-dipropylbenzenepropanamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 55837-29-1

Trade Name	Manufacturer	Country	Year Introduced
Maiorad	Rotta	Italy	1982
Alfospas	Rorer	US	-

Raw Materials

N-Benzoyl-DL-tyrosil-di-n-propylamide
Sodium methylate
2-Diethylaminoethyl chloride

Manufacturing Process

36.8 g (0.1 mol) of N-benzoyl-DL-tyrosil-di-n-propylamide are suspended in 350 cc of toluene; there are then added, under agitation, 5.4 g (0.1 mol) of sodium methylate and 50 cc (0.1 mol) of a titrated toluenic solution of 2-

diethylamino-ethyl-chloride. The temperature is taken up to 105°C and the solution is left at this temperature, in agitation, for 12 hours. The toluenic solution is extracted with HCl 2 N; the aqueous acid phase is alkalized, cold, with sodium carbonate, and then reextracted with successive portions of ethyl acetate.

The reunited organic phases are anhydrified upon anhydrous Na_2SO_4,filtered and dried off. The oily residue which is obtained crumbles after a few hours of rest. Amount obtained 39.2 g. Yield 84%. Melting point 65°C to 67°C (crystallizes with petroleum ether).

The free base can be salified so as to render it hydrosoluble. For this purpose, for example, it is dissolved in acetone and precipitated as an oxalate by the addition of a solution of oxalic acid in ethanol. Recrystallizes with ethanol. Melting point (oxalate): 159°C to 162°C. Alternatively it can be dissolved in acetone and precipitated with an acetone solution of HCl. Recrystallizes with acetone-ethanol. Melting point (chlorhydrated): 181°C to 183°C.

References

Merck Index 9301
DFU 7 (6) 413 (1982)
DOT 19 (2) 114 and (5) 271 (1983)
I.N. p. 956
Makovec, F., Rovati, L. and Senin, P.; US Patent 4,004,008; January 18, 1977; assigned to Rotta Research Laboratorium S.p.A. (Italy)

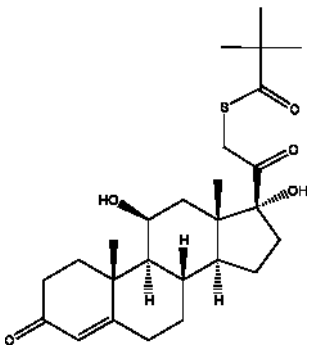
TIXOCORTOL PIVALATE

Therapeutic Function: Antiinflammatory

Chemical Name: 11,17-Dihydroxy-21-mercaptopregn-4-ene-3,20-dione

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 55560-96-8; 61951-99-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Pivalone	Jouveinal	France	1978

Raw Materials

S-Thiopivalic acid
Sodium methylate
Dihydroxy-11β,17α-iodo-21-dioxo-3,20-pregnene-4

Manufacturing Process

In a reactor of 50 liters, sodium S-thiopivalate is prepared from 100 g of S-thiopivalic acid (0.844 mol), 214 cc of solution of sodium methylate, 3.95 M (0.844 mol) in 25 liters of anhydrous acetone.

There are then added 285 g (0.603 mol) of dihydroxy-11β,17α-iodo-21-dioxo-3,20-pregnene-4 and the mixture is brought up to the acetone reflux for two hours. The solvent is eliminated by distillation under vacuum until there is obtained a syrupy residue which is poured into 10 liters of iced water. The insoluble part is filtered and dried under vacuum.

The crude product is purified by recrystallization from ethanol; weight: 250 g; yield: 89.5%.

References

Merck Index 9315
Kleeman and Engel p. 895
I.N. p. 957
Torossian, D.R., Aubard, G.G. and Legeai, J.M.G.; US Patent 4,014,909; March 29, 1971; assigned to Jouveinal S.A. (France)

TIZANIDINE HYDROCHLORIDE

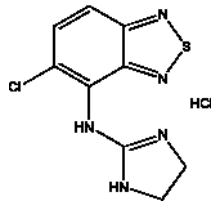
Therapeutic Function: Muscle relaxant, Spasmolytic

Chemical Name: 2,1,3-Benzothiadiazol-4-amine, 5-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-, monohydrochloride

Common Name: Tizanidine hydrochloride

Chemical Abstracts Registry No.: 64461-82-1; 51322-75-9 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Nimzox	Rapross Pharmaceuticals Pvt. Ltd.	India	-
Proxyvon-MR	Wockhardt Ltd.	India	-
Sirdalud	Novartis Pharma	Germany	-
Sirdalud	Novartis Enterprises Private Ltd.	India	-
Zanaflex	Elan Pharmaceuticals, Inc.	-	-
Zanaflex	Novartis	-	-

Raw Materials

Benzoyl chloride
Sodium hydroxide
Ethylene diamine
Hydrochloric acid
Ammonium thiocyanate
4-Amino-5-chloro-2,1,3-benzothiadiazole
Methyl iodide

Manufacturing Process

14 ml of benzoyl chloride are added to a solution of 11.5 g of ammonium thiocyanate in 150 ml of acetone in an ice bath and the mixture is then stirred for 10 min. This solution is heated to the boil at reflux together with 19 g of 4-amino-5-chloro-2,1,3-benzothiadiazole. The solution is cooled to room temperature and diluted with a 4-fold quantity of water. The precipitate is filtered off and rapidly brought to a boil together with 150 ml of a 2 N aqueous sodium hydroxide solution and kept at the boil for 5 min. The solution is cooled to room temperature, is acidified weakly with glacial acetic acid, the precipitate is filtered off, washed with ether and recrystallized from methanol. The N-(5-chloro-2,1,3-benzothiadiazol-4-yl)thiourea, obtained and this is boiled for 1 h together with 9 g of methyl iodide in 150 ml of methanol. After concentrating by evaporation, crude S-methyl-N-(5-chloro-2,1,3-benzothiadiazol-4-yl)isothiuronium iodide is obtained. 9.8 g of S-methyl-N-(5-chloro-2,1,3-benzothiadiazol-4-yl)isothiuronium iodide are heated to the boil at reflux for 1 h together with 50 ml of methanol and 1.8 ml of ethylene diamine. The solvent is then removed by evaporation and the moist residue is boiled at reflux for 1 h together with 20 ml of n-amyl alcohol. The mixture is subsequently shaken with 50 ml of chloroform and 150 ml of water until all the material is dissolved. 40 ml of a 2 N aqueous sodium hydroxide solution are added to the aqueous phase and extraction is effected with 200 ml of chloroform. The organic phase is dried and concentrated by evaporation. After recrystallizing the residue from methanol with the addition of some active charcoal, 4-(2-imidazolin-2-yl-amino)-5-chloro-2,1,3-benzothiadiazole, having

a melting point of 221-223°C, is obtained.

The 4-(2-imidazolin-2-yl-amino)-5-chloro-2,1,3-benzothiadiazole hydrochloride may be obtained by the teaction of 4-(2-imidazolin-2-yl-amino)-5-chloro-2,1,3-benzothiadiazole with hydrochloric acid.

References

Neumann P.; US Patent No. 3,843,668; Oct. 22, 1974; Assigned: Sandoz-Wander Inc., Hanover, N. J.

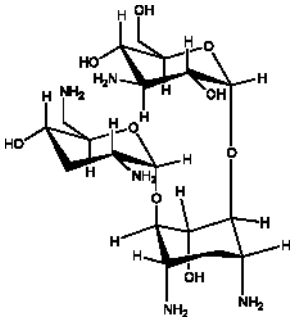
TOBRAMYCIN

Therapeutic Function: Antibiotic

Chemical Name: Streptamine, O-3-amino-3-deoxy-α-D-glucopyranosyl-(1-4)-O-(2,6-diamino-2,3,6-trideoxy-α-D-ribohexopyranosyl-(1-6))-2-deoxy-, D-

Common Name: Nebramycin Factor 6; Tobramicina; Tobramycetin; Tobramycin

Structural Formula:



Chemical Abstracts Registry No.: 32986-56-4

Trade Name	Manufacturer	Country	Year Introduced
Brulamycin	Biogal S.A.	Hungary	-
Obra	Syntho Pharmaceuticals (P) Ltd.	India	-
Tobacin	Aristo Pharmaceutical Ltd.	India	-
Tobracin	Swiss Pharma	Switz.	-
Tobraflex	Alcon	-	-
Tobramycin	American Pharmaceutical Partners, Inc.	USA	-
Tobramycin	Roxane Laboratories	USA	-
Tobrex	Alcon	Belgium	-

Raw Materials

Glycerol
Yeast extract
Kanamycin B
Magnesium acetate
Trimethylchlorosilane
Triphenylphosphine
Hydrogen
Polypeptone
Meat extract
Escherichia coli R11 (IFO-13560)
Adenosine triphosphate
Bis(trimethylsilyl)acetamide
Nickel Raney

Manufacturing Process

Two thousand parts by volume of an aqueous culture medium (pH 7.2) comprising 0.5% of glycerol, 0.5% of polypeptone, 0.5% of yeast extract and 0.3% of meat extract is inoculated with Escherichia coli R11 (IFO-13560). The medium is incubated at 37°C under aeration for 18 h. The culture broth is subjected to centrifuge to recover 4.4 parts of wet cells. The cells are suspended into 17.6 parts by volume of 0.05 M phosphate buffer (pH 7.0). The suspension is subjected to ultrasonic oscillation (Kaijo Denki Co., Ltd.; T-A-4201, 4280-type, 2A) to disintegrate the cells, followed by removing the debris (insoluble materials) by centrifugation, whereby 17 parts by volume of crude enzyme solution is obtained.

To 17 parts by volume of the crude enzyme solution are added 5 parts of kanamycin B, 50 parts by volume of 0.5 M phosphate buffer (pH 7.0), 100 parts by volume of 1 M adenosine triphosphate solution, 50 parts by volume of 0.1 M magnesium acetate solution and 50 parts by volume of 0.1 M 2-mercaptoethanol, which is filled up to 500 parts by volume with distilled water. The mixture is subjected to enzymic reaction at 37°C for 20 h.

The reaction mixture is heated at 80°C for 5 min to cease the reaction, followed by centrifugation. The supernatant is run onto a column of 100 parts by volume of cation-exchange resin [Amberlite IRC-50, NH_4^+-form]. The column is washed with water, and then eluted with 1 N-aqueous ammonia to give fractions which contain kanamycin B-3'-phosphate. The fractions are collected and concentrated under reduced pressure, and then the concentrate is run onto a column of 100 parts by volume of cation-exchange resin [carboxy-methyl Sephadex C-25, NH_4^+-form]. The column is washed with water, and eluted with 0.2 N-aqueous ammonia to give fractions which contain kanamycin B-3'-phosphate. The fractions are collected, concentrated and lyophilized, whereby 4.5 parts of kanamycin B-3'-phosphate.

A solution of one part of kanamycin B-3'-phosphate, 10 parts by volume of bis(trimethylsilyl)acetamide, 2 parts by volume of trimethylchlorosilane and 0.4 part of triphenylphosphine is heated at 115°C for 30 h. After cooling, the reaction mixture is concentrated under reduced pressure, and to the concentrate is added 100 parts by volume of methanol and 50 parts by volume of water, and then the mixture is stirred for 1 h. Methanol is removed by distillation, and ethyl acetate-soluble portion is removed. The water layer is run onto a column of 60 parts by volume of cation-exchange resin [Amberlite CG-50, NH_4^+-form]. The column is washed with 200 parts by volume of water, and fractionated by linear gradient method with 600 parts by volume of water and 600 parts by volume of 0.5 N-aqueous ammonia, each fraction being 10

parts by weight. Upon concentration of some fractions 0.61 part of 2',3'-epimino-2'-deamino-3'-deoxykanamycin B is obtained.

In 40 parts by volume of water is dissolved 0.6 part of 2',3'-epimino-2'-deamino-3'-deoxykanamycin B, and in the presence of 9 parts by volume of Raney nickel the mixture is stirred while introducing hydrogen gas at a pressure of 100 kg/cm^2 at 60°C for 6 h. After the reaction Raney nickel is separated by filtration. The Raney nickel is washed well with 300 parts by volume of 1 N-aqueous ammonia and the washing is added to the filtrate. The whole is concentrated to about 100 parts by volume. The precipitated insolubles are removed by filtration, and the pH of the supernatant is adjusted to about 5.0 with hydrochloric acid. The mixture is run onto a column of 50 ml of cation-exchange resin [Amberlite CG-50, NH_4^+-form].

The column is washed with 150 parts by volume of water, and fractionated by linear gradient method with 1400 parts by volume of water and 1400 parts by volume of 0.3 N-aqueous ammonia, each fraction being 14 parts by weight. From No. 146 to 162 fractions 0.30 part of 3'-deoxykanamycin B (Tobramycin) is obtained.

References

Hiraga K. et al.; US Patent No. 4,020,269; April 26, 1977; Assigned: Takeda Chemical Industries, Ltd., Osaka, Japan

TOBRAMYCIN SULFATE

Therapeutic Function: Antibiotic

Chemical Name: Streptamine, O-3-amino-3-deoxy-α-D-glucopyranosyl-(1-6)-O-(2,6-diamino-2,3,6-trideoxy-α-D-ribohexopyranosyl-(1-4))-2-deoxy-, D-, sulfate (salt)

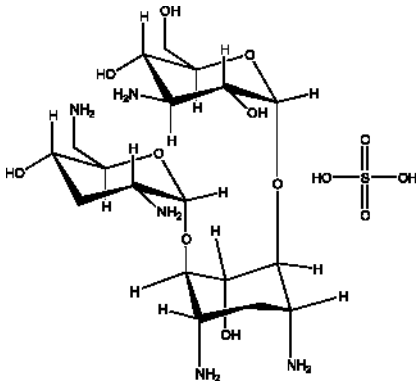
Common Name: Nebramycin Factor 6 sulfate; Tobramicina sulfate; Tobramycetin sulfate; Tobramycin sulfate

Chemical Abstracts Registry No.: 49842-07-1

Raw Materials

Glycerol	Polypeptone
Yeast extract	Meat extract
Kanamycin B	Escherichia coli R11 (IFO-13560)
Magnesium acetate	Adenosine triphosphate
Trimethylchlorosilane	Bis(trimethylsilyl)acetamide
Triphenylphosphine	Nickel Raney
Sulfuric acid	Hydrogen

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Distobram	Lilly	Portugal	-
Gernebcin	Eli Lilly	USA	-
Nebcin	Eli Lilly	USA	-
Nebicina	Lilly	Italy	-
Obracine	Lek D.D.	Slovenia	-
Teflin	Xenon Pharma	-	-
TOBI	PathoGenesis Corp.	USA	-
TOBI	Chiron Inc.	USA	-
TOBI	Pulmopharm	Germany	-
Tobramycin sulphate	GensiaSicor Pharmaceuticals, Inc.	USA	-
Tobramycin sulfate	Abbott	-	-
Tobramycin sulfate	Baxter	-	-

Manufacturing Process

Two thousand parts by volume of an aqueous culture medium (pH 7.2) comprising 0.5% of glycerol, 0.5% of polypeptone, 0.5% of yeast extract and 0.3% of meat extract is inoculated with Escherichia coli R11 (IFO-13560). The medium is incubated at 37°C under aeration for 18 h. The culture broth is subjected to centrifuge to recover 4.4 parts of wet cells. The cells are suspended into 17.6 parts by volume of 0.05 M phosphate buffer (pH 7.0). The suspension is subjected to ultrasonic oscillation (Kaijo Denki Co., Ltd.; T-A-4201, 4280-type, 2A) to disintegrate the cells, followed by removing the debris (insoluble materials) by centrifugation, whereby 17 parts by volume of crude enzyme solution is obtained.

To 17 parts by volume of the crude enzyme solution are added 5 parts of kanamycin B, 50 parts by volume of 0.5 M phosphate buffer (pH 7.0), 100 parts by volume of 1 M adenosine triphosphate solution, 50 parts by volume of 0.1 M magnesium acetate solution and 50 parts by volume of 0.1 M 2-mercaptoethanol, which is filled up to 500 parts by volume with distilled

water. The mixture is subjected to enzymic reaction at 37°C for 20 h.

The reaction mixture is heated at 80C for 5 min to cease the reaction, followed by centrifugation. The supernatant is run onto a column of 100 parts by volume of cation-exchange resin [Amberlite IRC-50, NH_4^+-form]. The column is washed with water, and then eluted with 1 N-aqueous ammonia to give fractions which contain kanamycin B-3'-phosphate. The fractions are collected and concentrated under reduced pressure, and then the concentrate is run onto a column of 100 parts by volume of cation-exchange resin [carboxy-methyl Sephadex C-25, NH_4^+-form]. The column is washed with water, and eluted with 0.2 N-aqueous ammonia to give fractions which contain kanamycin B-3'-phosphate. The fractions are collected, concentrated and lyophilized, whereby 4.5 parts of kanamycin B-3'-phosphate.

A solution of one part of kanamycin B-3'-phosphate, 10 parts by volume of bis(trimethylsilyl)acetamide, 2 parts by volume of trimethylchlorosilane and 0.4 part of triphenylphosphine is heated at 115°C for 30 h. After cooling, the reaction mixture is concentrated under reduced pressure, and to the concentrate is added 100 parts by volume of methanol and 50 parts by volume of water, and then the mixture is stirred for 1 h. Methanol is removed by distillation, and ethyl acetate-soluble portion is removed. The water layer is run onto a column of 60 parts by volume of cation-exchange resin [Amberlite CG-50, NH_4^+-form]. The column is washed with 200 parts by volume of water, and fractionated by linear gradient method with 600 parts by volume of water and 600 parts by volume of 0.5 N-aqueous ammonia, each fraction being 10 parts by weight. Upon concentration of some fractions 0.61 part of 2',3'-epimino-2'-deamino-3'-deoxykanamycin B is obtained.

In 40 parts by volume of water is dissolved 0.6 part of 2',3'-epimino-2'-deamino-3'-deoxykanamycin B, and in the presence of 9 parts by volume of Raney nickel the mixture is stirred while introducing hydrogen gas at a pressure of 100 kg/cm^2 at 60°C for 6 h. After the reaction Raney nickel is separated by filtration. The Raney nickel is washed well with 300 parts by volume of 1 N-aqueous ammonia and the washing is added to the filtrate. The whole is concentrated to about 100 parts by volume. The precipitated insolubles are removed by filtration, and the pH of the supernatant is adjusted to about 5.0 with hydrochloric acid. The mixture is run onto a column of 50 ml of cation-exchange resin [Amberlite CG-50, NH_4^+-form].

The column is washed with 150 parts by volume of water, and fractionated by linear gradient method with 1400 parts by volume of water and 1400 parts by volume of 0.3 N-aqueous ammonia, each fraction being 14 parts by weight. From No. 146 to 162 fractions 0.30 part of 3'-deoxykanamycin B is obtained.

The aqueous solution containing 3'-deoxykanamycin B in free base form by addition of concentrated sulfuric acid give the 3'-deoxykanamycin B sulfate (tobramycin sulfate). The solution of this compound is decolorized by stirring of Darco G-60, filtered and purified by column chromatography.

References

Hiraga K. et al.; US Patent No. 4,020,269; April 26, 1977; Assigned: Takeda Chemical Industries, Ltd., Osaka, Japan

Tompson R.Q. et al.; US Patent No. 3,691,279; Sep. 12, 1972; Assigned: Eli Lilly and Company, Indianapolis, Ind.

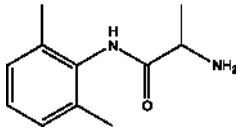
TOCAINIDE

Therapeutic Function: Antiarrhythmic

Chemical Name: 2-Amino-2',6'-propionoxylidide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 41708-72-0

Trade Name	Manufacturer	Country	Year Introduced
Tonocard	Astra	UK	1981
Xylotocan	Astra	W. Germany	1982
Tonocard	Hassle	Sweden	1983
Tonocard	Astra	Australia	1983

Raw Materials

2-Bromo-2',6'-propionoxylidide
Ammonia

Manufacturing Process

The compound 2-amino-2',6'-propionoxylidide was synthesized by saturating with gaseous ammonia at room temperature a suspension of 50 g (0.195 mol) of 2-bromo-2',6'-propionoxylidide in a mixture of 500 ml of 95% alcohol and 400 ml of concentrated aqueous ammonia. The saturation was carried out under mechanical stirring. After 25 hours the mixture was resaturated with ammonia gas. The stirring at room temperature was continued for a total period of 116 hours, and a sample was taken at that time. Gas chromatographic analysis indicated that about 95% of the bromo compound had been converted to the desired product.

The solvents were evaporated in vacuo, and the residue was taken up in 80 ml of 3 M hydrochloric acid. After addition of 220 ml of water, the insoluble material was filtered off, washed with 100 ml of water and then dried. The insoluble material weighed 9.5 g and was mainly unreacted bromo compound.

The filtrate was reacted with 50 ml of 7 M NaOH, extracted three times with methylene chloride (50 ml + 2 x 25 ml portions), dried over potassium carbonate, and then evaporated. The yield of residue was 26.8 g which corresponds to 71.4% of the theoretical yield. This residue was a colorless solidifying oil and was dissolved in 200 ml chloroform. Hydrogen chloride was bubbled in until a sample of the solution tested acidic to wet pH indicator paper. A precipitate was obtained and recovered by filtration. The precipitate was washed with chloroform and dried. The melting point was determined to be from 246°C to 247.5°C.

References

Merck Index 9319
DFU 2 (2) 141 (1977)
PDR p. 1216
OCDS Vol. 3 p. 55 (1984)
DOT 18 (3) 153 and (10) 548 (1982)
I.N. p. 958
REM p. 861
Boyes, R.N., Duce, B.R., Smith, E.R. and Byrnes, E.W.; US Patents 4,218,477; August 19, 1980; and 4,237,068; December 2, 1980; both assigned to Astra Pharmaceutical Products, Inc.

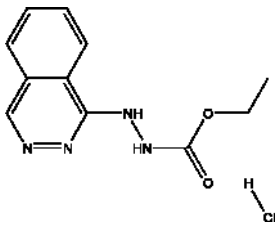
TODRALAZINE HYDROCHLORIDE

Therapeutic Function: Antihypertensive

Chemical Name: Hydrazinecarboxylic acid, 2-(1-phthalazinyl)-, ethyl ester, monohydrochloride

Common Name: Todralazine hydrochloride; Ecarazine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 3778-76-5

Trade Name	Manufacturer	Country	Year Introduced
Prorazin	Teisan	-	-

Raw Materials

Hydrazinophthalazine
Ethyl chlorocarbonate
Hydrochloric acid

Manufacturing Process

A suspension of 13 g of hydrazinophthalazine in 500 ml of anhydrous ethanol is cooled, under agitation to a temperature of -10°C. To the suspension is added dropwise within 30 min a solution of 4.5 g of ethyl chlorocarbonate in 150 ml of anhydrous ethanol and the reaction mass is agitated for about 2 hours, maintaining a temperature of -10°C. The temperature is then raised to about 20°C and stirring is continued for 2 hours, whereupon heating is applied and boiling is maintained for 15 min. After cooling, the separated 1-hydrazinophthalazine hydrochloride is filtered and washed with anhydrous ethanol.

The filtrate is evaporated to a dry state under decreased pressure at a temperature of below 50°C. The residue in a quantity of 8.5 g is dissolved in a boiling solution of 3 ml of concentrated hydrochloric acid in 15 ml of water, and after adding 5 ml of 90%-ethanol the solution is cooled to a temperature of below 0°C.

The separated 1-carboethoxyhydrazinophthalazine hydrochloride is filtered and washed with anhydrous ethanol. 11.5 g of a raw product are obtained which for the purpose of purification are dissolved in 15 ml of boiling water with an addition of 10 ml of 96%-ethanol and after cooling to below 0°C, the pure 1-carboethoxyhydrazinophthalazine hydrochloride is filtered. 9.8 g of the are obtained.

References

Stanislaw Biniecki, Stanislaw Chachula, Helena Jozwiak, Zbigniew Ludwicki, Stefan Labedzki, Wiktor Fietrzak, Stanislaw Pieta, Stanislaw Paradowski, Josef Izdebski, Alicja Maria Izdebska, Barbara Anieszka Izdebska; US Patent No. 3,591,588; July 6, 1971; As

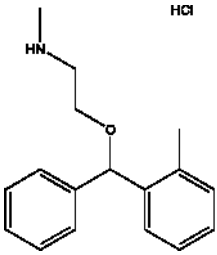
TOFENACIN HYDROCHLORIDE

Therapeutic Function: Psychostimulant

Chemical Name: N-Methyl-2-[(2-methylphenyl)phenylmethoxy]ethanamine hydrochloride

Common Name: N-Demethylorphenadrine hydrochloride; N-Methyl-2-[α-(2-tolybenzyl)oxy]ethylamine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 10488-36-5; 15301-93-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Elamol	Brocades	UK	1971
Tofalin	Brocades	Italy	1981

Raw Materials

2-Methylbenzhydrol
Methylamine
β-Chloroethanol
Hydrogen chloride

Manufacturing Process

A mixture of 39.5 grams of 2-methylbenzhydrol, 200 ml of β-chloroethanol and 10 ml of concentrated hydrochloric acid is boiled under reflux for 4 hours. After cooling, the reaction mixture is poured into water and extracted with petroleum ether (boiling range 40° to 60°C). The layers are separated and the ethereal solution dried with sodium sulfate. It is then filtered. The filtrate is concentrated by evaporation of the solvent. The residue is distilled under reduced pressure to give 51.0 grams (yield 98%) of β-chloroethyl-2-methylbenzhydryl ether, boiling at 156° to 158°C/2.5 mm.

A mixture of 51 grams of β-chloroethyl-2-methylbenzhydryl ether and 35 grams of methylamine in 140 ml of methanol is heated for 6 hours in a closed vessel at a temperature of 125° to 135°C. After cooling, the reaction mixture is poured into water and extracted with petroleum ether (boiling range 40° to 60°C). The ether layer is separated and washed with a 2 N hydrochloric acid solution. The acidic layer is made alkaline and extracted with ether. The ethereal solution is separated and dried with sodium sulfate. After filtration, the solvent is evaporated and the residue distilled under reduced pressure. There is thus obtained 40 grams (yield 80%) of N-methylaminoethyl-2-methylbenzhydrylether boiling at 139° to 143°C/0.7 mm.

The base is dissolved in anhydrous ether, and an ethereal solution of hydrochloric acid is added to form the hydrochloride of N-methylaminoethyl-2-methylbenzhydryl ether. The salt is crystallized from a mixture of ethanol and ether. Yield is 36 grams (78%); melting point 147° to 148°C.

References

Merck Index 9331
Kleeman and Engel p. 899
OCDS Vol. 2 p. 32 (1980)
DOT 8 (5) 189 (1972)
I.N. p. 960
Harms, A.F.; US Patent 3,407,258; October 22, 1968; assigned to Brocades-Stheeman and Pharmacia, Netherlands

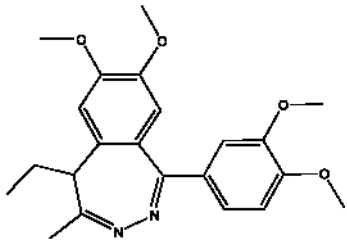
TOFISOPAM

Therapeutic Function: Tranquilizer

Chemical Name: 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzdiazepine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 22345-47-7

Trade Name	Manufacturer	Country	Year Introduced
Grandaxine	Ozothine	France	1975
Seriel	Fabre	France	-
Tavor	Gerardo Ramon	Argentina	-

Raw Materials

3,4,3',4'-Tetramethoxy-6-(α-acetopropyl)-benzophenone
Hydrazine hydrate

Manufacturing Process

A mixture of 38.6 g (0.1 mol) of 3,4,3',4'-tetramethoxy-6-(α-acetopropyl)-benzophenone, 5.5 g (0.11 mol) of 100% hydrazine hydrate or 3.52 g (0.11 mol) of hydrazine, and 500 ml of absolute ethanol is boiled for 5 hours. After

adding 100 ml of benzene, 400 ml of solvent mixture is distilled off from the reaction mixture by slow boiling for 3 hours. After cooling for 8 hours, 19 g of 5H-2,3-benzodiazepine derivative are separated from the residue as small, white crystals. The melting point is 133°C to 136°C (after recrystallizing from absolute ethanol, 136°C).

References

Merck Index 9332
Kleeman and Engel p. 899
DOT 9 (6) 240 (1973); 11 (5) 198 (1975) and 12 (2) 60 (1976)
I.N. p. 960
Egyesult Gyogszer es Tapszer Gyar; British Patent 1,202,579; August 19, 1970
Korosi, J., Lang, T., Komlos, E. and Erdelyi, L.; US Patent 3,736,315; May 29, 1973; assigned to Egyesult Gyogszer es Tapszer Gyar (Hungary)

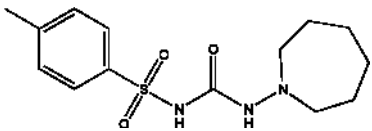
TOLAZAMIDE

Therapeutic Function: Oral hypoglycemic

Chemical Name: N-[[(Hexahydro-1H-azepin-1-yl)amino]carbonyl]-4-methylbenzenesulfonamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 1156-19-0

Trade Name	Manufacturer	Country	Year Introduced
Tolinase	Upjohn	Italy	1964
Tolanase	Upjohn	UK	1965
Norglycin	Upjohn	W. Germany	1966
Tolinase	Upjohn	US	1966
Diabewas	Wassermann	Italy	-
Diabutos	Medica	Finland	-
Tolazamide	Schein	US	-

Raw Materials

Hexamethyleneimine
Sodium nitrite
4-Methylbenzenesulfonylurethane
Lithium aluminum hydride

Manufacturing Process

1-Nitrosohexamethyleneimine: A solution of 89.5 grams of hexamethyleneimine, 75 ml of concentrated hydrochloric acid and 36 ml of water was heated to 70°C on a steam bath. The solution was made acidic by adding 5 ml of 2 N hydrochloric acid. While maintaining the reaction mixture at 70° to 75°C, a solution of 67 grams of sodium nitrite in 95 ml of water was added with stirring over a period of 1 hour. The mixture was then stirred at 70°C for 2 hours, and then cooled. The upper oily layer was separated and the aqueous layer was then extracted with ether. The combined ether extract and oil was dried over anhydrous magnesium sulfate and concentrated to dryness. Upon distillation of the residue there was obtained 1-nitrosohexamethyleneimine as a yellow oil, boiling at 136° to 138°C/34 mm.

1-Aminohexamethyleneimine: To a mixture of 15.18 grams of lithium aluminum hydride and 400 ml of anhydrous ether was added about 10% of a solution of 51.27 grams of 1-nitrosohexamethyleneimine in 100 ml of anhydrous ether. The mixture was refluxed until the reaction started. The remainder of the solution was added at such a rate as to maintain gentle reflux. Refluxing was continued for 2 hours more, followed by the successive addition of 16 ml of water, 12 ml of 20% aqueous sodium hydroxide solution and 56 ml of water. The inorganic precipitate was removed by filtration and washed with ether. The filtrate and ether washes were dried and the ether was removed by evaporation. Upon distillation of the residue there was obtained 25.46 grams (56%) of 1-aminohexamethyleneimine as a colorless liquid boiling at 94° to 96°C/55 mm.

N-(4-Methylbenzenesulfonyl)-N'-Hexamethyleneiminourea Free Base: A mixture of 11.42 grams of 1-aminohexamethyleneimine and 24.33 grams of 4-methylbenzenesulfonylurethane was heated at 130°C (oil-bath temperature) for 2 hours. The resulting ethanol and unreacted amine were removed at 15 mm pressure for 2 hours while keeping the oil bath at 130°C. The residue was cooled and recrystallized from methanol, giving 16.73 grams (54%) of N-(4-methylbenzenesulfonyl)-N'-hexamethyleneiminourea free base melting at 163° to 166°C. After a second recrystallization from methanol, the melting point was 163.5° to 166.5°C.

References

Merck Index 9334
Kleeman and Engel p. 900
PDR pp. 1606, 1862, 1999
OCDS Vol. 1 p. 137 (1977)
DOT 3 (2) 71 (1967)
I.N. p. 960
REM p.977
Wright, J.B.; US Patent 3,063,903; November 13, 1962; assigned to The Upjohn Company

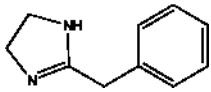
TOLAZOLINE

Therapeutic Function: Vasodilator

Chemical Name: 4,5-Dihydro-2-(phenylmethyl)-1H-imidazole

Common Name: Benzazoline; 2-Benzyl-4,5-imidazoline

Structural Formula:



Chemical Abstracts Registry No.: 59-98-3; 59-97-2 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Priscoline	Ciba	US	1948
Tolavad	Blue Line	US	1962
Benzimidon	Donau-Pharm.	Austria	-
Benzolin	Nissin	Japan	-
Dilatol	A.F.Z.	Norway	-
Dilazol	Phyteia	Switz.	-
Imidalin	Yamanouchi	Japan	-
Lambral	Maggioni	Italy	-
Priscol	Ciba	UK	-
Vaso-Dilatan	Agepha	Austria	-
Zoline	Protea	Australia	-

Raw Materials

Benzyl cyanide
Ethanol
Ethylenediamine

Manufacturing Process

The phenyl-acetiminoether hydrochloride of the formula

from 12 parts of benzylcyanide and ethanol and HCl is mixed with 8 parts of ethylenediamine hydrate which has been diluted with little alcohol, whereby the crystals go into solution. The whole is then heated on the water-bath until the ammonia odor has disappeared, cooled, concentrated caustic potash solution added, and the separated oil extracted with ether. The solution is dried with potassium carbonate and potassium hydroxide. After evaporation a pale oil is left which distills at 147°C under a pressure of 9 mm and which solidifies in the condenser to a white crystalline mass. The yield amounts to 90% of the theory. The hydrochloride melts at 168° to 170°C.

References

Merck Index 9335
Kleeman and Engel p. 900
PDR p. 808
OCDS Vol. 1 p.241 (1977) and 2, 106 (1980)
I.N. p. 960
REM p. 851
Sonn, A.; US Patent 2,161,938; June 13, 1939; assigned to the Society of Chemical Industry in Basle, Switzerland

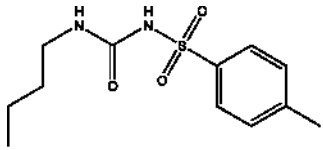
TOLBUTAMIDE

Therapeutic Function: Oral hypoglycemic

Chemical Name: N-[(Butylamino)carbonyl]-4-methylbenzenesulfonamide

Common Name: 1-Butyl-3-(p-tolylsulfonyl)urea

Structural Formula:



Chemical Abstracts Registry No.: 64-77-7

Trade Name	Manufacturer	Country	Year Introduced
Dolipol	Hoechst	France	1956
Orinase	Upjohn	US	1957
Abeformin T	Maruko	Japan	-
Aglicem	Wassermann	Spain	-
Aglycid	Wassermann	Italy	-
Artosin	Boehringer Mannheim	W. Germany	-
Chembutamide	Chemo-Drug	Canada	-
Diabetol	Polfa	Poland	-
Diabeton	Teknofarma	Italy	-
Diabex-T	Funai	Japan	-
Diatol	Protea	Australia	-
Dirastan	Spofa	Czechoslovakia	-
Fordex	Martin Santos	Spain	-
Glyconon	D.D.S.A.	UK	-
Guabeta N	O.T.W.	W. Germany	-
Insilange D	Horita	Japan	-

Trade Name	Manufacturer	Country	Year Introduced
Mellitos D	Ono	Japan	-
Mobinol	Horner	Canada	-
Neo-Dibetic	Neo	Canada	-
Neo-Insoral	Valeas	Italy	-
Nigloid	Nippon Universal	Japan	-
Novobutamide	Novopharm	Canada	-
Oramide	I.C.N.	Canada	-
Oribetic	Cenci	US	-
Orsinon	Teva	Israel	-
Oterben	Chinoin	Hungary	-
Pramidex	Berk	US	-
Proinsul	Crosara	Italy	-
Rankmin	Maruishi	Japan	-
Rastinon	Hoechst	W. Germany	-
Takazide	Fuso	Japan	-
Tolbusal	Krka	Yugoslavia	-
Tolbutol	Smallwood	Canada	-
Tolubetin	Kwizda	Austria	-
Tolumid	A.F.I.	Norway	-
Toluvan	Zambeletti	Italy	-
Unimide	Sankyo	Japan	-
Urerubon	Seiko	Japan	-
Wescotol	Saunders	Canada	-

Raw Materials

n-Butyl isocyanate
Sodium 4-methylbenzenesulfonamide

Manufacturing Process

50 grams of n-butyl isocyanate are stirred at room temperature into a suspension of 96 grams of sodium 4-methyl-benzenesulfonamide in 120 cc of dry nitrobenzene and the whole is then heated for 7 hours at 100°C. After being cooled, the reaction mixture, which is a thick magma, is diluted with methylene chloride or ethyl acetate and the sodium salt of the sulfonylurea formed is separated by centrifuging. The centrifuged crystalline residue freed from organic solvents is dissolved in 500 to 600 cc of water heated at 50°C and decolorized with animal charcoal.

The precipitate obtained by acidification with dilute hydrochloric acid is dissolved in an equivalent quantity of dilute ammonia solution (about 1:20), again treated with animal charcoal and reprecipitated with dilute hydrochloric acid. In this manner N-4-methylbenzenesulfonyl-N'-n-butyl-urea is obtained in analytically pure form in a yield of 70 to 80% of theory. It melts at 125° to 127°C (with decomposition).

References

Merck Index 9337

Kleeman and Engel p. 901
PDR pp. 830, 993, 1606, 1723, 1856, 1999
OCDS Vol. 1 p. 136 (1977) and 3, 62 (1984)
I.N. p. 961
REM p. 977
Ruschig, H., Aumuller, W., Korger, G., Wagner, H., Scholz, J. and Bander, A.; US Patent 2,968,158; January 17, 1961; assigned to The Upjohn Company

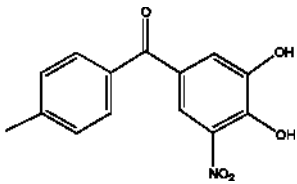
TOLCAPONE

Therapeutic Function: Antiparkinsonian

Chemical Name: Methanone, (3,4-dihydroxy-5-nitrophenyl)(4-methylphenyl)-

Common Name: Tolcapone

Structural Formula:



Chemical Abstracts Registry No.: 134308-13-7

Trade Name	Manufacturer	Country	Year Introduced
Tasmar	Roche	-	-

Raw Materials

Lithium
4-Bromotoluene
Nitric acid
4-Benzyloxy-3-methoxybenzaldehyde
Hydrogen bromide

Manufacturing Process

Condensation of 4-benzyloxy-3-methoxybenzaldehyde with 4-lithium-toluene (prepared from 4-bromotoluene and butyl lithium) leads to the corresponding benzhydrole. Oxidation of the new formed hydroxyl in benzhydrole gives the 4-benzyloxy-3-methoxyphenyl)-p-tolylmethanone. Treatment of this compound with hydrogen bromide selectively removes the benzyl ether that is additionally activated by the transannular carbonyl group. The intermediate is then nitrated under standart conditions to give the (4-hydroxy-3-methoxy-5-nitrophenyl)-p-tolylmethanone. A second treatment of the last compound with hydrogen bromide cleaves the ether group, which is now activated by the adjacent nitro group. This last step affords the (3,4-dihydroxy-5-

nitrophenyl)(4-methylphenyl)methanone.

References

Borgulya J. et al.; Helv. Chim. Acta, 1989, 72, 952

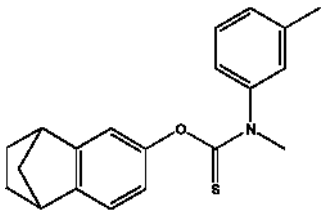
TOLCICLATE

Therapeutic Function: Topical antimycotic

Chemical Name: O-(1,4-Methano-1,2,3,4-tetrahydro-6-naphthyl)-N-methyl-N-(m-tolyl)-thiocarbamate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 50838-36-3

Trade Name	Manufacturer	Country	Year Introduced
Tolmicen	Carlo Erba	Italy	1979
Fungifos	Basotherm	W. Germany	1981
Kilmicen	Farmitalia	W. Germany	1983

Raw Materials

Thiophosgene
1,4-Methano-1,2,3,4-tetrahydro-6-naphthoxide
N-Methyl-m-toluidine

Manufacturing Process

Thiophosgene (1.15 g, 0.01 mol) in chloroform (40 ml) was slowly treated at room temperature with sodium 1,4-methano-1,2,3,4-tetrahydro-6-naphthoxide (1.82 g, 0.01 mol). After 30 minutes, N-methyl-m-toluidine (2.42 g, 0.02 mol) in chloroform (40 ml) was added dropwise to the solution so obtained at room temperature. The reaction mixture was stirred for 48 hours at room temperature and then refluxed for 2 hours. The solvent was evaporated, and the residue redissolved in water and extracted repeatedly with diethyl ether. The organic phase was dried (Na_2SO_4) and evaporated to

dryness to give, after crystallization from isopropanol, O-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-N-methyl-N-(m-tolyl)-thiocarbamate (1.3 g) melting point 92°C to 94°C.

References

Merck Index 9338
DFU 1 (11) 543 (1976)
OCDS Vol. 3 p. 69 (1984)
DOT 17 (3) 94 (1981)
I.N. p. 961
Melloni, P., Metalli, R., Vecchietti, V., Logeman, W., De Carneri, I., Castellino, S. and Monti, G.; US Patent 3,855,263; December 17, 1974; assigned to Carlo Erba SpA

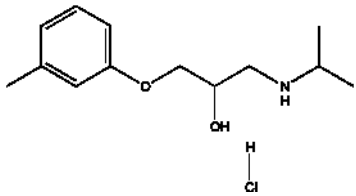
TOLIPROLOL HYDROCHLORIDE

Therapeutic Function: Beta-adrenergic blocker

Chemical Name: 1-(Isopropylamino)-3-(m-tolyloxy)-2-propanol hydrochloride

Common Name: Toliprolol; Sinorytmal

Structural Formula:



Chemical Abstracts Registry No.: 306-11-6

Trade Name	Manufacturer	Country	Year Introduced
Doberol	Boehringer, Ing.	-	-

Raw Materials

Isopropylamine
1-(3'-Methylphenoxy)propylene oxide

Manufacturing Process

59 g (1 mol) of isopropylamine in 60 ml of water are added to a solution of 82 g (0.5 mol) of 3-(3'-methylphenoxy)propylene oxide (prepared from 3-methyl

phenol and epichlorohydrin) in 400 ml of ethanol. After the exothermic reaction has subsided, the mixture is heated for 2 hours at 60°C. After distillation of the volatile components, the free base remains as a solid residue. It is dissolved in hydrochloric acid the acid solution is extracted with ether and then made alkaline with caustic soda solution. The base crystallizes out and is dried over P_2O_5; 101.9 g (91.3% of theory) of 1-(isopropylamino)-3-(m-tolyloxy)-2-propanol being obtained; it is recrystallized from ethyl acetate/petroleum ether, and then has MP: 75-76°C. Upon addition of ethereal hydrogen chloride to an alcoholic solution of the base, the hydrochloride precipitates, and after recrystallization from alcohol/ether, has MP: 120-121°C.

References

Boehringer Ingelheim, B.m.b.H., a German Body Corporate of Ingelheim am Rhein, Germany; G.B. Patent No. 1,084,793; August 26, 1964

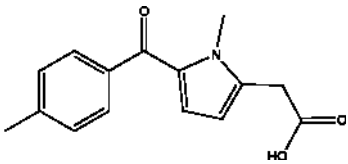
TOLMETIN

Therapeutic Function: Antiinflammatory

Chemical Name: 5-(p-Toluoyl)-1-methylpyrrole-2-acetic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 26171-23-3; 35711-34-3 (Sodium salt)

Trade Name	Manufacturer	Country	Year Introduced
Tolectin	McNeil	US	1976
Tolectin	Cilag	Italy	1977
Tolectin	Cilag	W. Germany	1977
Tolectin	Ortho	UK	1979
Tolectin	Dainippon	Japan	1979
Reutol	Errekappa	Italy	-
Safitex	Montpellier	Argentina	-

Raw Materials

p-Toluoyl chloride
Aluminum chloride

1-Methylpyrrole-2-acetonitrile
Sodium hydroxide

Manufacturing Process

5-(p-Toluoyl)-1-methylpyrrole-2-acetonitrile - To a cooled suspension of 26.6 g (0.2 mol) aluminum chloride in 80 ml dichloroethane is added dropwise 30.8 g (0.2 mol) p-toluoyl chloride. The resulting solution is added dropwise to a solution of 1-methylpyrrole-2-acetonitrile in 80 ml dichloroethane cooled externally with an ice bath. After the addition, the resulting solution is stirred at room temperature for 20 minutes and then refluxed for 3 minutes. The solution is poured into ice acidified with dilute hydrochloric acid. The organic and aqueous fractions are separated. The aqueous fraction is extracted once with chloroform.

The organic fractions are combined and washed successively with N,N-dimethyl-1,3-propanediamine, dilute hydrochloric acid, saturated sodium bicarbonate solution and saturated sodium chloride solution. The organic fraction is dried over anhydrous magnesium sulfate. The solvent is then evaporated off. Upon trituration of the residue with methanol, a solid crystallizes, 5-(p-toluoyl)-1-methylpyrrole-2-acetonitrile, which is removed by filtration and purified by recrystallization from benzene.

Additional product is isolated from the mother liquors which are combined, concentrated in vacuo and the resulting oily residue column chromatographed on neutral alumina using hexane, benzene and ether as successive solvents. The product is isolated by concentrating in vacuo the first few major compound-bearing fractions (10% ether in benzene). The solids are combined and recrystallized from methanol and then from benzene-hexane, melting point 102°C to 105°C.

5-(p-Toluoyl)-1-methylpyrrole-2-acetic acid - A solution of 3.67 g (0.015 mol) of 5-(p-toluoyl)-1-methylpyrrole-2-acetonitrile, 24 ml of 1 N sodium hydroxide and 50 ml of 95% ethanol is stirred and refluxed for 24 hours.

The resulting solution is poured into ice acidified with dilute hydrochloric acid. A white solid precipitates which is extracted into ether. The ether phase is washed with a saturated solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent is evaporated and a white solid, 5-(p-toluoyl)-1-methylpyrrole-2-acetic acid is obtained which is recrystallized twice from isopropanol, melting point 155°C to 157°C.

References

Merck Index 9346
Kleeman and Engel p. 902
PDR p. 1094
OCDS Vol. 2 p. 234 (1980)
DOT 8 (1) 39 (1972) and 11 (3) 109 (1975)
I.N. p. 962
REM p. 1121
Carson, J.R.; US Patents 3,752,826; August 14, 1973; 3,865,840; February 11, 1975; and 3,952,012; April 20, 1976; all assigned to McNeil Laboratories, Inc.

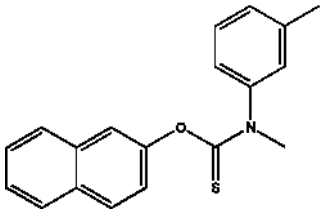
TOLNAFTATE

Therapeutic Function: Antifungal

Chemical Name: Methyl (3-methylphenyl)carbamothioic acid O-2-naphthalenyl ester

Common Name: Naphthiomate T

Structural Formula:



Chemical Abstracts Registry No.: 2398-96-1

Trade Name	Manufacturer	Country	Year Introduced
Tinactin	Schering	US	1965
Tonoftal	Essex	W. Germany	1965
Tinaderm	Kirby-Warrick	UK	1967
Aftate	Plough	US	-
Alarzin	Yamanouchi	Japan	-
Chinofungin	Chinoin	Hungary	-
Pitrex	Ikapharm	Israel	-
Separin	Sumitomo	Japan	-
Sorgoa	Scheurich	W. Germany	-
Sporiderm	Cetrane	France	-
Sporilene	Cetrane	France	-
Tinavet	Schering	W. Germany	-

Raw Materials

N-Methyl-3-toluidine
2-Naphthol
Sodium hydrogen carbonate
Thiophosgene

Manufacturing Process

In a first step, 2-naphthol is reacted with thiophosgene to give 2-naphthyl chlorothionoformate.

A mixture of 4.0 grams of N-methyl-3-toluidine and 2.8 grams of sodium hydrogencarbonate in 50 cc of acetone was stirred at 0° to 10°C and 7.4

grams of 2-naphthyl chlorothionoformate was added in small portions thereto and the mixture was heated under reflux for 30 minutes. The cooled mixture was poured into about 150 cc of cold water and 2-naphthyl-N-methyl-N-(3-tolyl)thionocarbamate was obtained as white crystals. Yield is 9.1 grams (90%). Recrystallization from alcohol gave colorless needle crystals, MP 110.5° to 111.5°C.

References

Merck Index 9347
Kleeman and Engel p. 903
PDR pp. 888, 1429
OCDS Vol. 2 p. 211 (1980) and 3, 69 (1984)
DOT 2 (1) 20 (1966)
I.N. p. 962
REM p. 1230
Miyazaki, K., Hashimoto, K., Kaji, A., Sakimoto, R., Taniguchi, K., Noguchi, T. and Igarashi, Y.; US Patent 3,334,126; August 1, 1967; assigned to Nippon Soda KK, Japan

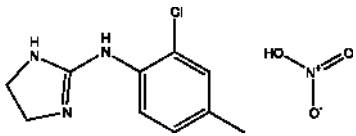
TOLONIDINE NITRATE

Therapeutic Function: Antihypertensive

Chemical Name: N-(2-Chloro-4-methylphenyl)-4,5-dihydro-1H-imidazol-2-amine nitrate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 4201-23-4; 4201-22-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Euctan	Essex	Switz.	1978
Euctan	Delalande	France	1978

Raw Materials

Methyl iodide
Nitric acid
Ethylenediamine
2-Chloro-4-methylaniline
Ammonium thiocyanate

Manufacturing Process

43 g of the thiourea compound (melting point 124°C) obtained in known fashion from 2-chloro-4-methylaniline and ammonium thiocyanate and 20 cc of methyl iodide were dissolved in 200 cc of methanol, and the solution was refluxed for two hours.1 Thereafter, the solvent was evaporated in vacuo, leaving 73.2 g of the isothiouronium hydroiodide of the formula as a residue. This isothiouronium salt was admixed with 20 cc of ethylenediamine, and the mixture was heated for about 30 minutes at 150°C to 160°C, accompanied by stirring; methyl mercaptan escaped during that time. Subsequently, the reaction mixture was taken up in hot dilute acetic acid, and the resulting solution was made alkaline with 2 N sodium hydroxide. A precipitate formed, which was separated by vacuum filtration, washed with water and dried. It was identified to be 2-(2'-chloro-4'-methylphenyl)-amino-1,3-diazacyclopentene-(2) having a melting point of 142°C to 145°C. The yield was 10.2 g.

The nitrate of the base, obtained by acidifying a solution of the free base with nitric acid, had a melting point of 162°C to 164°C and was soluble in water and methanol.

References

Merck Index 9348
DFU 1 (5) 263 (1976)
Kleeman and Engel p. 903
DOT 15 (6) 303 (1979) and 18 (10) 550 (1982)
Zelle, K., Hauptmann, K.H. and Stahle, H.; US Patent 3,236,857; February 22, 1966; and US Patent 3,454,701; July 8, 1969; both assigned to Boehringer Ingelheim GmbH (Germany)

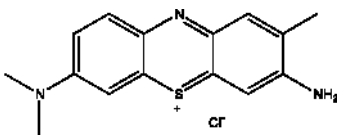
TOLONIUM CHLORIDE

Therapeutic Function: Coagulant

Chemical Name: 3-Amino-7-(dimethylamino)-2-methylphenothiazin-5-ium chloride

Common Name: Dimethyltoluthionine chloride; Blutene chloride; Toluidine blue O

Structural Formula:



Chemical Abstracts Registry No.: 92-31-9

Trade Name	Manufacturer	Country	Year Introduced
Blutene	Abbott	US	1953
Gabilin	Simons	W. Germany	-

Raw Materials

Zinc
Sodium nitrite
o-Toluidine
Dimethyl-p-phenylenediamine
Sodium thiosulfate
Zinc chloride

Manufacturing Process

As taken from US Patent 416,055 (probably the oldest patent on the manufacture of a currently-used drug): In carrying out this process about 6 pbw of dimethyl-p-phenylenediamine was dissolved in about 18 pbw of hydrochloric acid of about 1.16 specific gravity and then a solution of about 3.8 pbw of nitrite of soda in about 6 pbw of water was gradually added. The hydrochlorate of nitroso-dimethylaniline thus produced in the well-known manner is then submitted to the reducing action of zinc-dust by adding, first about 30 pbw of hydrochloric acid of about 1.16 specific gravity and then (in small portions at a time) about 10 pbw of zinc-dust as is well understood by chemists. The solution of hydrochlorate of paramido-dimethylaniline thus obtained is afterwards diluted with about 250 pbw of water and then the uncombined hydrochloric acid contained in the solution is, if any, neutralized by the addition of an alkali. There are then added about 16 pbw of sulfate of alumina and about 13 pbw of thiosulfate of sodium, (hyposulfite of soda) and immediately afterwards a solution of about 5 pbw of bichromate of potash in about 60 pbw of water is quickly run in.

In this stage of the process the formation of an acid sulfureted compound of paramidodimethylaniline takes place, possessing the formula $C_8H_{11}N_2SSO_3H$(paramido-dimethylaniline-thiosulfonic acid). Without previous separation of this intermediate compound a solution of about 5.3 pbw of orthotoluidine, in the requisite amount of dilute hydrochloric acid (about 6 pbw of hydrochloric acid, SG about 1.16, diluted with about 6 pbw water) and shortly afterwards a solution of about 14 pbw of bichromate of potash in about 160 parts by weight of water is then added under constant agitation, when a precipitate will be formed chiefly consisting of a green indamine possessing in its dry condition the formula $C_{15}H_{17}N_3S_2O_3$. In order to transform the same into toluidine-blue, about 50 pbw of a solution of chloride of zinc of about 1.5 specific gravity are added and the mixture thus obtained is boiled during about half an hour, when, after cooling, the toluidine-blue thus formed will separate out and may then be filtered and purified, if necessary, by repeated solution in water and precipitation by means of chloride of sodium and chloride of zinc.

In the above described process the sulfate of alumina may be dispensed with and replaced by as much hydrochloric, sulfuric, or acetic acid as will be required to liberate the thiosulfuric acid from the thiosulfate of sodium employed.

Toluidine-blue prepared as above described presents the following characteristic properties: It consists principally of the hydrochlorate of

dimethyltoluthionine, the composition of which corresponds to the formula $C_{15}H1_5N_3SHCl$.

References

Merck Index 9349
I.N. p. 962
Dandliker, G. and Bernthsen, H.A.; US Patent 416,055; November 26, 1889; assigned to Badische Anilin and Soda Fabrik, Germany
March, B. and Moore, E.E.; US Patent 2,571,593; October 16, 1951; assigned to Abbott Laboratories
Hoff, D.A.; US Patent 2,809,913; October 15, 1957; assigned to The Warren-Teed Products Company

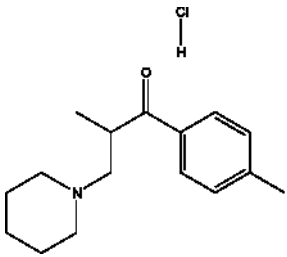
TOLPERISONE HYDROCHLORIDE

Therapeutic Function: Muscle relaxant, Vasodilator

Chemical Name: 1-Propanone, 2-methyl-1-(4-methylphenyl)-3-(1-piperidinyl)- hydrochloride

Common Name: Menopatol; Tolperisone hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 728-88-1 (Base); 3644-61-9

Trade Name	Manufacturer	Country	Year Introduced
Tolperisone hydrochloride	Shanghai Abochem Chemical Co.	-	-
Mydocalm	Gedeon Richter	-	-
Miorelax	Lefa	-	-
Myolaxin	Nichiiko	-	-
Myolaxin	Geno Pharmaceuticals Ltd.	-	-
Tolperisone hydrochloride	ZYF Pharm Chemical	-	-

Raw Materials

4-Methylpropiophenon
Paraformaldehyde
Piperidin hydrochloride

Manufacturing Process

To 1-(4-methylphenyl)-3-(1-piperidinyl)-1-propanol in chloroform was added an excess of thionyl chloride and the reaction mixture refluxed until completed. It was then taken to dryness under reduced pressure and the residue crystallized by dissolving in hot alcohol and diluting with ethyl acetate.

An aqueous solution of the obtained N-[3-chloro-3-(p-tolyl)propyl]piperidine hydrochloride was hydrogenated at 3 atmospheres in the presence of buffered palladium-on-charcoal catalyst. 1-Piperidino-2-methyl-3-(p-tolyl)-3-propanone was purified by distilling the base (boiling point 106-107°C/1 mm) and reconverting to the hydrochloride, melting point 216-217°C.

References

Ruddy A.W.,.Buckley J.S.; J.Amer.Chem.Soc., 1950, 72, 718-721

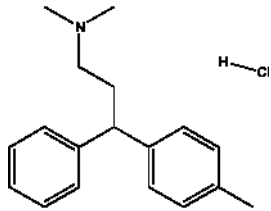
TOLPROPAMINE HYDROCHLORIDE

Therapeutic Function: Antihistaminic, Antipruritic

Chemical Name: N,N,4-Trimethyl-γ-phenylbenzenepropanamine hydrochloride

Common Name: Tolpropamine; Tylagel

Structural Formula:



Chemical Abstracts Registry No.: 3339-11-5

Trade Name	Manufacturer	Country	Year Introduced
Tolpropamine	Hoechst (Aventis)	-	-
Pragman	Albert Roussel	-	-

Raw Materials

Hydrogen
β-Dimethylaminopropiophenone

Phosphoric acid
Palladium
Grignard solution (prepared from 53 g bromtoluene and 7.2 g magnesium in 300 ml of ether)

Manufacturing Process

The Grignard solution (prepared from 53 g bromtoluene and 7.2 g magnesium in 300 ml of ether) was added dropwise to a solution of 35 g β-dimethylaminopropiophenone in 50 ml ether. The mixture was refluxed for 3 hours. Then the liquid phase was added to 500 parts of ice and 100 parts concentrated hydrochloric acid. 1-Phenyl-1-p-tolyl-3-dimethylaminopropanol-1 was crystallized. M.P. of hydrochloride of 1-phenyl-1-p-tolyl-3-dimethylaminopropanol-1 185°C.

10 g of 1-phenyl-1-p-tolyl-3-dimethylaminopropanol-1 was dissolved in 30 ml of 85% phosphoric acid and the solution was heated at 130-135°C for 1 hour. After cooling to the mixture was added a water and an aqueous solution of sodium hydroxide. γ-Phenyl-γ-p-tolylallyldimethylamine was extracted with ether and extract was dried with sodium sulfate.

γ-Phenyl-γ-p-tolylallyldimethylamine hydrochloride was hydrogenated with palladium catalyst. γ-Phenyl-γ-p-tolyl-3-dimethylaminopropan obtained has melting point 156°C.

References

Bockmuehl M., Stein L.; DE Patent No. 925,468; March 21, 1955

TOLTERODINE TARTRATE

Therapeutic Function: Anticholinergic

Chemical Name: Phenol, 2-((1R)-3-(bis(1-methylethyl)amino)-1-phenylpropyl)-4-methyl-, L-tartrate (1:1) (salt)

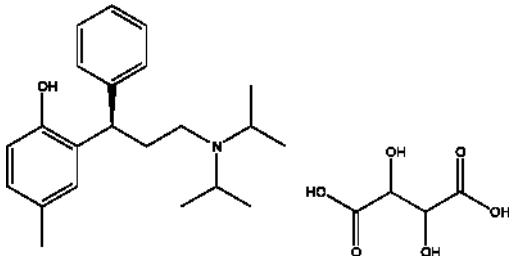
Common Name: Tolterodine tartrate

Chemical Abstracts Registry No.: 124937-52-6; 124937-51-5 (Base)

Raw Materials

Sulfuric acid
4-Cresol
Cinnamic acid
Citric acid
Diisopropylamine
Sodium hydroxide
Tartaric acid, L-
trans-Cinnamic acid
Potassium carbonate
Diisobutylaluminum hydride
Palladium on carbon
Hydrochloric acid
Sodium carbonate

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Detrol	Pharmacia and Upjohn	-	-
Detrusitol	Pharmacia and Upjohn	Italy	-
Roliten	Ranbaxy Global Consumer Healthcare	India	-

Manufacturing Process

Trans-cinnamic acid (100 g, 675 mmol) is added to a 1 L 4-neck round bottom flask equipped with a mechanical stirrer, thermocouple, and nitrogen inlet. Para-cresol (76.6 g, 708 mmol) is preheated in a water bath at 60°C and added to the cinnamic acid followed by concentrated sulfuric acid (13.0 ml, 243 mmol). The reaction is immediately heated to a set point of 122.5°C and stirred at 120°-125°C until judged to be complete by HPLC analysis. When the reaction is complete the mixture is cooled to 100°C and added to a prewarmed separatory funnel (500 ml). The bottom layer containing the sulfuric acid is removed and toluene (280 ml), water (50 ml) and potassium carbonate (47%, 10 ml) are added to the separatory funnel containing the crude product. The pH of the aqueous layer is adjusted to between 5-8 with additional 47% potassium carbonate. The layers are separated and the organic layer is then washed once with water (50 ml). The organic layer is concentrated to a final volume of approximately 150 ml under reduced pressure. Isopropanol (350 ml) is then added, and distillation is continued to a volume of 350 ml. Isopropanol (150 ml) is again added and again distilled to 350 ml (2 times). The mixture is then cooled to 30°-40°C with rapid stirring until the product crystallizes. The rapid stirring is continued after crystallization. The product is cooled to 0°-5°C and held at this temperature for 1 h, filtered and washed with isopropanol (200 ml) cooled to 0°-5°C. If the last portion of the wash is colored the wash is continued until no more color is removed. The solids are then dried at 60°C under reduced pressure to give the 3,4-dihydro-6-methyl-4-phenyl-2H-benzopyran-2-one, melting point (uncorrected) 83°-85°C.

3,4-Dihydro-6-methyl-4-phenyl-2H-benzopyran-2-one (100.0 g, 420.2 mmol) is added to toluene (500 ml). The mixture is degassed by purging alternately with vacuum and nitrogen and then cooled to -21°C. Diisobutylaluminum hydride in toluene solution (DIBAL, 1.5 M, 290 ml, 435 mmol) is then slowly added over 2 h via add funnel while maintaining the reaction temperature at -20°-25°C. The reaction is usually done when the DIBAL add is completed. If

the reaction is not done additional DIBAL can be added in increments. When the reaction is done (<1% lactone) ethyl acetate (45 ml) is added at -20°-25°C via add funnel. Very little exotherm is observed. Next, citric acid (23%, 500 ml) is added. The mixture is stirred at 45°-50°C for 1 h (or stirred overnight at 20°-25°C), the phases are separated, the organic phase is washed with water (2 times 300 ml). The organic phase is concentrated to 250 ml under reduced pressure. Methanol (500 ml) is added, and the mixture is concentrated to 250 ml. The methanol addition and distillation is repeated to give the 3,4-dihydro-6-methyl-4-phenyl-2H-benzopyran-2-ol in methanol solution.

3,4-Dihydro-6-methyl-4-phenyl-2H-benzopyran-2-ol in methanol (500 ml) is slowly added to palladium on carbon (5%, 22 g, 1.5 mmol) while maintaining a slight nitrogen purge. If 3,4-dihydro-6-methyl-4-phenyl-2H-benzopyran-2-ol is added too quickly without a nitrogen purge the catalyst will ignite the methanol. Diisopropylamine (147.0 ml, 1.05 mol) is added, and the mixture is hydrogenated at 45-50 psi and 48°C until the reaction is judged to be complete by HPLC (<2% lactol). The reaction is usually done after 10 h, but can be run overnight. The reaction mixture is cooled and removed from the hydrogenator using a methanol (150 ml) rinse. The combined reaction mixture and rinse is filtered through a bed of solka floc (10 g). The solka floc is washed thoroughly with methanol (100 ml) and the filtrate is concentrated to remove methanol while ethyl acetate is being added back. The volume of this solution of the (2-diisopropylamino)ethyl)benzyl)-p-cresol is adjusted to 700 ml using ethyl acetate and the mixture is heated to 55°C.

To form the hydrochloride salt of the (2-diisopropylamino)ethyl)benzyl)-p-cresol (Tolterodine), concentrated hydrochloric acid (52.5 ml, 630 mmol) is added over 15 min. The resulting slurry is gradually cooled to -15°-20°C and held at this temperature for 1 h. Tolterodine hydrochloride is collected by filtration, washed 3 times with ethyl acetate, and dried overnight under reduced pressure at 600 to give the tolterodine hydrochloride, melting point 199°-201°C.

Tolterodine hydrochloride (130.0 g, 359 mmol), methylene chloride (1.3 L) and water (650 ml) are mixed. The mixture is stirred rapidly while adding sodium hydroxide (50%, 13.0 ml) and sodium carbonate (13.0 g, 123 mmol). The pH as determined by pH paper is 10-11. After stirring thoroughly for approximately 15 min two clear homogeneous phases form. Stirring is continued for another 45 min, the layers are separated and the organic phase is washed with water (2 times 650 ml). The methylene chloride mixture is concentrated under reduced pressure. The concentrate is dissolved in ethanol (325 ml) and warmed to 60°-70°C. L-tartaric acid (80.84 g, 539 mmol) slurried in hot ethanol (810 ml) is added via add funnel at 60°-70°C over approximately 30 min. When the addition is done the slurry is refluxed for 1 h, gradually cooled to 0°C and held at this temperature for 1 h. The slurry is filtered, washed with ethanol (2 times 260 ml) previously cooled to 0°C, and dried overnight under reduced pressure at 60°C to give the crude title compound. The crude product (136.0 g) and ethanol (5.44 L) are mixed and heated to 80°C for 30 min. The mixture is concentrated to half the initial volume by distilling 2.72 L of ethanol. The mixture is gradually cooled to 20°-25°C over 1 h, placed in an ice bath, and held at 0°C for 1 h. The tolterodine L-tartrate is collected by filtration, washed with ethanol (2 times 272 ml) previously cooled to 0°C, and dried overnight under reduced pressure at 60°C

to give product. This procedure was repeated a second time on 81.0 g of once recrystallized tolterodine L-tartrate to give the optically active (+)-(R)-2-(α-(2-(diisopropylamino)ethyl)benzyl)-p-cresol L-tartrate, melting point (uncorrected)=210°-211°C.

References

Gage J.R., Cabaj J.E.; US Patent No. 5,922,914; July 13, 1999; Assigned: Pharmacia and Upjohn Company, Kalamazoo, Mich.

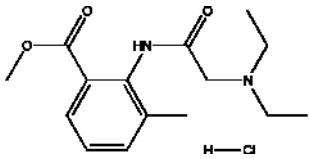
TOLYCAINE HYDROCHLORIDE

Therapeutic Function: Local anesthetic

Chemical Name: Methyl 2-(2-(diethylamino)acetamido)-m-toluate monohydrochloride

Common Name: Tolycaine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 3686-58-6 (Base); 7210-92-6

Trade Name	Manufacturer	Country	Year Introduced
Tolycaine Hydrochloride	ZYF Pharm Chemical	-	-
Baycain	Sopharma	-	-

Raw Materials

2-Amino-3-methylbenzoic acid methyl ester
Chloracetylchloride
Diethyl amine

Manufacturing Process

A suspension of 40 g 2-amino-3-methylbenzoic acid methyl ester in 125 ml of benzene was added 125 ml of saturated solution of sodium acetate and then at 0-5°C was added 37 g chloracetylchloride. The mixture was stirred for 1 hour at room temperature. The mixture was filtered. The organic layer was with 10% solution of potassium carbonate and dries under calcium chloride. By distillation of the mixture was obtained 15 g of 2-(2-chloroacetylamino)-3-

methylbenzoic acid methyl ester; melting point 86-87.5°C (crystallization from a mixture acetic acid and ligroin); yield 21.8 g.

A mixture of 16 g of 2-(2-chloroacetylamino)-3-methylbenzoic acid methyl ester and 10 g diethyl amine in benzene was refluxed for 5 hours. After cooling the diethyl amine hydrochloride was deleted by filtration. The organic layer was washed with 2 N hydrochloric acid. To the solution was added potassium carbonate. The product was extracted with ether and distilled.

References

DE Patent No. 1,018,070; Oct. 24, 1957; Assigned to Farbenfabriken Bayer Aktiengesellschaft, Levercusen-Bayerwerk

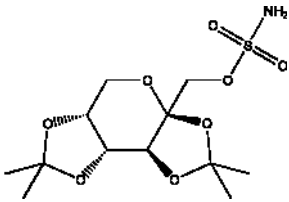
TOPIRAMATE

Therapeutic Function: Anticonvulsant

Chemical Name: β-D-Fructopyranose, 2,3:4,5-bis-O-(1-methylethylidene)-, sulfamate

Common Name: Topiramate

Structural Formula:



Chemical Abstracts Registry No.: 97240-79-4

Trade Name	Manufacturer	Country	Year Introduced
Topamax	Janssen Farmaceutica LDA	Portugal	-
Topamax	Ortho-McNeil	-	-
Topamax	Ethnor	-	-

Raw Materials

2,3:4,5-Di-O-isopropylidene-β-fructopyranose
Sodium hydride
Sulfamoyl chloride

Manufacturing Process

To a cold solution (-4°C) of 2,3:4,5-di-O-isopropylidene-β-fructopyranose (75 g, 0.29 mol) in DMF (725 ml) was added 50% oily sodium hydride (16.34 g,

0.34 mol). After stirring for 90 min, sulfamoyl chloride (54.9 g, 0.48 mol) was added and the stirring continued for an additional 3.5 h at that temperature. The reaction mixture was poured into cold water and extracted with toluene. The organic layer was dried (Na_2SO_4) and the solvents removed under vacuum to give a syrup which crystallized immediately. Recrystallization from ethylacetate/hexane gave pure 2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate, melting point 125°-126°C.

References

Maryanoff B.E., Gardocki J.F.; US Patent No. 4,513,006; April 23, 1985; Assigned: Mc Neil Lab., Inc., Fort Washington, Pa

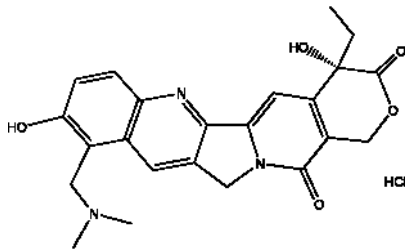
TOPOTECAN HYDROCHLORIDE

Therapeutic Function: Antineoplastic

Chemical Name: 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione, 10-((dimethylamino)methyl)-4-ethyl-4,9-dihydroxy-, (S)-, monohydrochloride

Common Name: Topotecan hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 119413-54-6; 123948-87-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Hycamtin	SmithKline Beecham Pharmaceuticals	UK	-

Raw Materials

Camptothecin
Acetic acid
Lead(IV) acetate
Hydrogen chloide
Dibromomethane
Platinum oxide
Hydrogen
Dimethylamine
Dichloromethane

Manufacturing Process

Camptothecin (CPT) - a compound isolated from the bark, leaves and fruit of Camptotheca acuminate (Wall M. E. et al., J. Am. Chem. Soc. 88, 3888, 1966).

10-Hydroxycamptothecin (10-HCPT) was prepared by subjecting CPT (3.2 g 0.0092 mol), 0.8 g of Pt^0 (prepared by pre-reduction of 8 g of amorphous PtO_2 in 80 ml of acetic acid for 1.5 h under 1 atm hydrogen pressure) and acetic acid to 1 atm of H_2 for 8.5 h after which theoretical amount of H_2 absorbed (slightly more than 0.4 L) and uptake of H_2 gets slowed down. The reaction mixture was degassed under steam of helium and filtered through celite and washed with acetic acid (20 ml). The resulting solution was treated immediately with $Pb(OAc)_4$ (6.4 g 0.014 mol) in portions and reaction mixture, stirred vigorously under helium for 30 min. Gumy residue was obtained on evaporation of solvent which was triturated with cold water (100 ml) to produce light brown solid. The solid was collected, washed with cold water and air dried overnight when a mixture of 10-HCPT (44%), acetyl 10-hydroxycamptothecin (10-AcHCPT, 26%) and unreacted CPT (32%) on HPLC basis was obtained. This crude mixture was combined with 150 ml of 50% acetic acid and heated under reflux conditions overnight. The reaction mixture was cooled, concentrated to 20 ml and treated with cold water (100 ml) to produce precipitate, which is filtered, washed with more cold water and dried to afford 2.1 g of solid containing 10-HCPT (70%), 10-AcCPT (1.2%) and CPT (21.3%) on the basis HPLC. Mixture was triturating with 0.5% aq HCl to dissolve the water-soluble. When insoluble CPT was removed by filtration. Water-soluble was extracted with chloroform and crystallized from boiling solution of 20% of MeOH in $CHCl_3$ by adding EtOAC dropwise until turbidity appeared to obtain pure yellow 10-(HCPT), melting point 268°-270°C.

10-HCPT (0.364 g 0.01 mmol) and 40% aqueous dimethylamine (12 ml) was added in dichloromethane (50 ml) in which anhydrous potassium carbonate (2.17 g, 15 mmol) has been suspended. The reaction mixture was stirred at room temperature for 5 h, then filtered and solid extracted with ethylacetate (20 ml). The solvent is evaporated in vacuo giving a residue. The residue was triturated with 0.5% aq HCl (50 ml) to dissolve the water-soluble adduct. Water-soluble were partitioned with petroleum ether (3 times 50 ml) and followed by ethylacetate (3 times 50 ml). The aqueous layer was lyophilized as an off white hydrochloride salt of 9-[(dimethylamino)methyl]10-hydroxy(20S)-camptothecin (topotecan hydrochloride) yield 0.236 g (65%).

References

Puri S.C. et al.; US Patent No. 6,660,861 B1; Dec. 9, 2003; Assigned: Council of Scientific and Industrial Research, New Delhi

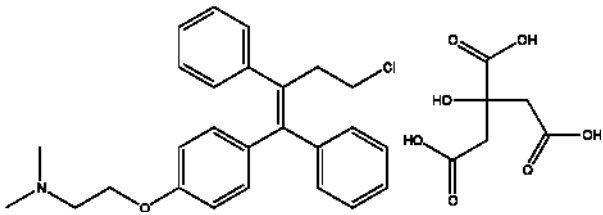
TOREMIFENE CITRATE

Therapeutic Function: Antiestrogen, Antineoplastic

Chemical Name: Ethanamine, 2-(4-(4-chloro-1,2-diphenyl-1-butenyl)phenoxy)-N,N-dimethyl-, (Z)-, citrate salt (1:1)

Common Name: Toremifene citrate

Structural Formula:



Chemical Abstracts Registry No.: 89778-27-8; 89778-26-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Fareston	Orion Corporation	Finland	-
Fareston	Schering Laboratories/Key Pharmaceuticals	-	-

Raw Materials

Cinnamaldehyde
Acetic anhydride
Thionyl chloride
4-[2-(N,N-Dimethylamino)-ethoxy]benzophenone
Lithium aluminum hydride
Acetyl chloride
Ammonium chloride

Manufacturing Process

The reaction is performed under dry conditions. 2.1 g of lithium aluminum hydride and 50 ml of dry tetrahydrofuran are placed in a flask. Then 13.2 g of cinnamaldehyde in 50 ml of dry tetrahydrofuran are added while stirring and keeping the temperature at 25°-35°C. The stirring is continued for another 30 min at room temperature. Then 26.9 g of 4-[2-(N,N-dimethylamino)-ethoxy]benzophenone in 70 ml of dry tetrahydrofuran are added while stirring. The temperature is kept at 35°-45°C during the addition. After stirring for 2 h at 40°C the reaction mixture is poured into 150 ml of 25% ammonium chloride solution, and aluminium hydroxide is precipitated and filtered off. The filtrate is transferred to a separating funnel and the organic layer is separated. The aqueous layer is once again extracted with 60 ml of ethyl acetate. The organic layers are combined and dried over sodium sulfate. The solvent is evaporated. The residue is recrystallized from toluene. The yield is 27.5 g (68%) of 1,2-diphenyl-1-[4-[2-(N,N-dimethylamino)ethoxy]phenyl]-butane-1,4-diol.

The reaction is performed under dry conditions. 40.5 g 1,2-diphenyl-1-[4-[2-(N,N-dimethylamino)ethoxy]phenyl]butane-1,4-diol and 150 ml of acetic acid anhydride are placed in a flask. The temperature is raised to 90°C, where it is kept until the primary OH-group is completely acetylated. [4-Acetoxy-1,2-

diphenyl-1-[4-[2-(N,N-dimethylamino)ethoxy]phenyl]butan-1-ol is obtained as intermediate; melting point of the (RR, SS)-isomer pair is 97°-99°C. While stirring the reaction mixture, 30 ml of acetyl chloride in 50 ml of acetic acid anhydride are added at 90°C. The stirring is continued at this temperature for 2 h. The solvent is evaporated. Then 1 M sodium carbonate solution is added in excess, after which the product is extracted in toluene. The solution is dried over sodium sulfate, and the solvent is evaporated. The yield of the pure isomer mixture (Z:E 2:1) of 4-acetoxy-1,2-diphenyl-1-[4-[2-(N,N-dimethylamino)ethoxy]-phenyl]-1-butene is quantitative.

The4-acetoxy-1,2-diphenyl-1-[4-[2-(N,N-dimethylamino)ethoxy]-phenyl]-1-butene are dissolved in 94% ethanol, after which water and 20% sodium hydroxide solution are added. The mixture is refluxed for 1 h. The solution is neutralized with 2 M hydrochloric acid, after wich the ethanol is evaporated. Water is added into the residue. The product is extracted in ethyl acetate, the ethyl acetate solution is dried and the solvent is avaporated. The product is recrystallized from a mixture of water and methanol. The yield of the pure mixture of the isomers (Z:E 2:1) of 1,2-diphenyl-1-[4-[2-(N,N-dimethylamino)ethoxy]phenyl]-1-buten-4-ol, melting point 93°-100°C, is quantitative.

Isolation of the (Z)-isomer as a free base: the mixture of the isomers (Z:E 2:1) of 1,2-diphenyl-1-[4-[2-(N,N-dimethylamino)ethoxy]phenyl]-1-buten-4-ol is recrystallized from toluene, and 15.9 g (41%) of the (Z)-isomer is obtained, melting point 110°-112°C.

The reaction is performed under dry conditions. 42.4 g of (Z)-1,2-diphenyl-1-[4-[2-(N,N-dimethylamino)ethoxy]phenyl]-1-buten-4-ol are dissolved in 250 ml of chloroform. Then 23.8 g of thionyl chloride are added dropwise. The mixture is refluxed 3 h. The solvent is evaporated, after which the product is recrystallized from ethyl acetate. The yield of the hydrochloride salt of 4-chloro-1,2-diphenyl-1-[4-[2-(N,N-dimethylamino)ethoxy]-phenyl]-1-butene (Z) is 36.7 g (83%), melting point 194°-196°C.

The base can be liberated from the salt with 1 M sodium carbonate solution, after which the base is extracted in toluene. The toluene solution is dried and the solvent is evaporated. The free base, 4-chloro-1,2-diphenyl-1-[4-[2-(N,N-dimethylamino)ethoxy]-phenyl]-1-butene (Z), has melting point 108°-110°C (from acetone).

In practice it is usually used as citrate salt (1:1).

References

Toivola R.J. et al.; US Patent No. 4,696,949; Sep. 29, 1987; Assigned: Farmos Group Ltd., Turku, Finland

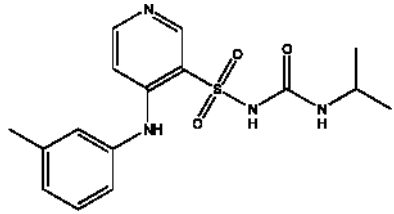
TORSEMIDE

Therapeutic Function: Diuretic

Chemical Name: 3-Pyridinesulfonamide, N-(((1-methylethyl)amino) carbonyl)-4-((3-methylphenyl)amino)-

Common Name: Torasemide; Torsemide

Structural Formula:



Chemical Abstracts Registry No.: 56211-40-6

Trade Name	Manufacturer	Country	Year Introduced
Demadex	Roche	-	-
Demadex	Boehringer Mannheim	-	-

Raw Materials

Ammonium hydroxide
3-Methylbenzylamine
Isopropylisocyanate
3-Sulfonylchloride-4-chloropyridine
Sodium hydroxide
Triethylamine

Manufacturing Process

In a 100 ml three-necked flask equipped with magnetic stirrer, condenser, thermometer and dropping funnel 3-sulfonylchloride-4-chloropyridine (10 g, 1 eq., 46.7 mmoles) was suspended in t-butyl-methyl ether (MTBE) (30 ml) at room temperature. Ammonium hydroxide, 25% solution (13.5 ml, 2.13 eq.) was dropped into the suspension in a rate such that the temperature is allowed to increase to 22°-26°C, this temperature was maintained until all the ammonium hydroxide was added. The suspension was then to cooled to room temperature and was stirred for 1 h. The pH of the suspension was adjusted to 80.1 by the addition of a few drops of ammonium hydroxide, 25% solution. The suspension was filtered and washed with water (2 times 10 ml) and the wet product (8 g) dried at 40°C, under the 1 mm Hg vacuum. 3-Sulfonamide-4-chloropyridine was isolated in 74.4% yield, 6.7 g.

A mixture of 0.01 moles of 3-sulfonamido-4-chloropyridine, 0.02 mole of 3-methylbenzylamine and 50 ml of dry ethanol was heated to reflux temperature for 9 h. After distillation of the ethanol the residue was taken up in an excess of diluted NaOH and the excess of amine was extracted by means of ether.

The aqueous solution was then decolourized with charcoal and filtered, and the filtrate was neutralized with acetic acid. The precipitated product was separated and purified by crystallization from a mixture of water and acetone.

The 3-sulfonamido-4-(3-methylbenzyl)amino-pyridine crystallized in the form of beige coloured cristals having a melting point of 184°-186°C.

0.01 mole of 3-sulfonamido-4-(3-methylbenzyl)amino-pyridine was reacted with 0.015 mole of isopropylisocyanate in the presence of 0.02 mole of triethylamine and of 20 ml of dichloromethane, at room temperature for 20 h. After evaporation under vacuum, the residue was taken up in an excess of diluted Na_2CO_3, filtered off and acidified by means of acetic acid. After precipitation of the product it was filtered and washed several times with ice cold water. The 3-isopropylcarbamoylsulfonamido-4-(3-methylbenzyl)amino-pyridine (Torsemide) showing as a white powder, has a melting point of 147°-149°C.

References

De Ridder R.R. et al.; US Patent No. 4,244,950; Jan. 13, 1981; Assigned: A. Christiaens Societe Anonyme, Brussels, Belgium
Kordova M.; US Patent No. 6,635,765 B2; Oct. 21, 2003; Assigned: Teva Pharmaceutical Industries, Ltd., Petah Tiqva

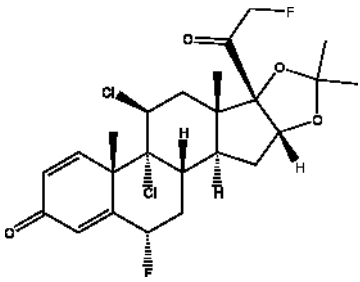
TRALONIDE

Therapeutic Function: Glucocorticoid

Chemical Name: (6α,11β,16α)-9,11-Dichloro-6,21-difluoro-16,17-((1-methylethylidene)bis(oxy))pregna-1,4-diene-3,20-dione

Common Name: Tralonide, Talidan

Structural Formula:



Chemical Abstracts Registry No.: 21365-49-1

Trade Name	Manufacturer	Country	Year Introduced
Tralonide	Tianjin TianMao Technology Development Corp., Ltd.	-	-

Raw Materials

Sodium	Methanol
Tosyl chloride	Potassium fluoride
Chlorine	Pyridine

6α-Fluoro-16α,17α-isopropylidenedioxy-21-acetoxypregna-1,4,9(11)-triene-3,20-dione

Manufacturing Process

90 g of 6α-fluoro-16α,17α-isopropylidenedioxy-21-acetoxypregna-1,4,9(11)-triene-3,20-dione are suspended in 152 ml of methanol to which has been added 475 mg of sodium in 38 ml of methanol. This reaction mixture is stirred for 45 min at from 20 to 25°C and then neutralized with acetic acid. After evaporation to dryness, the residue is dissolved in methylene chloride and this solution is washed with water, dried over sodium sulfate and concentrated. Addition of methanol to the concentrate followed by further concentration yields a slurry which is filtered. The solid thus collected is washed with cold methanol and dried to yield 6α-fluoro-16α,17α-isopropylidenedioxypregna-1,4,9(11)-trien-21-ol-3,20-dione, M.P. 245°C (dec.), $[\alpha]_D$ = +24°.

To a cooled solution of 3.4 g of 6α-fluoro-16α,17α-isopropylidenedioxypregna-1,4,9(11)-trien-21-ol-3,20-dione in 20 ml of 9:1 chloroform:pyridine is added in small portions 1.4 g of tosyl chloride. The reaction mixture is allowed to stand for 14 hours at 0°C and is then washed with dilute hydrochloric acid, water and sodium bicarbonate solution. The chloroform is removed by evaporation under reduced pressure and the residue is dissolved in acetone. This acetone solution is added to a refluxing suspension of 10 g of potassium fluoride in 50 ml of dimethylformamide. After refluxing for 5 hours, the mixture is cooled and poured into water. The solid which forms is collected by filtration, dried and recrystallized from acetone and hexane to yield 6α,21-difluoro-16α,17α-isopropylidenedioxypregna-1,4,9 (11)-triene-3,20-dione, M.P. 267°C (dec.), $[\alpha]_D$ = +9°.

5 g of 6α,21-difluoro-16α,17α-isopropylidenedioxypregna-1,4,9(11)-triene-3,20-dione are dissolved in 50 ml of chloroform containing 5 ml of pyridine. The mixture is held at 0°C for 15 min while a stream of chlorine is bubbled through. The mixture is then poured into a 10% aqueous sulfuric acid solution and the organic layer separated. This layer is washed with 5% aqueous sodium bicarbonate and water to neutrality, dried over sodium sulfate and evaporated to dryness to yield 6α,21-difluoro-9α,11β-dichloro-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione, M.P. 245°C (dec.), $[\alpha]_D$ = +133°.

References

Alvarex F.S.; US Patent No. 3,728,335; Apr.17, 1973; Assigned to Syntex Corporation, Panama, Panama

John H. Fried, Palo Alto; US Patent No. 3,409,613; July 28, 1966; Assigned to Syntex Corporation, Panama, Panama

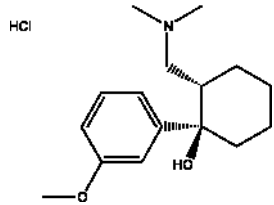
TRAMADOL HYDROCHLORIDE

Therapeutic Function: Analgesic

Chemical Name: (+/-)-trans-2-[(Dimethylamino)methyl]-1-(m-methoxyphenyl)cyclohexanol hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 22204-88-2; 27203-92-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Tramadol	Gruenenthal	W. Germany	1977
Crispin	Kowa	Japan	1978
Tramal	Gruenenthal	Switz.	1978

Raw Materials

m-Bromoanisole
2-Dimethylaminomethyl-cyclohexanone
Magnesium
Hydrogen chloride

Manufacturing Process

5 g of magnesium turnings are treated while stirring with a mixture of 37.4 g of m-bromoanisole and 160 ml of absolute tetrahydrofuran at such a rate that the reaction mixture boils gently because of the heat produced by the immediately starting reaction. Thereafter, the reaction mixture is boiled under reflux while stirring until all the magnesium dissolves. The reaction mixture is cooled to 0°C to -10°C and then a mixture of 23.25 g of 2-dimethylaminomethylcyclohexanone and 45 ml of absolute tetrahydrofuran is added dropwise.

The resulting mixture is stirred for 4 hours at room temperature and then poured, while stirring slowly, into a mixture of 25 g of ammonium chloride, 50 ml of water and 50 g of ice. The layers are separated and the aqueous layer is extracted twice with 50 ml portions of ether. The organic layers are combined, dried with sodium sulfate and evaporated. The residue is distilled, and 1-(m-methoxyphenyl)-2-dimethylaminomethyl-cyclohexanol-(1), boiling point at 0.6 mm Hg 138°C to 140°C, is obtained in a yield of 78.6% of theoretical.

The hydrochloride obtained from the product, e.g., by dissolving in ether and treating with dry hydrogen chloride, melts at 168°C to 175°C. By recrystallization from moist dioxan this hydrochloride is separated into isomers melting at 162°C to 163°C and 175°C to 177°C, respectively.

References

Merck Index 9388
Kleeman and Engel p. 906
OCDS Vol. 2 p. 17 (1980)
DOT 13 (8) 345 (1977)
I.N. p. 966
Chemie Grunenthal GmbH; British Patent 997,399; July 7, 1965
Flick, K. and Frankus, E.; US Patent 3,652,589; March 28, 1972; assigned to Chemie Gruenenthal GmbH

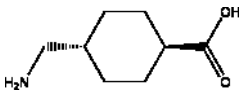
TRANEXAMIC ACID

Therapeutic Function: Coagulant

Chemical Name: trans-4-(Aminomethyl)cyclohexanecarboxylic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 1197-18-8

Trade Name	Manufacturer	Country	Year Introduced
Anvitoff	Knoll	W. Germany	1967
Transamin	Bayer-Daiichi	Japan	1970
Ugorol	Bayer	Italy	1970
Frenolyse	Specia	France	1971
Cyklokapron	Kabi	UK	1978
Amcacid	Bonomelli-Hommel	Italy	-
Amchafibrin	Fides	Spain	-
Amikapron	Kabi Vitrum	Sweden	-
Carxamin	Sankyo	Japan	-
Emorhalt	Bayropharm	W. Germany	-
Exacyl	Choay	France	-
Hexakapron	Teva	Israel	-
Hexapromin	Kowa	Japan	-
Hexatron	Nippon Shinyaku	Japan	-

Trade Name	Manufacturer	Country	Year Introduced
Mastop	Sawai	Japan	-
Rikaverin	Toyo Jozo	Japan	-
Spiramin	Mitsui	Japan	-
Tranex	Malesci	Italy	-
Tranexan	Taiyo	Japan	-
Transamin	Daiichi	Japan	-
Transamlon	Toho	Japan	-
Vasolamin	Daiichi	Japan	-

Raw Materials

p-Aminomethylbenzoic acid
Hydrogen

Manufacturing Process

In an autoclave, 2 grams of a mixture of cis- and trans-4-aminomethylcyclohexane-1-carboxylic acid, which is obtained by catalytic reduction of p-aminomethylbenzoic acid in the presence of platinum catalyst and contains 60% by weight of cis-isomer was reacted at 200°C, for 8 hours with 20 ml of ethyl alcohol in which 0.44 gram of sodium metal had been dissolved. After cooling, the reaction solution was concentrated under a reduced pressure to give a white residue. This residue was dissolved in 40 ml of water and passed through a column of a strongly acidic cation ion-exchanger resin (NH_4^+). The eluate was concentrated under reduced pressure to form a white mass. An adequate amount of acetone was added thereto and 1.95 grams of white powder was obtained. This powder was recrystallized from water-acetone to give 1.85 grams (yield, 92.5%) of white crystalline powder having a melting point of 380° to 390°C (decomposition). This product was identified as trans-4-aminomethylcyclohexane-1-carboxylic acid by means of infrared spectrum.

References

Merck Index 9390
Kleeman and Engel p. 907
OCDS Vol. 2 p. 9 (1980)
DOT 2 (1) 26 (1966)
I.N. p. 39
REM p. 831
Naito, T., Okano, A., Aoyagi, T., Miki, T., Kadoya, S., Inaoka, M. and Shindo, M.; US Patent 3,499,925; March 10, 1970; assigned to Daiichi Seiyaku Company Limited, Japan and Mitsubishi Chemical Industries Limited, Japan

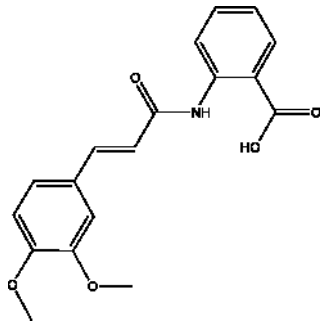
TRANILAST

Therapeutic Function: Antiallergic

Chemical Name: 2-[[3-(3,4-Dimethoxyphenyl)-1-oxo-2-propenyl]amino]-benzoic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 53902-12-8

Trade Name	Manufacturer	Country	Year Introduced
Rizaben	Kissei Pharmaceutical Co., Ltd.	Japan	1982

Raw Materials

3,4-Dimethoxycinnamic acid
Methyl anthranilate
Benzene sulfonyl chloride
Sodium hydroxide

Manufacturing Process

4 g of 3,4-dimethoxycinnamic acid was dissolved in 20 ml of dry pyridine. To this solution were added under cooling with ice and agitation 2 g of benzenesulfonyl chloride whereby a red orange precipitate was formed. The reaction mixture was stirred for about one hour and then 2 g of methyl anthranilate were added to the mixture under cooling with ice. The mixture was stirred for 2 hours at room temperature to complete the reaction. After completion of the reaction, the reaction mixture was concentrated and the residue was taken up in about 10 ml of chloroform. The solution was washed first with a 10% aqueous solution of caustic soda, then with a 10% aqueous solution of hydrochloric acid and finally with water and then distilled to remove chloroform whereby crystals of N-(3',4'-dimethoxycinnamoyl)-anthranilic acid methyl ester were obtained.

This product was dissolved in 10 ml of chloroform. To this solution were added 10 ml of a 10% aqueous solution of caustic soda and the mixture was warmed at 50°C to effect hydrolysis of the ester group. After completion of the reaction, the organic phase was separated, washed with water and distilled to remove the solvent whereby 2.1 g (yield: 48%) of the end product, i.e., N-(3',4'-dimethoxycinnamoyl)-anthranilic acid, were obtained. This product had

a melting point of 211°C to 213°C.

References

Merck Index 9392
DFU 7 (12) 907 (1982)
DOT 19 (2) 114 and (9) 485 (1983)
I.N. p. 966
Harita, K., Ajisawa, Y., Iizuka, K., Kinoshita, Y., Kamijo, T. and Kobayashi, M.; US Patent 3,940,422; February 24, 1976; assigned to Kissei Yakuhin Kogyo K.K. (Japan)

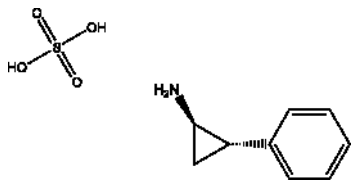
TRANYLCYPROMINE SULFATE

Therapeutic Function: Psychostimulant

Chemical Name: trans(+/-)-2-Phenylcyclopropanamine sulfate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 13492-01-8; 155-09-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Parnate	SKF	UK	1960
Parnate	SKF	US	1961
Tylciprine	Theraplix	France	1963
Parnate	Rohm	W. Germany	1969
Parmodalin	Maggioni	Italy	-

Raw Materials

Styrene
Sodium azide
Ethyl diazoacetate
Hydrogen chloride
Sodium hydroxide
Sulfuric acid
Thionyl chloride

Manufacturing Process

A solution containing 167 grams of stabilized styrene and 183 grams of ethyl diazoacetate is cooled to 0°C and dropped into 83.5 grams of styrene with stirring, in a dry nitrogen atmosphere, at 125° to 135°C. This produced the ester ethyl 2-phenylcyclopropanecarboxylate.

A solution of the above ester (207.8 grams) and 64.5 grams of sodium hydroxide in 80 cc of water and 600 cc of ethanol is refluxed for 9 hours. The carboxylic acid of 2-phenylcyclopropane is liberated with 200 cc of concentrated hydrochloric acid. The 2-phenylcyclopropanecarboxylic acid contains 3 to 4 parts of the trans isomer to 1 part of the cis isomer. The acid is recrystallized from hot water. The pure trans isomer comes out as crystalline material (solid) while the cis isomer stays in solution.

A solution of 4.62 grams of 2-phenylcyclopropanecarboxylic acid in 15 cc of dry benzene is refluxed with 4 cc of thionyl chloride for 5 hours, the volatile liquids are removed and the residue once more distilled with benzene. Fractionation of the residue yields the carbonyl chloride of 2-phenylcyclopropane.

A mixture of 15 grams of technical sodium azide and 50 cc of dry toluene is stirred and warmed and a solution of 10 grams of 2-phenylcyclopropanecarbonyl chloride in 50 cc of dry toluene is added slowly. Inorganic salts are filtered and washed well with dry benzene and the solvents are removed under reduced pressure. The $RCON_3$ compound produced undergoes the Curtius rearrangement to RNCO + N_2. The residual isocyanate is a clear red oil of characteristic odor. It is cooled to 10°C and treated cautiously with 100 cc of 35% hydrochloric acid whereupon RNCO + H_2O gives RNH_2 + CO_2.After most of the evolution of carbon dioxide has subsided the mixture is refluxed for 13 hours, the cooled solution is diluted with 75 cc of water and extracted with three 50 cc portions of ether. The acid solution is evaporated under reduced pressure with occasional additions of toluene to reduce foaming.

The almost dry residue is cooled to 0°C and made strongly alkaline with a 50% potassium hydroxide solution. The amine is extracted into several portions of ether, dried over potassium hydroxide, the solvent removed, and the base fractioned. Reaction of the base with a half-molar quantity of sulfuric acid gives the sulfate.

References

Kleeman and Engel p. 907
PDR p. 1719
OCDS Vol. 1 p. 73 (1977) and 2, 7, 50 (1980);
I.N. p. 967
REM p. 1097
Tedeschi, R.E.; US Patent 2,997,422; August 22, 1961; assigned to Smith Kline and French Laboratories

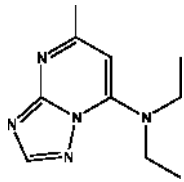
TRAPIDIL

Therapeutic Function: Coronary vasodilator

Chemical Name: 5-Methyl-7-diethylamino-1-triazolo-(1,5-a)-pyrimidine

Common Name: Trapymin

Structural Formula:



Chemical Abstracts Registry No.: 15421-84-8

Trade Name	Manufacturer	Country	Year Introduced
Rocornal	Mochida	Japan	1978
Rocornal	Deutsches Hydrierwerk	E. Germany	-

Raw Materials

5-Methyl-7-chloro-s-triazolo-(1,5-a)-pyrimidine
Diethylamine

Manufacturing Process

8.4 g of 5-methyl-7-chloro-s-triazolo-(1,5-a)-pyrimidine were suspended in 30 cc of water and 7.3 g of diethylamine added. After 2 hours heating with stirring, the mixture was concentrated under vacuum. The residue was recrystallized from n-heptane. This process yielded 8.1 g of the 5-methyl-7-diethylamino-s-triazolo-(1,5-a)-pyrimidine having a melting point of 103°C to 104°C. The hydrochloride produced in the usual manner had a melting point of 212°C.

References

Merck Index 9396
DOT 8 (1) 25 (1972)
I.N. p. 967
Tenor, E., Fuller, H. and Hausschild, F.; British Patent 1,148,629; April 16, 1969; assigned to Veb. Deutsches Hydrierwerk Rodleben

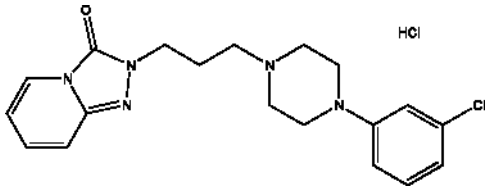
TRAZODONE HYDROCHLORIDE

Therapeutic Function: Tranquilizer

Chemical Name: 2-[3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl]-1,2,4-triazolo[4,3-a]pyridin-3(2H)-one hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 25332-39-2; 19794-93-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Trittico	Angelini	Italy	1972
Thombran	Thomae	W. Germany	1977
Pragmazone	U.P.S.A.	France	1980
Molipaxin	Roussel	UK	1980
Desyrel	Bristol	Canada	1982
Desyrel	Mead Johnson	US	1982
Beneficat	Nemi	Argentina	-
Bimaran	Roux-Ocefa	Argentina	-
Manegan	Argentia	Argentina	-
Tramensan	Medica	Finland	-

Raw Materials

2-Chloropyridine
Semicarbazide
Sodium hydride
1-(3-Chloropropyl)-4-m-chlorophenylpiperazine

Manufacturing Process

In an initial step, 2-chloropyridine is reacted with semicarbazide to give s-triazolo-[4,3-a]-pyridine-3-one.

To a boiling solution of 6.7 grams s-triazolo-[4,3-a]-pyridine-3-one in 80 ml dioxane, there is added 2.4 grams 50% NaH. The mixture is refluxed during 1 hour under stirring, then 13.5 grams 1-(3-chloropropyl)-4-m-chlorophenylpiperazine is added. The mixture is refluxed under stirring for 20 hours, cooled, diluted with an equal volume of ether, the sodium chloride filtered out, and ethereal HCl added. The solid which precipitates is filtered out

and crystallized from 95% alcohol. Yield is 13.5 grams, MP 223°C.

The following is an alternative method of preparation: 1 gram 2-(γ-chloropropyl)-s-triazolo-[4,3-a]-pyridine-3-one and 5 ml saturated ammonia alcoholic solution are heated for 5 hours in a closed tube at 100°C. The contents of the tube are cooled, the ammonium chloride filtered out and the solvent is removed. There remains a residue of 0.9 grams 2-(γ-aminopropyl)-s-triazolo-[4,3-a]-pyridine-3-one.

This residue is dissolved in isopropyl alcohol and 1 gram N-bis-chloroethyl-aniline is added to it. The mixture is refluxed for 3 hours. The solvent is removed at a reduced pressure, the residue is treated with 50% potassium carbonate, and extracted with ether. By treating with ethereal hydrochloric acid, 2-N'-m-chlorophenylpiperazino-propyl-s-triazole[4,3-a]pyridine-3-one hydrochloride is precipitated; MP 223°C.

References

Merck Index 9398
Kleeman & Engel p. 908
PDR p. 1123
OCDS Vol. 2 p. 472 (1980)
DOT 9 (3) 115 (1973)
I.N. p. 968
REM p. 1097
Palazzo, G. and Silvestrini, B.; US Patent 3,381,009; April 30, 1968; assigned to Aziende Chimiche Riunite Angelini Francesco a Roma, Italy

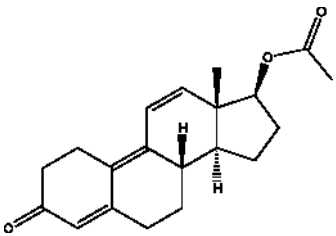
TRENBOLONE ACETATE

Therapeutic Function: Anabolic steroid

Chemical Name: 17β-Aceto-3-oxoestra-4,9,11-triene-3-one

Common Name: Trienbolone acetate

Structural Formula:



Chemical Abstracts Registry No.: 10161-34-9; 10161-33-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Parabolan	Negma	France	1980
Finaject	Distrivet	France	-
Finaplix	Distrivet	France	-
Hexabolan	Phartec	France	-

Raw Materials

Sodium-t-amylate
Acetic acid
Methanol
Acetic anhydride
17β-Benzyloxy-4,5-seco-estra-9,11-diene-3,5-dione

Manufacturing Process

Stage A: Preparation of 17β-Benzoyloxy-Estra-4,9,11-Trien-3-one - 0.400 g of 17β-benzoyloxy-4,5-seco-estra-9,11-diene-3,5-dione is dissolved in 4 cc of toluene under an inert atmosphere. The solution is cooled to 3°C, then 0.48 cc is added of the solution of sodium tert-amylate in anhydrous toluene, diluted by the addition of a further 4.8 cc of anhydrous toluene.

This reaction mixture is kept between 0°C and +5°C for six hours, with agitation and under an inert atmosphere, then 5 cc of a 0.2 N solution of acetic acid in toluene are added. The mixture is extracted with toluene, and the extracts are washed with water and evaporated to dryness. The residue is taken up in ethyl acetate, and then the solution is evaporated to dryness in vacuo, yielding a resin which is dissolved in methylene chloride, and the solution passed through a column of 40 g of magnesium silicate. Elution is carried out first with methylene chloride, then with methylene chloride containing 0.5% of acetone, and 0.361 g is thus recovered of a crude product, which is dissolved in 1.5 cc of isopropyl ether; then hot methanol is added and the mixture left at 0°C for one night.

0.324 g of the desired 17β-benzoyloxy-estra-4,9,11-trien-3-one are thus finally obtained, being a yield of 85%, melting point is 154°C.

Stage B: Preparation of 17β-Hydroxy-Estra-4,9,11-Trien-3-one - 3 g of 17β-benzoyloxy-estra-4,9,11-trien-3-one, obtained as described in Stage A are dissolved in 15 cc of methanol. 0.03 g of hydroquinone is added, and the mixture is taken to reflux while bubbling in nitrogen. Then 1.2 cc of 11% methanolic caustic potash is added and reflux is maintained for three hours, after which the reaction product is acidified with 0.36 cc of acetic acid.

The methyl benzoate thus formed is eliminated by steam distillation, and 2.140 g of crude product are obtained, which are dissolved in 20 cc of methylene chloride. This solution is passed through 10 parts of magnesium silicate, elution being performed with 250 cc of methylene chloride containing 5% of acetone. After evaporation of the solvent 2.050 g of product is recovered, which is recrystallized from isopropyl ether.

In this way 1.930 g of the desired 17β-hydroxy-estra-4,9,11-trien-3-one is obtained being a yield of 89%, melting point is 186°C. It is converted to the acetate by acetic anhydride.

References

Merck Index 9402
Kleeman and Engel p. 908
DOT 12 (3) 121 (1976)
I.N. p. 968
Roussel-Uclaf; British Patent 1,035,683; July 13, 1966

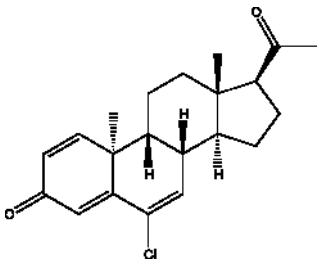
TRENGESTONE

Therapeutic Function: Progestin

Chemical Name: 6-Chlore-9β,10α-pregna-1,4,6-triene-3,20-dione

Common Name: Trengestone; Reteroid

Structural Formula:



Chemical Abstracts Registry No.: 5192-84-7

Trade Name	Manufacturer	Country	Year Introduced
Retrone	Roche	-	-

Raw Materials

9β,10α-Pregna-4,6-diene-3,20-dione
Perbenzoic acid
Hydrochloric acid
2,3-Dichlorobenzoquinone

Manufacturing Process

10 g of 9β,10α-pregna-4,6-diene-3,20-dione (Rec. Trav. Chim. 79, 771 (1960)) were dissolved in a solution of 26 g of perbenzoic acid in 565 ml of chloroform at 0°C, after which the reaction mixture was allowed to stand at the same temperature in a refrigerator. The consumption of peracid was determined by iodometrical titration, where by the decrease of content of peracid of a blank was taken into account. After 1, 5, 20, 29 and 45 hours 18, 55, 155, 173 and 190% of peracid were consumed, respectively. After a

reaction time of 20, 27 and 46 hours samples of the reaction mixture contained according to the ultraviolet absorption spectrum 24, 18 and 16.4% of the starting material, respectively. After 50 hours the reaction mixture was diluted with 2 1 of ether and washed (at 0°C) with 4 x 750 ml of a 3 % sodium carbonate solution and then with 3 x 500 ml of ice-water (until neutral). The solution was dried over sodium sulphate, filtered and the solvent evaporated in vacuo at 30°C. The resin (9.02 g), showed a maximum at 234 and 285 nm.

A small sample of the epoxydation product was purified chromatographically (silicage) for analytical purposes. Melting point: 186(s)-189°C, ε (λ_{max} 241 nm) = 14000. The infrared absorption spectrum showed bands at 1703, 1677, 1627, 1354, 1233, 953, 881 and 808 cm^{-1}. The crude epoxidation product was dissolved in 400 ml of ethanol-free chloroform. To this solution were added 280 ml of a 6.5% solution of hydrochloric acid in acetic acid, after which the dark colored reaction mixture was allowed to stand at room temperature for 3.5 hours. Then the reaction mixture was poured into 2 1 of ice-water and the water layer extracted once with chloroform. The combined chloroform layers were washed with 3 x 1500 ml of ice-water, 3 x 500 ml of 5% sodium bicarbonate solution at 0°C and finally with water until neutral After drying over sodium sulphate the solution was filtered and the solvent evaporated in vacuo. The resinous residue was treated with a small amount of cold ether by which 1.5 g of crystals were obtained. Recrystallization from ethyl acetate at -5°C yielded 0.76 g of crystals with a melting point of 168-170°C (decomposition), λ_{max} 287 nm. Repeated recrystallization finally gave 0.64 g of 6-chloro-9β,10α-pregna-4,6-diene-3,20-dione with a melting point of 169(s)-175.5°C (dec.). The melting (decomposition) point of the substance proved to be no standard for the purity of the compound. ε (λ_{max} = 21600).

A solution of 1.04 g of 6-chloro-9β,10α-pregna-4,6-diene-3,20-dione and 0.95 g of 2,3-dichlorobenzoquinone in 50 ml of dry benzene was heated to reflux for 10 hours. The reaction mixture was diluted with 70 ml of benzene and extracted three times with 50 ml of 2 N sodium hydroxide solution. The benzene layer was washed with water to neutral, dried with sodium sulfate and evaporated to dryness. The residue (0.7 g) was chromatographed on 20 g 0f aluminum oxide (activity II). The fraction eluted with benzene-petroleum ether were combined and recrystallized from acetone. The 6-chloro-9β,10α-pregna-1,4,6-triene-3,20-dione melted at 208-209°C(decomposition), λ_{max} 229 nm.

References

Reerink E. H., Westerhof P., Scholer H. F. L., Weesp, Netherlands; US Patent No. 3,422,122; Sept. 25, 1964; Assigned to North American Philips Company, Inc., New York, N.Y., a corporation of Delaware

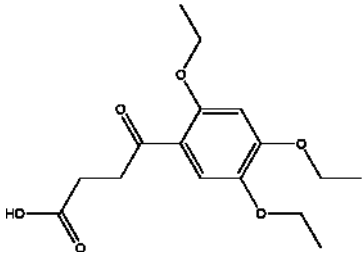
TREPIBUTONE

Therapeutic Function: Choleretic

Chemical Name: 3-(2',4',5'-Triethoxybenzoyl)-propionic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 41826-92-0

Trade Name	Manufacturer	Country	Year Introduced
Supacal	Takeda	Japan	1981
Cholibil	Takeda	Japan	-

Raw Materials

1,2,4-Triethoxybenzene
Succinic anhydride

Manufacturing Process

To a mixture of 7.5 parts by weight of 1,2,4-triethoxybenzene, 40 parts by volume of tetrachloroethane and 7.5 parts by weight of succinic anhydride are added 23 parts by weight of anhydrous aluminum chloride. The mixture is stirred for 1 hour at 25°C and for another 2 hours at 60°C. After addition of 50 parts by weight of ice and 50 parts by volume of concentrated hydrochloric acid, the reaction mixture is subjected to steam distillation.

After cooling crystals separated from the remaining liquid are collected by filtration and recrystallized from aqueous ethanol, whereby 2.5 parts by weight of 3-(2',4',5'-triethoxybenzoyl)-propionic acid are obtained as colorless needles, melting point 150°C to 151°C.

References

Merck Index 9404
DFU 3 (11) 846 (1978)
DOT 17 (12) 566 (1981)
I.N. p. 969
Mutara, T.,Nohara, A., Sugihara, H. and Sanno, Y.; US Patent 3,943,169; March 9, 1976; assigned to Takeda Chemical Industries, Ltd.

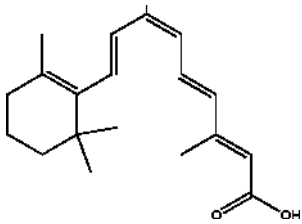
TRETINOIN

Therapeutic Function: Keratolytic

Chemical Name: 3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid

Common Name: Vitamin A acid; Retinoic acid

Structural Formula:



Chemical Abstracts Registry No.: 302-79-4

Trade Name	Manufacturer	Country	Year Introduced
Aberel	McNeil	US	1973
Vitamin-A-Saure	Roche	W. Germany	1973
Retin-A	Ortho	UK	1973
Airol	Roche	Italy	1975
Effederm	Sauba	France	1975
Retin-A	Cilag	Italy	1975
Acnelyse	Abdi Ibrahim	Turkey	-
Aknoten	Krka	Yugoslavia	-
Cordes-Vas	Icthyol-Ges.	W. Germany	-
Dermojuventus	Juventus	Spain	-
Epi-Aberel	Cilag	W. Germany	-
Eudyna	Nordmark	W. Germany	-
Stie Vaa	Stiefel	US	-
Tretin-M	Ikapharm	Israel	-
Vitacid-A	Merima	Yugoslavia	-

Raw Materials

Ionol, β-
Triphenylphosphine hydrobromide
4-Methyl-1-al-hexadiene-(2,4)-acid-(6)

Manufacturing Process

100 parts of beta-ionol are dissolved in 200 parts of dimethylforrnamide and after the addition of 165 parts of triphenylphosphine hydrobromide, stirred for

7 hours at room temperature. Then 70 parts of 4-methyl-1-al-hexadiene-(2,4)-acid-(6) (melting point 177°C, white needles from water) are added to the now clear solution. 150 parts of isopropanol are added and the whole cooled to -30°C. Into this solution, while stirring vigorously, 190 parts by volume of a 30% solution of sodium methylate in methanol are allowed to flow in. A vigorous exothermic reaction takes place and the temperature in the interior of the flask rises to +5°C. It is stirred for another 5 minutes and neutralized with 10% of sulfuric acid (until acid to Congo).

After stirring for 2 hours at room temperature, the mass of vitamin A acid has crystallized out. It is sharply filtered off by suction and washed with a little ice-cold isopropanol. From the filtrate, a further small amount of mainly all trans vitamin A acid crystallizes out upon the addition of water. The filter cake is suspended in 600 parts of water and stirred for 4 hours at room temperature; it is filtered by suction and the product washed with water. It is dried in vacuo at 40° to 50°C and 115 parts of vitamin A acid are obtained. The melting point lies between 146° and 159°C.

The mixture of the all trans and mainly 9,10-cis vitamin A acid may be separated by fractional crystallization from ethanol. All trans vitamin A acid has a melting point of 180° to 182°C and 9,10-cis vitamin A acid, which crystallized in the form of pale yellow fine needles collected into clusters, has a melting point of 189° to 190°C.

References

Merck Index 8065
Kleeman and Engel p. 910
PDR p. 1309
DOT 8 (8) 305 (1972)
I.N. p. 970
REM p. 785
Pommer, H. and Sarnecki, W.; US Patent 3,006,939; October 31,1961; assigned to Badische Anilin and Soda-Fabrik AG, Germany

TRIACETIN

Therapeutic Function: Topical antifungal

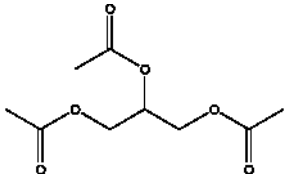
Chemical Name: 1,2,3-Propanetriol triacetate

Common Name: Glyceryl triacetate

Chemical Abstracts Registry No.: 102-76-1

Trade Name	Manufacturer	Country	Year Introduced
Enzactin	Ayerst	US	1957
Fungacetin	Blair	US	1957
Vanay	Ayerst	US	1959

Structural Formula:



Raw Materials

Allyl acetate
Acetic acid
Oxygen

Manufacturing Process

200 grams of allyl acetate, 450 grams of glacial acetic acid and 3.71 grams of cobaltous bromide were charged to the reactor and the mixture was heated to 100°C. Pure oxygen was then introduced into the reactor below the surface of the liquid reaction mixture at the rate of 0.5 standard cubic feet per hour. Initially, all of the oxygen was consumed, but after a period of time oxygen introduced into the mixture passed through unchanged. During the course of the reaction, a small quantity of gaseous hydrogen bromide (a total of 1.9 grams) was introduced into the reaction zone, along with the oxygen. The reaction was allowed to continue for 6 hours following which the reaction mixture was distilled. Essentially complete conversion of the allyl acetate took place. A yield of 116 grams of glycerol triacetate was obtained, this being accomplished by distilling the glycerol triacetate overhead from the reaction mixture, at an absolute pressure of approximately 13 mm of mercury.

References

Merck Index 9407
PDR pp. 618, 1397
I.N. p. 970
REM p. 1231
Keith, W.C.; US Patent 2,911,437; November 3,1959; assigned to Sinclair Refining Co.

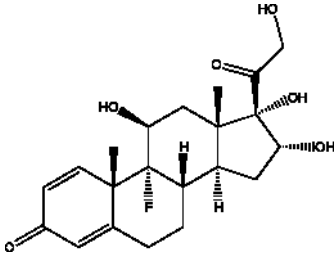
TRIAMCINOLONE

Therapeutic Function: Glucocorticoid

Chemical Name: 9-Fluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione

Common Name: δ^1-16α-Hydroxy-9α-fluorohydrocortisone

Structural Formula:



Chemical Abstracts Registry No.: 124-94-7

Trade Name	Manufacturer	Country	Year Introduced
Kenacort	Squibb	US	1958
Aristocort	Lederle	US	1958
Aristogel	Lederle	US	1975
Albacort	Teknofarma	Italy	-
Cinolone	Pierrel	Italy	-
Cortinovus	Lampugnani	Italy	-
Delsolone	Medosan	Italy	-
Ditrizin	Ester	Spain	-
Delsolone	Medosan	Italy	-
Ditrizin	Ester	Spain	-
Eczil	Aesculapius	Italy	-
Flogicort	Francia	Italy	-
Ipercortis	A.G.I.P.S.	Italy	-
Ledercort	Cyanamid	Italy	-
Medicort	Medici	Italy	-
Neo-Cort	Italchemi	Italy	-
Oticortrix	Oti	Italy	-
Sadocort	Guistini	Italy	-
Sedozalona	Loa	Argentina	-
Sterocort	Taro	Israel	-
Tedarol	Specia	France	-
Trialona	Alter	Spain	-
Triamcort	Helvepharm	Switz.	-
Triam-Oral	Nattermann	W. Germany	-
Tricortale	Bergamon	Italy	-
Trilon	Panther-Osfa	Italy	-
Volon	Heyden	W. Germany	-

Raw Materials

Bacterium Corynebacterium simplex
$\delta(^4)$-Pregnene-9α-fluoro-11β,16α,17α,21-tetrol-3,20-dione-16,21-diacetate
Soy broth
Potassium hydroxide

Manufacturing Process

Preparation of $\delta^{1,4}$-Pregnandiene-9α-fluoro-11β,16α,17α,21-Tetrol-16,21-Diacetate: An agar slant of Corynebacterium simplex was washed with 5 ml of sterile saline and the spore suspension added to 100 ml of Trypticase soy broth in a 500 ml Erlenmeyer. The mixture was incubated at 32°C for 8 hr and 1 ml was used to inoculate 10 flasks, each containing 100 ml of Trypticase soy broth. The flasks were incubated with shaking at 32°C for 16 hr. 20 mg δ^4-pregnene-9α-fluoro-11β,16α,17α,21-tetrol-3,20-dione16,21-diacetate dissolved in 2 ml ethanol was added and the flasks pooled. This solution was extracted several times with methylene chloride, washed with saturated saline and evaporated under reduced pressure. The residue was dissolved in methanol, treated with activated charcoal, filtered through diatomaceous earth and reevaporated to afford 277 mg of oil and acetylated overnight.

Paper strip chromatography showed approximately equal amounts of substrate and a more polar product ($\delta^{1,4}$-pregnadiene-9α-fluoro-11β,16α,17α,21-tetrol-3,20-dione 16,21-diacetate) together with very small amounts of two less polar products. Partition chromatography of 0.25 gram of the residue (diatomaceous earth column; system: 2 parts ethyl acetate, 3 parts petroleum ether (90° to 100°C), 3 parts methanol and 2 parts water) separated the less polar products and the substrate. The desired most polar product remained on the column and was eluted with 500 ml of methanol. The residue (90 mg) from the evaporated methanol was repartitioned on diatomaceous earth [system: 3 parts ethyl acetate, 2 parts petroleum ether (90° to 100°C), 3 parts methanol, and 2 parts water] and the cut containing the desired product (determined by ultraviolet absorption spectrum) was evaporated under reduced pressure to afford 18 mg of solid.

Crystallization from acetone-petroleum ether gave 13 mg of colorless needles of $\delta^{1,4}$-pregnadiene-9α-fluoro-11β,16α,17α,21-tetrol-3,20-dione16,21-diacetate; melting point (Kofler block) about 150° to 240°C with apparent loss of solvent at 150°C. Recrystallization from acetone-petroleum ether did not alter the melting point.

Preparation of $\delta^{1,4}$-Pregnadiene-9α-Fluoro-11β,16α,17α,21-Tetrol-3,20-Dione: A solution of 100 mg of $\delta^{1,4}$-pregnadiene-9α-fluoro-11β,16α,17α,21-tetrol-3,20-dione16,21-diacetate was dissolved in 10 ml of methanol and cooled to 0°C. After flushing with nitrogen, a solution of 35 mg of potassium hydroxide in 2 ml of methanol was added to the steroid solution. After standing at room temperature for 1 hour, the solution was neutralized with glacial acetic acid and evaporated under a nitrogen atmosphere to a white solid. Water was added, and after cooling, the product was filtered and washed with water to afford 52 mg of $\delta^{1,4}$-pregnadiene-9α-fluoro-11β,16α,17α,21-tetrol-3,20-dione, melting point 246° to 249°C. Three crystallizations from acetone-petroleum ether gave 29 mg of the tetrol, melting point 260° to 262.5°C according to US Patent 2,789,118.

References

Merck Index 9412
Kleeman and Engel p. 911
PDR pp. 830, 998, 1606
OCDS Vol. 1 p. 201 (1977) and 2, 185 (1980)

I.N. p. 971
REM p. 970
Bernstein, S., Lenhard, R.H. and Allen, W.S.; US Patent 2,789,118; April 16, 1957: assigned to American Cyanamid Company
Allen, G.R., Marx, M. and Weiss, M.J.; US Patent 3,021,347; February 13, 1962: assigned to American Cyanamid Company

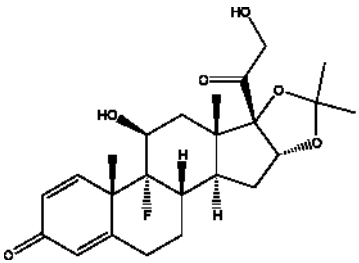
TRIAMCINOLONE ACETONIDE

Therapeutic Function: Glucocorticoid

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

Common Name: 9α-Fluoro-16α,17-isopropylidenedioxyprednisolone

Structural Formula:



Chemical Abstracts Registry No.: 76-25-5

Trade Name	Manufacturer	Country	Year Introduced
Kenalog	Squibb	US	1958
Aristocort A	Lederle	US	1958
Aristoderm	Lederle	US	1960
Aristogel	Lederle	US	1975
Triacort	Rowell	US	1981
Trymex	Savage	US	1982
Kenal	N.M.C.	US	1982
Triaget	Lemmon	US	1983
Acetospan	Reid-Provident	US	-
Adcortyl	Squibb	UK	-
Azmacort	Rorer	US	-
Azobicina Triamcin	Maggioni	Italy	-
Cinonide	Legere	US	-
Cremocort	Rougier	Canada	-
Cutinolone	Labaz	France	-
Extracort	Basotherm	W. Germany	-

Trade Name	Manufacturer	Country	Year Introduced
Flogicort	Francia	Italy	-
Ftorocort	Kobanyai	Hungary	-
Kenacort	Squibb	France	-
Kenacort-A	Squibb-Sankyo	Japan	-
Kortikoid	Ratiopharm	W. Germany	-
Ledercort N	Lederle	Japan	-
Lederspan	Lederle	UK	-
Mycolog	Squibb	US	-
Myco-Triacet	Lemmon	US	-
Mytrex	Savage	US	-
Neo-Cort	Italchimici	Italy	-
Nyst-Olone	Schein	US	-
Paralen	Heyden	W. Germany	-
Rineton	Sanwa	Japan	-
Sterocutan	Ifisa	Italy	-
Tedarol	Specia	Italy	-
Tramycin	Johnson and Johnson	US	-
Triaderm	K-Line	Canada	-
Trialona	Alter	Spain	-
Triamalone	Trans-Canada Derm.	Canada	-
Triam-Injekt	Nattermann	W. Germany	-
Tricilone	Vangard	US	-
Tricinolon	Kakenyaku Kako	Japan	-
Volon	Heyden	W. Germany	-

Raw Materials

Triamcinolone
Acetone

Manufacturing Process

A solution of 250 mg of 9α-fluoro-11β,16α,17α,21-tetrahydroxy-1,4-pregnadiene-3,20-dione in 70 ml of hot acetone and 7 drops of concentrated hydrochloric acid is boiled for 3 minutes. After standing at room temperature for 17 hours, the reaction mixture is poured into dilute sodium bicarbonate and extracted with ethyl acetate. The extract is washed with saturated saline solution, dried and evaporated to a colorless glass. The residue is crystallized from acetone-petroleum ether to afford 166 mg of the acetonide, MP 270° to 274°C, decomposition, (with previous softening and browning). Three recrystallizations from acetone-petroleum ether give 113 mg of 9α-fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxy-1,4-pregnadiene-3,20-dione, MP 274° to 279°C, decomposition, (with previous softening and browning).

References

Merck Index 9413
Kleeman and Engel p. 912
PDR pp. 888, 999, 1003, 1033, 1429, 1535, 1604, 1746, 1750

OCDS Vol. 1 p. 201 (1977)
I.N. p. 971
REM p. 971
Bernstein, S. and Allen, G.R. Jr.; US Patent 2,990,401; June 27, 1961; assigned to American Cyanamid Company
Hydorn, A.E.; US Patent 3,035,050; May 15, 1962; assigned to Olin Mathieson Chemical Corporation

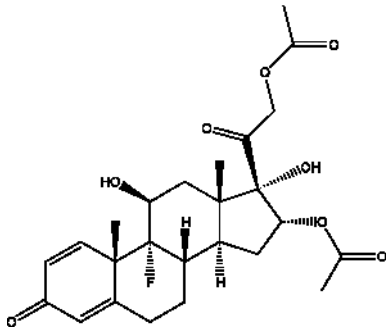
TRIAMCINOLONE DIACETATE

Therapeutic Function: Glucocorticoid

Chemical Name: 9-Fluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione-17,21-diacetate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 67-78-7

Trade Name	Manufacturer	Country	Year Introduced
Aristocort	Lederle	US	1959
Cenocort	Central	US	1975
Cino-40	Tutag	US	1976
Tracilon	Savage	US	1978
Cinalone	Legere	US	-
Delphicort	Lederle	W. Germany	-
Kenacort	Squibb	Italy	-
Ledercort	Lederle	Italy	-
Tedarol	Specia	France	-
Triam Forte	Hyrex	US	-
Triamcin	Johnson and Johnson	US	-

Raw Materials

16α,21-Diacetoxy-11β,17α-dihydroxy-9α-fluoro-4-pregnene-3,20-dione
Selenium dioxide

Manufacturing Process

To a solution of 16α,21-diacetoxy-11β,17α-dihydroxy-9α-fluoro-4-pregnene-3,20-dione (1.0 g) in tertiary-butanol (160 ml) and glacial acetic acid (1.6 ml) was added 600 mg of selenium dioxide, the mixture swept with nitrogen and kept at 70°C for 24 hours, selenium dioxide (350 mg) added, and the mixture swept with nitrogen and allowed to stand for another 24 hours. The reaction mixture was filtered, and the filtrate was evaporated to dryness under reduced pressure. The material so obtained was dissolved in ethyl acetate, washed with saturated sodium bicarbonate, water, cold freshly prepared ammonium sulfide solution, cold dilute ammonia water, cold dilute hydrochloric acid, and finally with water. After treatment with anhydrous sodium sulfate and activated charcoal, filtration through diatomaceous earth and evaporation to dryness under reduced pressure, 850 mg of a tan glass was obtained. Paper strip chromatographic analysis showed predominantly product plus a small amount of starting material. The 850 mg was chromatographed on 320 g of diatomaceous earth containing 160 ml of stationary phase of a solvent system composed of 3,4,3,2-ethyl acetate-petroleum ether (boiling point 90°C to 100°C), methanol, and water, respectively. The column dimensions were 3.8 cm x 78 cm with 460 ml hold back volume. The fifth and sixth hold back volumes were combined and evaporated under reduced pressure to 250 mg of product which, after a single crystallization from acetone petroleum ether, gave 173 mg, melting point 150°C to 190°C. Paper strip chromatography showed a single spot having the same polarity as an authentic sample of 16α,21-diacetoxy-11β,17α-dihydroxy-9α-fluoro-1,4-pregnadiene-3,20-dione. A further crystallization from the same solvent pair gave 134 mg, melting point 185°C to 189°C, bubbles to 230°C.

References

Kleeman and Engel p. 913
PDR pp. 998, 1000, 1033
I.N. p. 971
REM p. 971
American Cyanamid Co.; British Patent 835,836; May 25, 1960

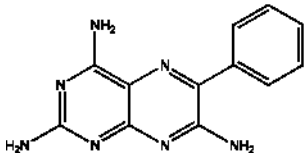
TRIAMTERENE

Therapeutic Function: Diuretic

Chemical Name: 6-Phenyl-2,4,7-pteridinetriamine

Common Name: Ademine; Pterophene

Structural Formula:



Chemical Abstracts Registry No.: 396-01-0

Trade Name	Manufacturer	Country	Year Introduced
Jatropur	Rohm	W. Germany	1962
Dytac	SKF	UK	1962
Teriam	Roussel	France	1963
Triamteril	Farmitalia	Italy	1963
Dyrenium	SKF	US	1964
Diurene	Medix	Spain	-
Dyazide	SKF	US	-
Kalistat	Disco	Israel	-
Maxzide	Lederle	US	-
Triamthiazid	Henning	W. Germany	-
Urocaudal	Jorba	Spain	-

Raw Materials

5-Nitroso-2,4,6-triaminopyrimidine
Phenylacetonitrile

Manufacturing Process

To a solution of 9 grams of 5-nitroso-2,4,6-triaminopyrimidine in 500 mi of refluxing dimethylformamide is added 9 grams of phenylacetonitrile and the refluxing is stopped. The 3 grams of anhydrous sodium methoxide is added and the mixture is refluxed for 15 minutes. The mixture is chilled and the solid is filtered and washed several times with warm water until the washings are neutral. Drying gives yellow crystals which are recrystallized with a Darco treatment from formamide-water heating the solution no hotter than 125°C. This product is then suspended in filtered deionized water and warmed for 15 minutes. This yields the 2,4,7-triamino-6-phenylpteridine as yellow crystals with a MP of 314° to 317°C.

References

Merck Index 9415
Kleeman and Engel p. 915
PDR pp. 1014, 1713
OCDS Vol. 1 p. 427 (1977)
I.N. p.972
REM p. 942
Weinstock, J. and Wiebelhaus, V.D.; US Patent 3,081,230; March 12, 1963; assigned to Smith Kline and French Laboratories

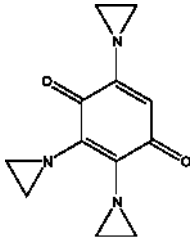
TRIAZIQUONE

Therapeutic Function: Antineoplastic

Chemical Name: 2,5-Cyclohexadiene-1,4-dione, 2,3,5-tris(1-aziridinyl)-

Common Name: Triaziquone; Oncoredox

Structural Formula:



Chemical Abstracts Registry No.: 68-76-8

Trade Name	Manufacturer	Country	Year Introduced
Trenimon	Bayer	-	-

Raw Materials

Aziridine
2,6-Dimethoxy-1,4-benzoquinone

Manufacturing Process

Under anaerobic conditions including an atmosphere of nitrogen, 104 ml (2.0 moles) of aziridine is added as a single portion with stirring to a suspension of 33.6 g (0.2 mole) of 2,6-dimethoxy-1,4-benzoquinone in 500 ml of absolute methanol at a temperature of 0° to 5°C. After the addition has been 2,6-dimethoxy-1,4-benzoquinone completed the external cooling of the reaction vessel is replaced by a room temperature water bath and the mixture is stirred at room temperature for 45 hours while a slow stream of nitrogen is passed therethrough to preserve the anaerobic reaction conditions. It is found that the yellow starting material, during this period, completely disappears into solution and that a violet or purple substance together with a colorless substance are formed as precipitated reaction products. This mixture of precipitated products is removed by filtration at -20°C and the residue is washed with a small quantity of cooled methanol. Then the mixture is dried in a vacuum desiccator yielding about 30.4 g of mixed product. The mixed product is extracted with benzene whereby the violet or purple colored component passes into solution and the substantially colorless product remains in a yield of about 16.0 g. The colorless 2,6-bis-aziridino-l,4-benzohydroquinone so obtained melts with decomposition at about 221-222°C with melting starting at about 200°C. It can be purified by recrystallization from a of dioxane yielding snow-white crystals that decompose when heated

at 222-224°C while starting to melt at 220°C.

The benzene extract of the colored reaction product is evaporated to dryness under vacuum, yielding a residue melting at 161-162°C which is recrystallized from 200 ml of ethyl acetate, filtered under suction at -20°C, washed with cold methanol and thus yields about 11.5 g of a pure, purple-colored crystalline 2,3,5-tris-aziridino-1,4-benzoquinone melting at 162.5-163°C.

References

Gauss W., Doniagk G.; US Patent No. 2,976,279; Mar. 11,1958; Wuppertal-Elberfeld, Germany; Assigned to Schenley Industries, Inc., a corporation of Delaware

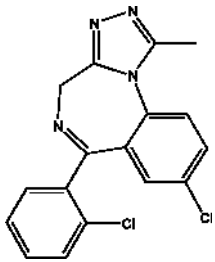
TRIAZOLAM

Therapeutic Function: Hypnotic

Chemical Name: 8-Chloro-1-methyl-6-(o-chlorophenyl)-4H-s-triazolo[4,3-a][1,4]-benzodiazepine

Common Name: Clorazolam

Structural Formula:



Chemical Abstracts Registry No.: 28911-01-5

Trade Name	Manufacturer	Country	Year Introduced
Halcion	Upjohn	Switz.	1978
Halcion	Upjohn	Italy	1978
Halcion	Upjohn	UK	1979
Halcion	Upjohn	W. Germany	1980
Halcion	Upjohn	US	1982
Halcion	Sumitomo	Japan	1983
Halcion	Upjohn	Japan	1983
Songar	Valeas	Italy	1983
Novidorm	Sintyal	Argentina	-

Raw Materials

7-Chloro-1,3-dihydro-5-(o-chlorophenyl)-2H-1,4-benzodiazepine-2-thione
Acetic acid hydrazide

Manufacturing Process

A mixture of 1.0g (0.0031 mol) of 7-chloro-1,3-dihydro-5-(o-chlorophenyl)-2H-1,4-benzodiazepine-2-thione, 0.8 g (0.0108 mol) of acetic acid hydrazide and 40 ml of 1-butanol was heated at reflux temperature under nitrogen for 24 hours. During the first 5 hours the nitrogen was slowly bubbled through the solution. After cooling and removing the solvent in vacuo, the product was well mixed with water and collected on a filter, giving 0.9 g of orange solid, melting point 210°C to 212°C. This was heated under nitrogen in an oil bath at 250°C and then cooled, The solid was crystallized from ethyl acetate, giving 0.5 g of tan solid of melting point 215°C to 216°C (decomposition). This was dissolved in 25 ml of 2-propanol, filtered, concentrated to10 ml and cooled, yielding 0.46 g (43%) of tan, crystalline 8-chloro-1-methyl-6-(o-chlorophenyl)-4H-s-triazolo[4,3-a][1,4]-benzodiazepine of melting point 223°C to 225°C.

References

Merck Index 9418
DFU 1 (8) 393 (1976)
Kleeman and Engel p. 916
PDR p. 1843
OCDS Vol. 1 p. 368 (1977)
DOT 11 (5) 20 (1975) and 15 (1) 30 (1979)
I.N. p. 972
REM p. 1064
Hester, J.B. Jr.; US Patents 3,741,957; June 26, 1973; 3,980,790; September 14, 1976; and 3,987,052; October 19, 1976; all assigned to The Upjohn Company

TRIBENOSIDE

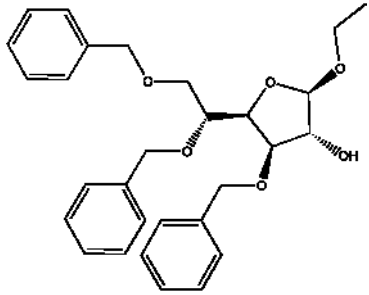
Therapeutic Function: Topical venotonic

Chemical Name: Ethyl-3,5,6-tris-O-(phenylmethyl)-D-glucofuranoside

Common Name: -

Chemical Abstracts Registry No.: 10310-32-4

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Glyvenol	Ciba	W. Germany	1967
Glyvenol	Ciba Geigy	France	1968
Glyvenol	Ciba	Italy	1968
Hemocuron	Takeda	Japan	1978
Alven	Firma	Italy	-
Flebosan	Dukron	Italy	-
Venalisin	A.G.I.P.S.	Italy	-
Venex	Oti	Italy	-
Venodin	Tosi-Novara	Italy	-

Raw Materials

1,2-Isopropylidene glucofuranose
Benzyl chloride

Manufacturing Process

4.9 g of 3,5,6-tribenzyl-1,2-isopropylidene glucofuranose are kept overnight at room temperature with 100 cc of N-ethanolic hydrochloric acid. Evaporation under vacuum at below 50°C is then carried out and the residue taken up in 150 cc of chloroform. The chloroform solution is thoroughly washed with sodium bicarbonate solution, dried with calcined sodium sulfate and evaporated under vacuum. The oily residue is then distilled under vacuum with a free flame. In this manner there is obtained the ethyl-3,5,6-tribenzyl-D-glucofuranoside of boiling point 270°C to 275°C under 1 mm pressure.

The glucofuranose used as starting material is obtained as follows: 8.8 g of 1,2-isopropylidene-D-glucofuranose and 50.6 g of benzyl chloride are treated with a total of 28 g of potassium hydroxide in portions with cooling and stirring. The mixture is then stirred for 3 hours at 80°C to 90°C. Working up from chloroform solution and distillation at 250°C to 260°C under 0.1 mm pressure give 8.9 g of 1,2-isopropylidene-3,5,6-tribenzyl-D-glucofuranose.

References

Merck Index 9420
Kleeman and Engel p.917

I.N. p. 973
Druey, J. and Huber, G.L.; US Patent 3,157,634; November 17, 1964; assigned to Ciba Corp.

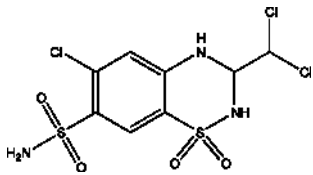
TRICHLORMETHIAZIDE

Therapeutic Function: Diuretic

Chemical Name: 6-Chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide

Common Name: Hydrotrichlorothiazide

Structural Formula:



Chemical Abstracts Registry No.: 133-67-5

Trade Name	Manufacturer	Country	Year Introduced
Naqua	Schering	US	1960
Metahydrin	Merrell National	US	1960
Esmarin	Merck	W. Germany	1960
Fluitran	Essex	Italy	1962
Trichlorex	Lannett	US	1980
Achletin	Toyama	Japan	-
Aitruran	Horita	Japan	-
Anatran	Tobishi	Japan	-
Anistadin	Maruko	Japan	-
Aponorin	Kodama	Japan	-
Carvacron	Taiyo	Japan	-
Chlopolidine	Tsuruhara	Japan	-
Cretonin	Hokuriku	Japan	-
Diu-Hydrin	Darby	US	-
Diurese	Amer. Urologicals	US	-
Flutoria	Towa	Japan	-
Hidroalogen	Bicsa	Spain	-
Intromene	Teikoku	Japan	-
Naquival	Schering	US	-
Nydor	Taro	Israel	-
Pluvex	Firma	Italy	-
Polynease	Sawai	Japan	-

Trade Name	Manufacturer	Country	Year Introduced
Sanamiron	Zensei	Japan	-
Schebitran	Nichiiko	Japan	-
Tachionin	San-A	Japan	-
Tolcasone	Toho	Japan	-
Trametol	Green Cross	Japan	-
Triazide	Legere	US	-
Trichlordiuride	Formenti	Italy	-
Tricloretic	Irfi	Italy	-
Triflumen	Serono	Italy	-

Raw Materials

5-Chloro-2,4-disulfamylaniline
Dichloroacetaldehyde

Manufacturing Process

A mixture of 5.7 grams (0.02 mol) of 5-chloro-2,4-disulfamylaniline and 4.9 grams (0.04 mol) of dichloroacetaldehyde in 25 ml of dimethyl formamide was heated at the boiling temperature and under reflux for 30 minutes. The reaction mixture was thereafter poured into a mixture of ice and water to precipitate the desired 6-chloro-7-sulfamyl-3-dichloromethyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide as a crystalline solid melting at 250° to 270°C with decomposition.

References

Merck Index 9437
Kleeman and Engel p. 917
PDR pp. 1033, 1230, 1605, 1634
OCDS Vol. 1 p. 359 (1977)
I.N. p. 974
REM p. 941
Close, W.J.; US Patent 3,264,292; August 2, 1966; assigned to Abbott Laboratories

TRICLOBISONIUM CHLORIDE

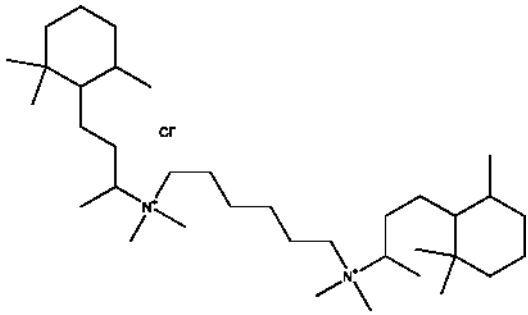
Therapeutic Function: Antiseptic

Chemical Name: N,N,N',N'-Tetramethyl-N,N'-bis[1-methyl-3-(2,2,6-trimethylcyclohexyl)-propyl]-1,6-hexanediaminium dichloride

Common Name: -

Chemical Abstracts Registry No.: 79-90-3

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Triburon	Roche	US	1959

Raw Materials

Hydrogen	cis-Tetrahydroionone
Formic acid	1,6-Hexanediamine
Formaldehyde	Methyl chloride

Manufacturing Process

To a solution of 49 grams (0.25 mol) of cis-tetrahydroionone and 14.1 grams (0.12 mol) of 1,6-hexanediamine in 150 ml of ethanol was added 1 teaspoon of Raney nickel. The volume was adjusted to 300 ml with ethanol and the mixture was hydrogenated at 50°C and a pressure of 200 psi. The catalyst was filtered off, the filtrate was concentrated and the residual oil fractionated in vacuo to obtain N,N'-bis[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]-1,6-hexanediamine; BP 192° to 202°C at 0.02 mm.

To 217 grams (0.456 mol) of N,N'-bis[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]-1,6-hexanediamine were added 182 ml (3.04 mols) of formic acid (90%). The resulting colorless solution was cooled, then 91.3 ml (1.043 mols) of formaldehyde (37%) were added. The solution was heated at steam temperature with occasional shaking for 2 hours and then refluxed for 8 hours. The volatiles were distilled off at steam temperature under water vacuum and the residual oil was made strongly alkaline with 50% potassium hydroxide. The reaction product was extracted with ether. The ether extract was washed with water, dried and concentrated in vacuo. The residual oil was fractionated in vacuo to obtain N,N'-bis[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]-N,N'-dimethyl-1,6-hexanediamine, $BP_{0.4}$ 230° to 240°C, n_D^{26} = 1.4833. An aliquot, when treated with an ethanolic hydrogen chloride, gave the crystalline dihydrochloride, MP 183° to 185°C (recrystallized from ethanol-acetonitrile).

To 5 grams of N,N'-bis[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]-N,N'-dimethyl-1,6-hexanediamine dissolved in 100 ml of methanol, at 4°C. were added 100 ml methanol containing 10 grams of methyl chloride. The solution was heated in a closed vessel at 60°C for 15 hours. The colorless solution was

concentrated and the resulting white solid crystallized from ethanol-acetonitrile-ether to obtain N,N'-bis[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]-N,N'-dimethyl-1,6-hexanediamine bis(methochloride) hemihydrate.

References

Merck Index 9465
I.N. p. 975
Goldberg, M.W. and Teitel, S.; US Patent 3,064,052; November 13, 1962; assigned to Hoffmann-La Roche Inc.

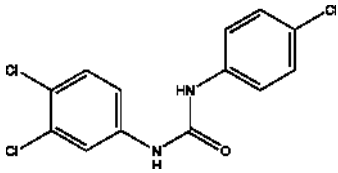
TRICLOCARBAN

Therapeutic Function: Disinfectant

Chemical Name: N-(4-Chlorophenyl)-N'-(3,4-dichlorophenyl)urea

Common Name: Trichlorocarbanilid

Structural Formula:



Chemical Abstracts Registry No.: 101-20-2

Trade Name	Manufacturer	Country	Year Introduced
Cutisan	Innothera	France	1960
Procutene	Bouty	Italy	1968
Nobacter	Innothera	France	-
Septivon-Lavril	Clin Midy	France	-
Solubacter	Innothera	France	-
Trilocarban	Armour-Montagu	France	-

Raw Materials

3,4-Dichloroaniline
4-Chlorophenyl isocyanate

Manufacturing Process

To a suitable reaction vessel equipped with a thermometer, agitator and reflux condenser and containing 8.1 parts by weight (substantially 0.05 mol) of 3,4-

dichloroaniline in approximately 57 parts by weight of diethyl ether is added dropwise a solution of 7.7 parts by weight (substantially 0.05 mol) of 4-chlorophenyl isocyanate in approximately 15 parts by weight of diethyl ether at such a rate so as to maintain gentle reflux. Upon completion of the isocyanate addition the reaction mass is agitated for about one hour. The mass is filtered and the residue washed with diethyl ether. The dried product is a white fluffy solid which on recrystallization from ethanol gives fine white plates of 4,3',4'-trichlorocarbanilide, melting point 255.2°C to 256.0°C (88.0% yield).

References

Merck Index 9466
Kleeman and Engel p. 918
I.N. p. 975
Beaver, D.J. and Stoffel, P.J.; US Patent 2,818,390; December 31, 1957; assigned to Monsanto Chemical Co.

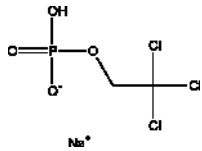
TRICLOFOS SODIUM

Therapeutic Function: Sedative, Hypnotic

Chemical Name: 2,2,2-Trichloroethanol dihydrogen phosphate monosodium salt

Common Name: Trichloroethyl phosphate monosodium salt

Structural Formula:



Chemical Abstracts Registry No.: 7246-20-6; 306-52-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Triclos	Merrell National	US	1972
Tricloran	C.T.S.	Israel	-
Tricloryl	Glaxo	UK	-

Raw Materials

Trichloroethanol
Phosphorus oxychloride
Sodium carbonate

Manufacturing Process

Trichloroethanol (500 grams) and phosphorus oxychloride (510 grams) were added to dry diethyl ether (3.5 liters) and stirred at 10°C with ice/water cooling. Dry pyridine (270 ml) was added dropwise over 1 hour, maintaining the temperature below 25°C. The resulting suspension was stirred for a further 1 hour and then stood at 0°C overnight. The pyridine hydrochloride was removed by filtration and washed with diethyl ether (2 x 300 ml) and dried in vacuo over P_2O_5 to give 380 grams.

The ether filtrate and washings were evaporated at room temperature under reduced pressure to give a clear liquid residue (801 grams). This residue was distilled under high vacuum to give trichloroethyl phosphorodichloridate (556 grams, 62.4% of theory), boiling point 75°C/0.8 mm.

The phosphorodichloridate was hydrolyzed by adding to a stirred solution of sodium carbonate (253 grams) in water (2.9 liters). After 1 hour the solution was cooled and acidified with a solution of concentrated sulfuric acid (30 ml) in water (150 ml) and then extracted with a mixture of tetrahydrofuran and chloroform (2.3/1; 3 x 1 liter). The tetrahydrofuran/chloroform liquors were bulked and evaporated to dryness to give a light brown oil. This was dissolved in water (1 liter) and titrated with 2 N sodium hydroxide solution to a pH of 4.05 (volume required 930 ml). The aqueous solution was clarified by filtration through kieselguhr and then evaporated under reduced pressure to a syrup (737 grams).

Hot acetone (4.5 liters) was added to this syrup and the clear solution stood at room temperature for 2 hours and then at 0°C overnight. The white crystalline solid was filtered off, washed with acetone (2 x 400 ml) and dried at 60°C in vacuo to give sodium trichloroethyl hydrogen phosphate (414 grams, 49.3% of theory from trichloroethanol).

References

Merck Index 9469
Kleeman and Engel p. 918
I.N. p. 975
Hems, B.A., Arkley, V., Gregory, G.I., Webb, G.B., Elks, J. and Tomich, E.G.; US Patent 3,236,920; February 22, 1966: assigned to Glaxo Laboratories Limited, England

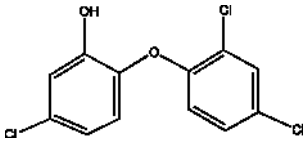
TRICLOSAN

Therapeutic Function: Antiseptic

Chemical Name: 2,4,4'-Trichloro-2'-hydroxydiphenyl ether

Common Name: Cloxifenol; Triclosan

Structural Formula:



Chemical Abstracts Registry No.: 3380-34-5

Trade Name	Manufacturer	Country	Year Introduced
Anti-Bac	Bentfield Europe BV	Netherlands	-
Anti-Bac Foam Soap	Bentfield Europe BV	Netherlands	-
Antibacterial Body Cleansing	Nu Skin International, Inc.	USA	-
Aquasept - Liquid	Lalema Inc.	Canada	-
Babysafe	Schering-Plough	-	-
Dermacne Nettoyant	Les Laboratories Bio-Santi Inc.	Canada	-
Gamophen	Johnson and Johnson	-	-
Fisohex	Sydney Ross	-	-
Irgaman	Asid Bonz	Germany	-
Lotion Kleen Green	Diversey Lever Canada, a Division of UL Canada Inc.	Canada	-
Novaderm	Johnson and Johnson	-	-
Promani	SmithKline Beecham	-	-
Tersaseptic	Trans-Canada Derm.	Canada	-
Sapoderm Medicated Skin Cleanser	Rickett and Colman Pharmaceuticals	USA	-
Sapoderm Medicated Soap	Rickett and Colman Pharmaceuticals	USA	-
Triclosan	Xian Medihealth Company Ltd.	China	-
Triclosan	Ciba Specialty Chemicals Inc.	Switz.	-
Triclosan	Ciba-Geigy SpA	Italy	-

Raw Materials

Nickel Raney
Hydrogen
Hydrochloric acid
Sodium nitrite
Copper sulfate
Aluminum chloride
3,4-Dichloro-1-nitrobenzene
Diethylene glycoldimethyl ether
Potassium hydroxide
Sodium bisulfate

4-Chloro-2-methoxyphenol (4-chloroguaiacol)

Manufacturing Process

476 g of 4-chloro-2-methoxyphenol(4-chloroguaiacol) and 578 parts of 3,4-dichloro-1-nitrobenzene are melted in 400 ml of diethylene glycoldimethyl ether in a three necked flask fitted with a stirrer and sloping condenser and, at about 120°C, 342 g of 49.6% potassium hydroxide solution are added drop-wise within about 4 h. The inner temperature is kept for 12 h at 140°-150°C whereby water and slight amounts of organic substances distill off, as partly occured during the dropwise addition of the potassium hydroxide solution. The reaction mixture is then poured into a mixture of water and sodium hydroxide solution, the precipitate is filtered off, dried and recrystallised from benzene. The 2-methoxy-4,2'-dichloro-4'-nitrodiphenyl ether obtained melts at 159°-161°C.

623 g of 2-methoxy-4,2'-dichloro-4'-nitrodiphenyl ether in 4000 ml of dioxan are catalytically hydrogenated in the presence of 250 g of Raney nickel at room temperature and under normal pressure. After the calculated amount of hydrogen, the Raney nickel is filtered off and the 2-methoxy-4,2'-dichloro-4'-aminodiphenyl ether is precipitated by the addition of water, filtered off, washed and dried, melting point 100°-102°C.

204 g of well milled 2-methoxy-4,2'-dichloro-4'-aminodiphenyl ether are added to a mixture of 254 ml of concentrated hydrochloric acid and 1600 ml of water, the addition being made at room temperature while stirring well. The suspension formed is cooled to 0°-5°C and at this temperature 225 g of 33% sodium nitrite solution is added under the level of the liquid. The mixture is stirred for another 12 h at 0°-5°C. A solution of 86 g of sodium bisulphate and 60 g of sodium hydroxide in 640 ml of water is added at 80°C to a solution of 400 g of crystallised copper sulfate and 106 g of sodium chloride in 1280 ml of water. The cuprous chloride formed is allowed to settle, the water is poured off and the precipitate is purified by decanting three times with water.

The residue is dissolved in 640 ml of concentrated hydrochloric acid, the solution is heated to 65°-70°C and the diazo suspension produced above is added while stirring. After cooling, the aqueous phase is poured off, the resin-like organic phase is taken up in ether, the ether solution is extracted with dilute sodium hydroxide solution, washed neutral, dried over sodium sulphate and concentrated. The residue is distilled under water jet vacuum. The 2-methoxy-4,2',4'-trichlorodiphenyl ether obtained boils at 210°-217°C.

243 g of aluminum chloride are added to the solution of 187.5 g of 2-methoxy-4,2',4'-trichlorodiphenyl ether in 800 ml of benzene and the reaction mixture is boiled for 30 min while stirring. After cooling, it is poured into ice and hydrochloric acid, the benzene phase is separated and extracted with water and sodium hydroxide solution. The mimosa alkaline aqueous phase is separated, the last remains of benzene are removed by blowing in steam, it is then filtered and acidified with hydrochloric acid. The precipitated 2-hydroxy-4,2',4'-tri-chlorodiphenyl ether is filtered off, washed and dried. After recrystallisation from petroleum ether it melts at 60°-61°C.

References

Model E., Bindler J.; GB Patent No. 1,051,823; Dec. 21, 1966; Assigned: J.R. Geigy AG, Basel

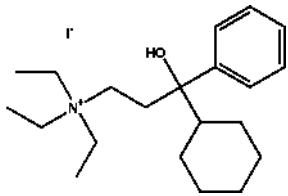
TRIDIHEXETHYL IODIDE

Therapeutic Function: Anticholinergic

Chemical Name: γ-Cyclohexyl-N,N,N-triethyl-γ-hydroxybenzene-propanaminium iodide

Common Name: Propethonium iodide; Tridihexethide

Structural Formula:



Chemical Abstracts Registry No.: 125-99-5

Trade Name	Manufacturer	Country	Year Introduced
Pathilon	Burroughs-Wellcome	US	1955
Duosetil	Dessy	Italy	-

Raw Materials

Acetophenone
Diethylamine
Cyclohexyl bromide
Paraformaldehyde
Magnesium
Ethyl iodide

Manufacturing Process

Acetophenone, paraformaldehyde and diethylamine are first reacted to give ω-diethylaminopropiophenone. That is reacted with cyclohexylmagnesium bromide to give 3-diethylamino-1-cyclohexyl-1-phenylpropanol-1.

To 1,320 parts of methyl isobutyl ketone is added 570 parts of 3-diethylamino-1-cyclohexyl-1-phenylpropanol-1 (2 mols) and the mixture is stirred until solution is complete. Then 500 parts (3.2 molsor 60% excess) of ethyl iodide are added. After filtration, the filtrate is diluted with an additional 300 parts of methyl isobutyl ketone and the solution is then heated at the reflux temperature (108°C to 110°C) for 9 hours. After cooling to 0°C, the precipitated solid material is removed by filtration, washed with isopropyl acetate and dried. Approximately 777 parts of product is obtained or a yield of

88.6% based on as-is starting material or 92.5% based on real starting material.

References

Merck Index 9474
Kleeman and Engel p. 918
I.N. p. 976
REM p. 919
Lobby, J.; US Patent 2,913,494; November 17, 1959; assigned to American Cyanamid Co.

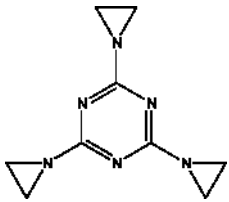
TRIETHYLENEMELAMINE

Therapeutic Function: Antineoplastic

Chemical Name: 2,4,6-Tris(1-aziridinyl)-s-triazine

Common Name: Tretamine

Structural Formula:



Chemical Abstracts Registry No.: 51-18-3

Trade Name	Manufacturer	Country	Year Introduced
Triethylene	Lederle	US	1954
Triameline	I.C.I.	-	-

Raw Materials

Cyanuric chloride
Ethylene imine

Manufacturing Process

Cyanuric chloride (which may or may not contain the usual commercial impurities) is dispersed into ice water by stirring in a ratio of 18.8 g of cyanuric chloride to a mixture of 100 g of ice and 100 g of water. The slurry may conveniently be prepared directly in a 3-necked flask equipped with an agitator, dropping funnel, and thermometer. The temperature of the flask and contents is maintained within the range of 2°C to 5°C, with an ice-salt mixture. A solution of ethylenimine in an aqueous solution of potassium

carbonate prepared in the proportions of 14 g ethylenimine, 44.5 g potassium carbonate, and 150 g of water, is added dropwise to the cyanuric chloride slurry. The reaction solution is then clarified with a little activated charcoal, filtered, and extracted with chloroform. Despite the fact that triethylenemelamine is more soluble in water than in chloroform, in a two-phase system (water-chloroform) nearly 75% of the triethylenemelamine is distributed in the chloroform, and hence a few extractions with that solvent suffice to separate the material from the original reaction medium. Five extractions with 50 ml portions of chloroform gave 19 g of product, and an additional 3 extractions with 25 ml portions gave 0.5 g, a total yield of 95.7%. The product obtained by evaporating such an extract is a white microcrystalline powder.

References

Merck Iindex 9481
I.N. p. 970
Wystrach, V.P. and Kaiser, D.W.; US Patent 2,520,619; August 29, 1950; assigned to American Cyanamid Co.

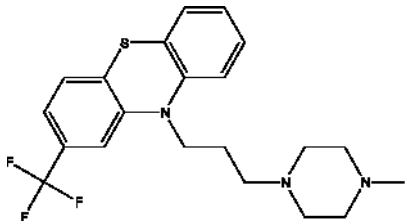
TRIFLUOPERAZINE

Therapeutic Function: Tranquilizer

Chemical Name: 10-[3-(4-Methylpiperazin-1-yl)propyl]-2-trifluoromethylphenothiazine

Common Name: Triftazin; Triphthasine

Structural Formula:



Chemical Abstracts Registry No.: 117-89-5; 440-17-5 (Dihydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Stelazine	SKF	US	1958
Terfluzine	Theraplix	France	1962
Triazine	Cord	US	1981
Calmazine	Protea	Australia	-
Chemflurazine	Chemo-Drug	Canada	-
Dymoperazine	Dymond	Canada	-
Flurazine	Taro	Israel	-

Trade Name	Manufacturer	Country	Year Introduced
Jatroneural	Rohm	W. Germany	-
Modalina	Maggioni	Italy	-
Normaln P	Sawai	Japan	-
Novoflurazine	Novopharm	Canada	-
Pentazine	Pentagone	Canada	-
Sedizine	Trima	Israel	-
Solazine	Horner	Canada	-
Telazin	Dincel	Turkey	-
Terflurazine	Lennon	S. Africa	-
Tranquis	Sumitomo	Japan	-
Trifluoper-Ez-Ets	Barlow Cote	Canada	-
Triflurin	Paul Maney	Canada	-

Raw Materials

2-Trifluoromethylphenothiazine
Sodium amide
1-(3'-Chloropropyl)-4-methylpiperazine

Manufacturing Process

A mixture of 17.2 grams of 2-trifluoromethylphenothiazine, 3.1 grams of sodamide and 14 grams of 1-(3'-chloropropyl)-4-methylpiperazine in 200 ml of xylene is heated at reflux for 2 hours. The salts are extracted into 150 ml of water. The xylene layer is then extracted with several portions of dilute hydrochloric acid. The acid extracts are combined and neutralized with ammonium hydroxide solution. The product, 10-[3'-(4''-methyl-1''-piperazinyl)-propyl]-2-trifluoromethylphenothiazine, is taken into benzene and purified by vacuum distillation, BP 202° to 210°C at 0.6 mm.

References

Merck Index 9489
Kleeman and Engel p. 919
PDR pp. 1606, 1723, 1999
DOT 9 (6) 228 (1973)
I.N. D. 976
REM p. 1091
Ullyot, G.E.; US Patent 2,921,069; January 12, 1960; assigned to Smith Kline and French Laboratories

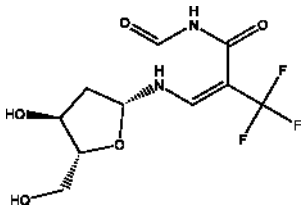
TRIFLUOROTHYMIDINE

Therapeutic Function: Antiviral (ophthalmic)

Chemical Name: 2'-Deoxy-5-(α,α,α-trifluoromethyl)uridine

Common Name: Trifluridine

Structural Formula:



Chemical Abstracts Registry No.: 70-00-8

Trade Name	Manufacturer	Country	Year Introduced
Trifluorothymidine	Mann	W. Germany	1975
Bephen	Thilo	W. Germany	-
Triherpine	Dispersa	Switz.	-
Viroptic	Burroughs-Wellcome	US	-

Raw Materials

3',5'-Bis-O-(p-nitrobenzoyl)-2'-deoxy-5-(trifluoromethyl)uridine
Diisopropylamine

Manufacturing Process

A suspension of 4.00g (6.75 mmol) of 3',5'-bis-O-(p-nitrobenzoyl)-2'-deoxy-5-(trifluoromethyl)uridine in 250 ml of methanol was treated with 10 ml of diisopropylamine and refluxed until it had dissolved (about 18 minutes), and the solution was concentrated. The dry residue was partitioned between 50 ml of chloroform and 50 ml of water. The chloroform layer was washed with 20 ml of water, and the combined aqueous layers were concentrated. A low ultraviolet extinction (ε 7200 and 262 μm; pH 1) and the presence of isopropyl signals in the NMR spectrum (two singlets at γ8.73 and 8.85) indicated the dry residue contained diisopropylamine, probably as a salt with the relatively acidic heterocyclic N-H in 14.

A solution in 75 ml of water was treated with 8 ml (volume of resin) of Dowex 50 (H), prewashed with water and methanol. The resin was removed on a filter and washed with 25 ml of methanol and 50 ml of water, The combined filtrate was evaporated in vacuo to form 1.99 g of 2'-deoxy-4-(trifluoromethyl)uridine (100%), melting point 171°C to 175°C.

References

DFU 5 (11) 561 (1980)
Kleeman and Engel p. 921
PDR p. 768
DOT 16 (12) 430 (1980)
I.N. p. 977

REM p. 1232
Heidelberger, C.; US Patent 3,201,387; August 17, 1965; assigned to the US Secretary of Health, Education and Welfare
Ryan, K.J., Acton, E.M. and Goodman, L.; US Patent 3,531,464; September 29, 1970; assigned to the US Secretary of Health, Education and Welfare

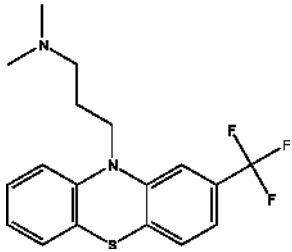
TRIFLUPROMAZINE

Therapeutic Function: Tranquilizer

Chemical Name: N,N-Dimethyl-2-(trifluoromethyl)-10H-phenothiazine-10-propanamine

Common Name: Fluopromazine

Structural Formula:



Chemical Abstracts Registry No.: 146-54-3; 1098-60-8 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Vesprin	Squibb	US	1957
Psyquil	Squibb	France	1970
Fluomazina	Firma	Italy	-
Fluorofen	Savio	Italy	-
Nivoman	Heyden	W. Germany	-
Siquil	Iquinosa	Spain	-

Raw Materials

2-Trifluoromethylphenothiazine
Sodium amide
3-Chloro-1-dimethylaminopropane

Manufacturing Process

Approximately 3.8 grams of sodamide is freshly prepared from 2.25 grams of sodium, 90 grams of liquid ammonia and a catalytic trace of ferric nitrate. The ammonia is allowed to evaporate. A solution of 19.1 grams of 2-

trifluoromethylphenothiazine (prepared by the Bernthsen thionation of 3-trifluoromethyldiphenylamine) in 160 ml of dry benzene is added to the reaction flask followed by 18 grams of 3-chloro-1-dimethylaminopropane. The reaction mixture is heated at reflux for 20 hours. After washing the cooled mixture with 130 ml of water, the organic layer is extracted with several portions of dilute hydrochloric acid. The acid extracts are combined and neutralized with ammonium hydroxide solution. The oily free base is extracted into benzene and purified by distillation to give 19.6 grams of 10-(3'-dimethylaminopropyl)-2-trifluoromethylphenothiazine, boiling point 177° to 181°C at 1 mm. The free base (7 grams) is converted to the hydrochloride salt by reacting an alcoholic solution of the base with hydrogen chloride gas. Evaporation of the volatiles in vacuo leaves an amorphous solid which is recrystallized from ethanol/ether to pink crystals, MP 173° to 174°C, the hydrochloride salt of the free base prepared above.

References

Merck Index 9492
Kleeman and Engel p. 920
OCDS Vol. 1 p. 380 (1977)
I.N. p. 977
REM p. 1092
Ullyot, G.E.: US Patent 2,921,069; January 12, 1960; assigned to Smith Kline and French Laboratories

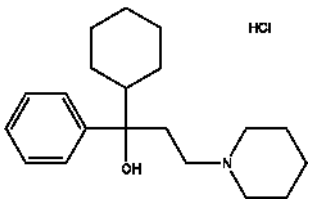
TRIHEXYPHENIDYL HYDROCHLORIDE

Therapeutic Function: Antiparkinsonian

Chemical Name: α-Cyclohexyl-α-phenyl-1-piperidinepropanol hydrochloride

Common Name: Benzhexol chloride

Structural Formula:



Chemical Abstracts Registry No.: 52-49-3; 144-11-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Artane	Lederle	US	1949
Pipanol	Winthrop	US	1952
Tremin	Schering	US	1964

Trade Name	Manufacturer	Country	Year Introduced
Antitrem	Roerig	US	1974
Anti-Spas	Protea	Australia	-
Aparkan	Chinoin	Hungary	-
Aparkane	I.C.N.	Canada	-
Broflex	Bio-Medical	UK	-
Novohexidyl	Novopharm	Canada	-
Paralest	Pharmachemie	Netherlands	-
Pargitan	Kabi Vitrum	Sweden	-
Parkinane	Lederle	France	-
Parkopan	Fahlberg-List	E. Germany	-
Partane	Taro	Israel	-
Peragit	Gea	Denmark	-
Pyramistin	Yamanouchi	Japan	-
Rodenal	Abic	Israel	-
Sedrena	Daiichi	Japan	-
Trihexane	Darby	US	-
Trihexy	Barlow Cote	Canada	-
Triphedinon	Toho	Japan	-

Raw Materials

Acetophenone
Magnesium
Cyclohexyl bromide
Piperidine
Paraformaldehyde
Hydrogen chloride

Manufacturing Process

Acetophenone, paraformaldehyde and piperidine are first reacted to give ω-(1-piperidyl)propiophenone.

To an absolute ethyl ether solution of cyclohexylmagnesium bromide (prepared from 261 parts of cyclohexyl bromide, 38.8 parts magnesium turnings and 700 parts by volume absolute ethyl ether) a dry solution of 174 parts omega-(1-piperidyl)-propiophenonein 600 parts by volume of ether is added, with stirring, at such a rate that gentle reflux is maintained with no external cooling or heating. The reaction mixture is stirred for about 5 hours and then allowed to stand at room temperature until reaction appears complete. While being cooled the reaction mixture is then decomposed by the dropwise addition of 500 parts by volume of 2.5 N hydrochloric acid, and finally is made strongly acidic to Congo red by the addition of concentrated hydrochloric acid.

The resulting white solid is collected on a filter, air dried, redissolved in 2,500 parts water at 95°C and the resulting solution treated with decolorizing charcoal and clarified by filtration. The cooled filtrate is made alkaline with ammonia and the product, crude 3-(1-piperidyl)-1-cyclohexyl-1-phenyl-1-propanol is collected. The hydrochloride melts with decomposition in ten seconds in a bath held at 258.5°C. The alcohol melts at 114.3° to 115.0°C, according to US Patent 2,716,121.

References

Merck Index 9501
Kleeman and Engel p. 921
PDR p. 830
OCDS Vol. 1 p. 47 (1977)
DOT 9 (6) 247 (1973)
I.N. p. 978
REM p. 931
Adamson, D.W. and Wilkinson, S.; US Patent 2,682,543; June 29, 1954; assigned to Burroughs Wellcome and Co. (USA.) Inc.
Denton, J.J.; US Patent 2,716,121; August 23, 1955; assigned to American Cyanamid Co.

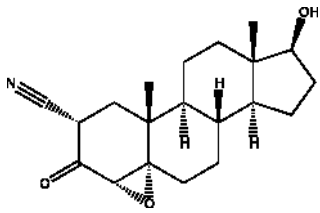
TRILOSTANE

Therapeutic Function: Corticosteroid antagonist

Chemical Name: 2α-Cyano-4α,5α-epoxyandrostan-17β-ol-3-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 13647-35-3

Trade Name	Manufacturer	Country	Year Introduced
Modrenal	Sterling Winthrop	UK	1980
Winstan	Winthrop	W. Germany	1982

Raw Materials

Maleic anhydride
17α-Acetoxy-4-androsteno[2,3-d]isoxazole
Hydrogen peroxide
Sodium methoxide

Manufacturing Process

(A)17β-acetoxy-4α,5α-epoxyandrostano[2,3-d]isoxazole, melting point

228.6°C to 229.8°C (corrected) recrystallized from a benzene-methanol mixture, $[\alpha]_D^{25}$ = +76.5°C (1% in chloroform), was prepared by treating 17β-acetoxy-4-androsteno[2,3-d] isoxazole with maleic anhydride and hydrogen peroxide in methylene dichloride solution.

(B)2α-cyano-4α,5α-epoxandrostan-17β-ol-3-one was prepared by treating 17β-acetoxy-4α,5α-epoxyandrostano[2,3-d] isoxazole with sodium methoxide, and was obtained in the form of tan crystals, melting point 257.8°C to 270.0°C (decomposition) (corrected) when recrystallized from a pyridine-dioxane mixture.

References

Merck Index 9505
DFU 6 (8) 494 (1981)
OCDS Vol. 2 p. 158 (1980)
DOT 17 (5) 203 (1981)
I.N. p. 979
Clinton, R.O. and Manson, A.J.; US Patent 3,296,255; January 3, 1967; assigned to Sterling Drug, Inc.

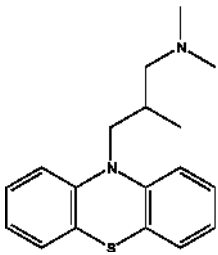
TRIMEPRAZINE

Therapeutic Function: Antipruritic

Chemical Name: N,N,β-Trimethyl-10H-phenothiazine-10-propanamine

Common Name: Alimemazine

Structural Formula:



Chemical Abstracts Registry No.: 84-96-8

Trade Name	Manufacturer	Country	Year Introduced
Temaril	SKF	US	1958
Theralene	Theraplix	France	1958
Alimezine	Daiichi	Japan	-
Nedeltran	Bournonville	Belgium	-
Panectyl	Rhone Poulenc	Canada	-

Trade Name	Manufacturer	Country	Year Introduced
Repeltin	Bayer	W. Germany	-
Vallergan	May and Baker	UK	-
Variargil	Rhodia Iberica	Spain	-

Raw Materials

Phenothiazine
Sodium amide
1-Chloro-2-methyl-3-dimethylaminopropane

Manufacturing Process

95% sodamide (2.77 grams) is added to a solution of phenthiazine (9.6 grams) in xylene (140 cc) at a temperature of 130°C and the mixture is heated with reflux for 2 hours.

A 0.61 N solution (90 cc) of 1-chloro-2-methyl-3-dimethylaminopropane in xylene is then added over 50 minutes and heating with reflux is continued for 20 hours. After cooling, the mixture is treated with water (40 cc) and N methanesulfonic acid (70 cc). The aqueous layer is washed with ether, treated with aqueous sodium hydroxide (density = 1.33; 10 cc) and extracted with ether.

The extract is dried over potassium carbonate and evaporated and the residue is distilled in vacuo. 3-(10-phenthiazinyl)-2-methyl-1-dimethylaminopropane (12.6 grams) is collected, distilling between 150° and 175°C under a pressure of about 0.3 mm Hg. By dissolving this base in acetone and adding ethereal hydrogen chloride, a hydrochloride is obtained, MP 216° to 217°C.

References

Merck Index 9510
Kleeman and Engel p. 25
PDR p. 1727
OCDS Vol. 1 p. 378 (1977)
I.N. p. 55
REMp.1130
Jacob, R.M. and Robert, J.G.; US Patent 2,837,518; June 3, 1958; assigned to Societe des Usines Chimiques Rhone-Poulenc, France

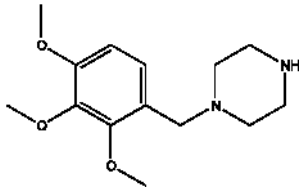
TRIMETAZIDINE

Therapeutic Function: Coronary vasodilator

Chemical Name: 1-[(2,3,4-Trimethoxyphenyl)methyl]piperazine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 5011-34-7; 13171-25-0 (Dihydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Vastarel	Biopharma	France	1963
Cartoma	Ohta	Japan	-
Coronanyl	Toho	Japan	-
Hiwell	Toa Eiyo	Japan	-
Lubomanil	Maruko	Japan	-
Sainosine	Nippon Chemiphar	Japan	-
Trimeperad	Kotobuki	Japan	-
Vassarin-F	Taiyo	Japan	-
Vastazin	Takeda	Japan	-
Yosimilon	Kowa Yakuhin	Japan	-

Raw Materials

2,3,4-Trimethoxybenzyl chloride
1-Formylpiperazine
Sodium carbonate

Manufacturing Process

Monoformylpiperazine is reacted molecule for molecule with 2,3,4-trimethoxybenzyl chloride in the presence of 1 1/2 molecules of sodium carbonate and in suspension in ethyl alcohol, during 2 to 3 hours.

The reaction product is filtered and the filtrate is evaporated in vacuo to remove the alcohol. There remains an oily product from which the excess formyl-ethylenediamine is removed by distillation under 1 mm Hg pressure up to 125°C. The dark yellow, residual product is treated with 10% hydrochloric acid at 100°C for 12 hours to eliminate the formyl group; it is evaporated to a syrupy consistency and taken up with ethyl alcohol at the boiling point until complete miscibility is attained; it is then discolored over carbon, filtered and stored at low temperature.

The (2,3,4-trimethoxyphenyl) methylpiperazine hydrochloride precipitates as white needles: the precipitate is drained and washed with anhydrous sulfuric ether. Melting point: 222°C to 226°C.

References

Merck Index 9511
Kleeman and Engel p. 922
I.N. p. 980
Servier, J.; US Patent 3,262,852; July 26, 1966: assigned to Biofarma S.A. (France)

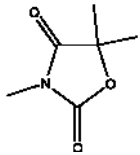
TRIMETHADIONE

Therapeutic Function: Anticonvulsant

Chemical Name: 3,5,5-Trimethyl-2,4-oxazolidinedione

Common Name: Troxidone

Structural Formula:



Chemical Abstracts Registry No.: 127-48-0

Trade Name	Manufacturer	Country	Year Introduced
Tridione	Abbott	US	1946
Trimethadione	Abbott	France	1960
Absentol	Noury Pharma	Netherlands	-
Epidione	Roger Bellon	France	-
Mino-Aleviatin	Dainippon	Japan	-
Trioxanona	Bama-Geve	Spain	-

Raw Materials

Sodium
Ethanol
Methyl iodide
Ethyl α-hydroxyisobutyrate
Urea

Manufacturing Process

To a cooled solution of 23 parts of sodium in 400 parts of dry ethanol are added 60 parts of dry urea and 132 parts of ethyl α-hydroxy-isobutyrate. The mixture is heated on a steam bath under reflux for about 16 hours and the liberated ammonia is removed from the solution by drawing a current of dry air through it at the boiling point. The solution of the sodium salt of 5,5-dimethyloxazolidine-2,4-dione so obtained is cooled and treated with 284

parts of methyl iodide. The mixture is allowed to stand at room temperature for 3 days, excess methyl iodide and ethanol are then removed by distillation under reduced pressure.

The residue is dissolved in ether and the solution is washed with sodium chloride solution and then with a little sodium thiosulfate solution. The ethereal solution is dried over sodium sulfate and ether removed by distillation. A yield of 108 parts of 3,5,5-trimethyloxazolidine-2,4-dione is obtained having a melting point of 45° to 46°C with slight softening at 43°C. This represents a 75% theory yield on the ethyl α-hydroxy-iso-butyrate taken. The product may be further purified by dissolving the minimum quantity of dry ether and cooling to -10°C. The product so obtained melts sharply at 45.5° to 46.5°C according to US Patent 2,559,011.

References

Merck Index 9512
Kleeman and Engel p. 922
PDR p. 554
OCDS Vol. 1 p. 232 (1977)
I.N. p. 980
REM p. 1082
Davies, J.S.H. and Hook, W.H.; US Patent 2,559,011; July 3, 1951; assigned to British Schering Research Laboratories Limited, England
Spielman, M.A.; US Patent 2,575,692; November 20, 1951; assigned to Abbott Laboratories

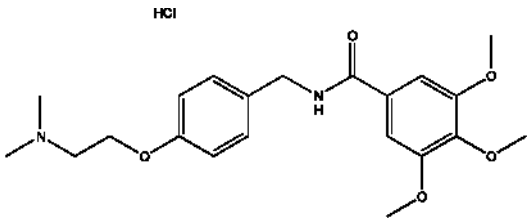
TRIMETHOBENZAMIDE HYDROCHLORIDE

Therapeutic Function: Antinauseant

Chemical Name: N-[(2-Dimethylaminoethoxy)benzyl]-3,4,5-trimethoxybenzamide hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 554-92-7; 138-56-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Tigan	Beecham	US	1973
Hymetic	Hyrex	US	1983
Ticon	Hauck	US	1983
Ametik	Lafare	Italy	-
Anaus	Molteni	Italy	-
Anti-Vomit	Deva	Turkey	-
Contrauto	Aterni	Italy	-
Emedur	Dif-Dogu	Turkey	-
Ibikin	I.B.P.	Italy	-
Kantem	Kansuk	Turkey	-
Poligerim	Biotifar	Portugal	-
Stemetic	Legere	US	-
Xametina	Zambeletti	Italy	-

Raw Materials

p-Hydroxybenzaldehyde
Sodium methoxide
Hydrogen
2-Dimethylaminoethyl chloride
3,4,5-Trimethoxybenzoic acid chloride

Manufacturing Process

To 122 grams (1 mol) of p-hydroxybenzaldehyde in 1 liter of chlorobenzene were added 66 grams (1.04 mols) of sodium methoxide (85%) and 108 grams (1 mol) of 2-dimethylaminoethyl chloride. The mixture was stirred and refluxed for 15 hours, then cooled and the precipitated sodium chloride filtered off. The filtrate was concentrated at steam temperature under water vacuum and the residual oil was fractionated in high vacuum, to give 4-(2-dimethylaminoethoxy)benzaldehyde, BP2.2145°C.

Two teaspoons of Raney nickel catalyst were added to a solution of 65.6 grams (0.34 mol) of 4-(2-dimethylaminoethoxy)benzaldehyde in 300 ml of 10% ammoniacal ethanol. The mixture was hydrogenated at 80°C and a pressure of 1,000 psi. The catalyst was filtered off, the volatiles were distilled off and the residual oil was fractionated in high vacuum, to obtain 4-(2-dimethylaminoethoxy)benzylamine, BP0.3120° to 123°C.

To 9.7 grams (0.05 mol) of 4-(2-dimethylaminoethoxy)benzylamine, dissolved in 100 ml of acetonitrile, was added all at once 12 grams (0.051 mol) of 3,4,5-trimethoxybenzoyl chloride, dissolved in 75 ml of acetonitrile. The mixture was stirred and refluxed for 8 hours, and then cooled. The crystalline solid, which had formed, was filtered off, washed with acetonitrile and recrystallized from acetonitrile, to give 4-(2-dimethylaminoethoxy)-N-(3,4,5-trimethoxybenzoyl)benzylamine hydrochloride, MP 185° to 186°C.

References

Merck Index 9515
Kleeman and Engel p. 923
PDR pp. 665, 1033, 1606
OCDS Vol. 1 p. 110 (1977)

I.N. p. 980
REM p. 810
Goldberg, M.W. and Teitel, S.; US Patent 2,879,293; March 24, 1959; assigned to Hoffmann-La Roche Inc.

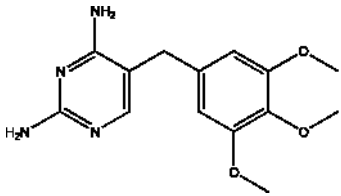
TRIMETHOPRIM

Therapeutic Function: Antibacterial (urinary)

Chemical Name: 5-[(3,4,5-Trimethoxyphenyl)methyl]-2,4-pyrimidinediamine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 738-70-5

Trade Name	Manufacturer	Country	Year Introduced
Eusaprim	Wellcome	Italy	1970
Bactrim	Roche	Italy	1970
Baktar	Shionogi	Japan	1976
Ipral	Squibb	UK	1979
Trimopam	Berk	UK	1979
Trimanyl	Tosse	W. Germany	1980
Syraprim	Wellcome	UK	1980
Proloprim	Burroughs-Wellcome	US	1980
Trimpex	Roche	US	1980
Wellcoprim	Wellcome	France	1981
Trimopan	Farmitalia	Italy	1982
Monotrim	Gea	Switz.	1983
Cistal	Gamir	Spain	-
Comoxol	Squibb	US	-
Cotrim	Lemmon	US	-
Idotrim	Ferrosan	Denmark	-
Oratrim	Medica	Finland	-
Proloprim	Calmic	Canada	-
Septra	Burroughs-Wellcome	US	-

Trade Name	Manufacturer	Country	Year Introduced
Tiempe	D.D.S.A.	UK	-
Trimanyl	Gea	Denmark	-
Trimecur	Leiras	Finland	-
Trimfect	Neofarma	Finland	-
Trimpex	Roche	US	-
Triprim	Berk	UK	-

Raw Materials

β-Methoxypropionitrile
Sodium
3,4,5-Trimethoxybenzaldehyde
Guanidine

Manufacturing Process

6 grams (0.26 mol) sodium was dissolved in 300 ml methanol under stirring and refluxing. 47.5 grams (0.55 mol) β-methoxypropionitrile and 98 grams (0.5 mol) 3,4,5-trimethoxybenzaldehyde were added and the mixture refluxed gently for 4 hours. The mixture was then chilled and 150 ml of water was added. The product crystallized rapidly. Crystallization was allowed to proceed at 5° to 10°C under stirring for 1 hour. The product was filtered by suction and washed on the filter with 200 ml of 60% ice cold methanol. The crude material was air-dried and used for further steps without purification. It melted at 78° to 80°C. A pure sample, recrystallized from methanol, melted at 82°C. The yield of 3,4,5-trimethoxy-2'-methoxymethylcinnamonitrile was 92 grams, corresponding to 70% of the theory.

19 grams (0.83 mol) sodium was dissolved in 300 ml methanol, 106 grams of 3,4,5-trimethoxy-2'-methoxymethylcinnamonitrile was added and the mixture gently refluxed for 24 hours. The solution, which had turned brown, was poured into 1 liter of water and the precipitated oil extracted repeatedly with benzene. The combined benzene layers (500 to 700 ml) were washed 3 times with 500 ml of water, the benzene removed by evaporation in a vacuum from a water bath, and the brown residual oil distilled in vacuo, boiling point 215° to 225°C/11 mm. The clear, viscous oil, 3,4,5-trimethoxy-2'-cyano-dihydrocinnamaldehyde dimethyl acetal, weighed 83 grams (71% of the theory), and showed a n_D^{23} = 1.5230. It solidified upon standing. A sample recrystallized from methanol melted at 69° to 70°C and showed a strong melting point depression with the starting material; n_D^{25} = 1.5190.

31.5 grams (0.107 mol) 3,4,5-trimethoxy-2'-cyano-dihydrocinnamaldehyde dimethyl acetal was refluxed with methanolic guanidine solution (200 ml containing 0.25 mol of guanidine) for 2 hours. The methanol completely distilled off under stirring, finally from a bath of 110° to 120°C until the residue solidified completely to a yellowish crystalline mass. After allowing to cool, it was slurried with 100 ml of water and collected by vacuum filtration and dried. The yield of 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine amounted to 28 grams (91% of the theory). The material showed the correct melting point of 199° to 200°C and was, however, yellowish discolored.

20 grams of the above product was added to 30 ml of 3 N aqueous sulfuric acid at 60°C under stirring. The solution was chilled under stirring to 5° to 10°C. The crystalline sulfate was collected by vacuum filtration and washed on

the filter twice with 10 ml of cold 3 N aqueous sulfuric acid each time. From the filtrate there was recovered 1.3 grams (6.5%) of discolored material melting at 195° to 196°C and which can be added to subsequent purification batches.

The sulfate on the filter was dissolved in 200 ml of hot water, the solution charcoaled hot, and the product precipitated from the clear colorless filtrate by the gradual addition of a solution of 20 grams of sodium hydroxide in 40 ml of water under chilling. The precipitate was filtered by suction and washed thoroughly with water on the filter. The white material, 17.5 grams (88%) showed the correct melting point of 200° to 201°C, according to US Patent 3,341,541.

References

Merck Index 9516
Kleeman and Engel p. 923
PDR pp. 673, 759, 830, 993, 1034, 1474, 1505, 1606, 1738
OCDS Vol. 1 p. 262 (1977) and 2, 302 (1980)
DOT 5 (3) 113 (1969); 12 (9) 377 (1976) and 16 (4) 128 (1980)
I.N. p. 980
REM p. 1215
Stanbuck, P. and Hood, H.M.; US Patent 3,049,544; August 14, 1962; assigned to Burroughs Wellcome and Co. (USA.) Inc.
Hoffer, M.; US Patent 3,341,541; September 12, 1967; assigned to Hoffmann-La Roche Inc.

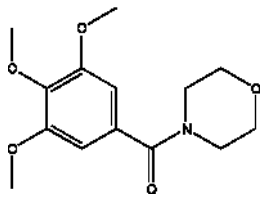
TRIMETOZINE

Therapeutic Function: Sedative

Chemical Name: 4-(3,4,5-Trimethoxybenzoyl)morpholine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 635-41-6

Trade Name	Manufacturer	Country	Year Introduced
Opalene	Theraplix	France	1966
Trioxazine	Labatec	Italy	1971

Raw Materials

3.4.5-Trimethoxybenzoyl chloride
Morpholine

Manufacturing Process

46 g 3,4,5-trimethoxybenzoyl chloride are dissolved in 300 ml anhydrous benzene and 25 g triethylamine and thereafter 19 g anhydrous morpholine are added in small portions with ice-cooling. The solution is boiled for 2 hours under reflux. The precipitate is filtered off, and the solution is washed with dilute sulfuric acid, then with sodium hydrogen carbonate solution and finally with water, and then evaporated. The residual yellow oil soon crystallizes; the crystalline mass of the desired material is taken up with ether, filtered and then recrystallized from 90% ethanol, from which it separates in prisms. It is slightly soluble in water. Yield: 80%. melting point 120°C to 122°C.

References

Merck Index 9527
Kleeman and Engel p. 927
OCDS Vol. 2 p. 94 (1980)
DOT 3 (3) 106 (1967)
I.N. p. 981
Egyesult Gyogyszer es Tapszer Gyar; British Patent 872,350; July 5, 1961

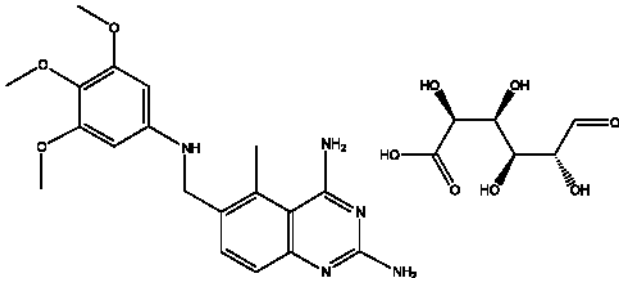
TRIMETREXATE GLUCURONATE

Therapeutic Function: Antineoplastic

Chemical Name: D-Glucuronic acid, compd. with 5-methyl-6-(((3,4,5-trimethoxyphenyl)amino)methyl)-2,4-quinazolinediamine (1:1)

Common Name: Trimetrexate glucuronate

Structural Formula:



Chemical Abstracts Registry No.: 82952-64-5

Trade Name	Manufacturer	Country	Year Introduced
Neutrexin	MedImmune Inc.	USA	-
Neutrexin	Ben Venue Laboratories, Inc.	USA	-
Oncotrex	Sun Pharma	-	-
Trimetrexate Glucuronate	MedImmune Inc.	USA	-

Raw Materials

2,4-Diamino-5-methyl-6-[(3,4,5-trimethoxyanilino)methyl]quinazoline
Glucuronic acid

Manufacturing Process

A mixture of 2,4-diamino-5-methyl-6-[(3,4,5-trimethoxyanilino)methyl]quinazoline (1.0 g) and glucuronic acid (0.7 g) in methanol (65 ml) is heated to dissolve the solid. The solution is cooled to 10°C and filtered to remove a small amount of solid. The filtrate is heated to reflux and ethyl acetate is added to the cloud point. The warm solution is filtered then slowly cooled. The solid that forms is collected, washed first with ethylacetate, then with ether and dried in vacuo at 60°C to give the 4-diamino-5-methyl-6-[(3,4,5-trimethoxyanilino)methyl]quinazoline D-glucuronate as a yellow powder with no definite melting point.

References

Colbry N.L.; US Patent No. 4,376,858; Mar. 15, 1983; Assigned: Warner Lambert Company, Morris Plains, N.J.

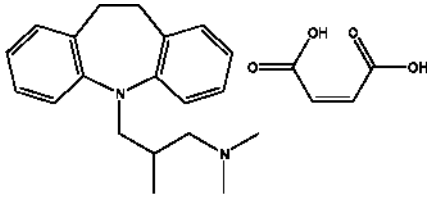
TRIMIPRAMINE MALEATE

Therapeutic Function: Antidepressant

Chemical Name: 5H-Dibenz(b,f)azepine, 5-(3-(dimethylamino)-2-methylpropyl)-10,11-dihydro-, maleate (1:1)

Common Name: Trimeprimine maleate; Trimepropriminum maleate; Trimipramine maleate

Structural Formula:



Chemical Abstracts Registry No.: 521-78-8; 739-71-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Surmontil	Wyeth-Ayerst Laboratories	-	-
Trimipramine Maleate	Pliva	Croatia	-

Raw Materials

Bis(3-dimethylamino-2-methylpropyl)-5-iminodibenzylyl carboxylic acid

Manufacturing Process

Bis(3-dimethylamino-2-methylpropyl)-5-iminodibenzylyl carboxylic acid at 185-250°C up to discontinue a separation of oxyde carbonique. The product was dissolved in ether, then washed with the hydrochloric acid. Then this solution was extracted with ether. The solvent was evaporated under vacuum, to give pure oil bis(3-dimethylamino-2-methyl-1-propyl)-5-iminodibenzyle with boiling point 153-154°C at 0.4 mm. Maleate of bis(3-dimethylamino-2-methyl-1-propyl)-5-iminodibenzyle have melting point 145-146°C.

References

Ablon J. R. M., Regnier G. L., FR Patent No. 1,172,014; Feb. 4, 1959; Assigneed to Societe des Usines Chimiques Rhone-Poulenc, France

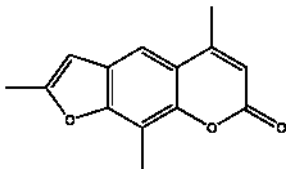
TRIOXSALEN

Therapeutic Function: Dermal pigmentation enhancer

Chemical Name: 2,5,9-Trimethyl-7H-furo[3,2-g]benzopyran-7-one

Common Name: 2',4,8-Trimethylpsoralen

Structural Formula:



Chemical Abstracts Registry No.: 3902-71-4

Trade Name	Manufacturer	Country	Year Introduced
Trisoralen	Elder	US	1965
Trisoralen	Santen	Japan	1969

Trade Name	Manufacturer	Country	Year Introduced
Trisoralen	Farmochimica	Italy	1970
Trisoralen	Panpharma	Switz.	1981
Levrison	Rovi	Spain	-

Raw Materials

Ethyl acetoacetate
Bromine
2-Methyl resorcinol
Sodium
Allyl bromide
Hydrogen chloride
Acetic anhydride

Manufacturing Process

(A) Preparation of 7-Hydroxy-4,8-Dimethylcoumarin: Chilled ethyl acetoacetate (157 ml, 1.20 mols) followed by 2-methyl-resorcinol (130 g, 1.04 mols) was dissolved in well-stirred concentrated sulfuric acid (600 ml) at such a rate as to keep the temperature below 10°C (ice bath). The stirred solution was allowed to warm gradually and after 3 hours was added to water (ca 8 liters) with mechanical stirring. The product was collected, washed twice with water, and dried at 70° to 80°C until the first sign of darkening. Yield 191.3 g (95.4%). Recrystallization from aqueous ethanol gave 7-hydroxy-4,8-dimethylcoumarin as colorless needles, MP 260.5° to 261°C. In dilute sodium hydroxide, the compound gives a yellow solution which exhibits blue fluorescence.

(B) Preparation of 7-Allyloxy-4,8-Dimethylcoumarin: 7-Hydroxy-4,8-dimethylcoumarin (191.3 g, 1.01 mols), anhydrous potassium carbonate (604 g, 4.37 mols), and allyl bromide (578 ml, 6.22 mols) were refluxed overnight in acetone (ca 3 liters) with mechanical stirring. The reaction mixture was concentrated nearly to dryness on a steam bath under reduced pressure, water (ca 8 liters) was added, and the product was collected by filtration. It was washed with 5% NaOH and water (ca 1.5-liter portions) and was dried in a vacuum desiccator. The dry solid was washed with petroleum ether (30° to 60°C) to remove excess allyl bromide. Removal of the petroleum ether under reduced pressure left 210.0 g (90.7% yield) of product. The 7-allyloxy-4,8-dimethylcoumarin was crystallized from aqueous ethanol as colorless needles, MP 108° to 109°C.

(C) Preparation of 6-Allyl-7-Hydroxy-4,8-Dimethylcoumarin: 7-Allyloxy-4,8-dimethylcoumarin (195.0 g, 0.84 mol) was heated (oil bath) to 2154°C (reaction mixture temperature) for 3 hours and was then poured into absolute alcohol (ca 1.5 liters). Activated carbon (Norite) (19.5 g) was added, and the solution was heated to boiling, filtered, and diluted with excess water (ca 12 liters). The product was collected by filtration and partially dried at 70°C for 6 hours. 6-Allyl-7-hydroxy-4,8-dimethylcoumarin was obtained as pale yellow microcrystalline prisms, MP 166° to 168°C, by two recrystallizations from aqueous ethanol of a portion of the partially dried solid. The remaining partially dried solid was used in the next step.

(D) Preparation of 7-Acetoxy-6-Allyl-4,8-Dimethylcoumarin: A solution of the partially dried 6-allyl-7-hydroxy-4,8-dimethylcoumarin obtained in the previous step, acetic anhydride (915 ml, 9.7 mols) and fused sodium acetate (2 g) was refluxed for 4 hours and added to water (ca 8 liters) with

mechanical stirring. After excess acetic anhydride had decomposed, the 7-acetoxy-6-allyl-4,8-dimethylcoumarin was collected by filtration, dried, and recrystallized from absolute alcohol, MP 144.5° to 145.5°C. Yield 145.4 g (63.8%, based on 7-allyloxy-4,8-dimethylcoumarin).

(E) Preparation of 7-Acetoxy-6-(2',3'-Dibromopropyl)-4,8-Dimethylcoumarin: 7-Acetoxy-6-allyl-4,8-dimethylcoumarin (145.4 g, 0.534 mol) was dissolved in chloroform (ca 800 ml). The stirred solution was cooled in an ice bath and bromine (85.2 g, 0.534 mol) in chloroform (200 ml) was added at such a rate as to keep the temperature below 25°C. Evaporation of chloroform on the steam bath left an off-white residue of the crude dibromide. Yield 230.6 g (quantitative). 7-Acetoxy-6-(2',3'-dibromopropyl)-4,8-dimethylcoumarin was crystallized from ethanol as colorless prisms, MP 141.5° to 142.5°C.

(F) Preparation of 2',4,8-Trimethylpsoralen: Crude 7-acetoxy-6-(2',3'-dibromopropyl)-4,8-dimethylcoumarin (245.7 g, 0.57 mol) was refluxed for 1 1/2 hours with a stirred solution of sodium (65.4 g, 2.85 mols) in a magnesium-dried ethanol (2.1 liters). After standing at room temperature for 15 minutes, the reaction mixture was poured into a stirred mixture of ice (8,000 g) and a 3.5% HCl (8 liters). Twelve hours later, the precipitate had coagulated and was collected by filtration; it was thoroughly washed with successive 3-liter portions of 5% NaOH, water, 0.5% HCl, and water.

After partial drying at 60°C for 5 hours, the crude trimethylpsoralen material was thoroughly dried in a vacuum desiccator. Yield 110.1 g (85%). Fractional crystallization, using activated carbon (Norite) (30.8 g), from mixtures of chloroform and petroleum ether (30° to 60°C) and finally from chloroform alone gave colorless prisms of 2',4,8-trimethylpsoralen, MP 234.5° to 235°C. Yield 61.8 g (48%).

References

Merck Index 9538
PDR p. 871
OCDS Vol. 1 p. 334 (1977)
I.N. p. 982
REM p. 790
Kaufman, K.D.; US Patent 3,201,421; August 17, 1965

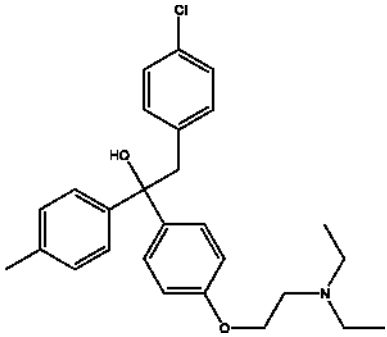
TRIPARANOL

Therapeutic Function: Antihyperlipidemic

Chemical Name: 4-Chloro-α-[4-[2-(diethylamino)ethoxy]phenyl]-α-(4-methylphenyl)benzene ethanol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 78-41-1

Trade Name	Manufacturer	Country	Year Introduced
Mer-29	Merrell National	US	1960

Raw Materials

Sodium methoxide
Magnesium
p-Chlorobenzyl chloride
4-Hydroxy-4-methylbenzophenone
β-Diethylaminoethyl chloride

Manufacturing Process

4-(β-diethylaminoethoxy)-4-methylbenzophenone was prepared as follows: a mixture of 200 g of 4-hydroxy-4-methylbenzophenone, 55 g of powdered sodium methoxide and 400 ml of ethanol was stirred for 30 minutes. A solution of 150 g of β-diethylaminoethyl chloride in 300 ml of toluene was added and the mixture was refluxed four hours. The solvent was removed, the residue was taken up in ether, extracted with 5% NaOH solution, twice with water, the ether was removed and the residue was distilled. The product was obtained as an oil boiling at 232°C at 0.6 mm.

1 liter of a 0.45 N ethereal solution of p-chlorobenzyl magnesium chloride was added in 30 minutes to a stirred solution of 104 g (0.35 mol) of 4-(β-diethylaminoethoxy)-4-methylbenzophenone in 400 ml of dry ether. After stirring an additional hour, the mixture was decomposed by pouring onto 1 liter of cold 10% ammonium chloride solution, the ether solution was washed with water, and the ether was replaced with hot isopropanol containing a trace of ammonia. 1-[p-(β-diethylaminoethoxy)phenyl]-1-phenyl-2-p-tolyl-2-p-chloroethanol separated as white crystals, melting at 104% to 106°C.

References

Merck Index 9541
I.N. p. 982
Allen, R.E., Palopoli, F.P., Schumann, E.L. and Van Campen, M.G. Jr.; US Patent 2,914,562; November 24,1959; assigned to Wm. S. Merrell Co.

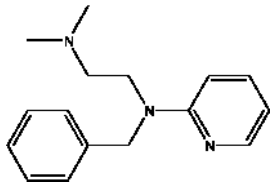
TRIPELENNAMINE

Therapeutic Function: Antihistaminic

Chemical Name: N,N-Dimethyl-N'-(phenylmethyl)-N'-2-pyridinyl-1,2-ethanediamine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 91-81-6; 154-69-8 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Pyribenzamine	Ciba	US	1946
PBZ-SR	Ciba Geigy	US	1977
Anhistamin	Pharmachim	Bulgaria	-
Antamine	Teva	Israel	-
Antiallergicum Medivet	Medivet	Switz.	-
Sedilene	Montefarmaco	Italy	-

Raw Materials

α-Aminopyridine
Benzaldehyde
Dimethylaminochloroethane
Sodium amide

Manufacturing Process

46 g of α-benzylaminopyridine in 50 cc of dry toluene are heated to 80°C [the α-benzylaminopyridine may be obtained either according to the method of Tchitchibabine and Knunjanz, Berichte, 64, 2839 (1931), which consists in warming α-aminopyridine with benzaldehyde in formic acid, or alternatively by the action of benzyl chloride on sodio-α-aminopyridine]. To the toluene solution there are added gradually 9.5 g of 85% sodamide. After evolution of ammonia, the major part of the toluene is distilled off; into the pasty mass which remains there are poured 120 cc of an ethereal solution of 27 g of dimethylaminochloroethane.

The mixture is heated until the temperature reaches 140°C, the ether distilling out, then finally heated under reduced pressure (150 mm Hg) for 1/2 hour. The mass is taken up with dilute hydrochloric acid and ether, neutralized at pH 7, and α-benzylaminopyridine separates. After making alkaline, using excess

of potash, it is extracted with benzene, dried and distilled. The product thereby obtained, dimethylamino-ethyl-N-benzyl-N-α-arninopyridine, boils at 135° to 190°C/1.7 mm, according to US Patent 2,502,151.

References

Merck Index 9542
Kleeman and Engel p. 928
PDR pp. 830, 898
OCDS Vol. 1 p. 51 (1977)
I.N. p. 983
REM p. 1130
Djerassi, C., Huttrer, C.P. and Scholz, C.R.; US Patent 2,406,594; August 27, 1946; assigned to Ciba Pharmaceutical Products Incorporated
Horclois, R.J.; US Patent 2,502,151; March 28, 1950; assigned to Societe des Usines Chimiques Rhone-Poulenc, France

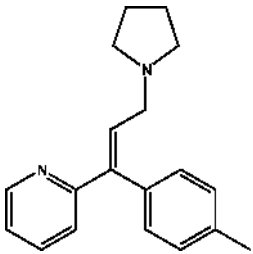
TRIPROLIDINE

Therapeutic Function: Antihistaminic

Chemical Name: (E)-2-[1-(4-Methylphenyl)-3-(1-pyrrolidinyl)-1-propenyl]pyridine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 486-12-4; 550-70-9 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Actidil	Burroughs-Wellcome	US	1958
Actidilon	Wellcome	France	1965
Bayidyl	Bay	US	1983
Actifed	Burroughs-Wellcome	US	-
Actiphyll	Gayoso Wellcome	Spain	-
Entra	Wellcome-Tanabe	Japan	-
Histradil	Trima	Israel	-
Pro-Actidil	Burroughs-Wellcome	UK	-

Trade Name	Manufacturer	Country	Year Introduced
Pro-Entra	Wellcome-Tanabe	Japan	-
Triafed	Schein	US	-
Tripodrine	Danbury	US	-
Venen	Tanabe	Japan	-

Raw Materials

Paraformaldehyde
Pyrrolidine
2-Bromopyridine
Lithium
4-Methylacetophenone

Manufacturing Process

4-Methylacetophenone is first reacted with paraformaldehyde and then with pyrrolidine to give p-methyl-ω-pyrralidinopropiophenone.

Atomized lithium (26 g, 3.75 mols) and sodium-dried ether (200 cc) are placed in a 3-liter, 3-necked flask fitted with a Herschberg stirrer, thermometer pocket and a water condenser closed by a calcium chloride tube. A slow stream of dry nitrogen is blown through the flask, which is cooled to -10°C and n-butyl chloride (138 g, 156 cc, 1.5 mols) is run in with rapid stirring; the mixture is stirred for a further 30 minutes, and then cooled to -60°C

2-Bromopyridine (193 g, 1.22 mols) is then added dropwise over 20 minutes, the temperature of the reaction mixture being maintained at -50°C. The mixture is stirred for 10 minutes at -50°C and p-methyl-ω-pyrrolidinopropiophenone (112.5 g, 0.5 mol) in dry benzene is then added dropwise over ca 30 minutes, at a temperature of -50°C. The mixture is stirred for a further 2 hours, the temperature being allowed to rise to -30°C but no higher.

The mixture is poured onto excess ice, acidified with concentrated hydrochloric acid, the ether layer separated and extracted with water (1 x 200 cc). The combined aqueous extracts are washed with ether (1 x 200 cc) basified with 0.880 ammonia and extracted with chloroform (3 x 350 cc); the extract is washed with water (2 x 100 cc), dried over sodium sulfate, evaporated, and the residue extracted with boiling light petroleum (BP 60° to 80°C; 10 volumes), filtered hot and evaporated to dryness. The residue is recrystallized from alcohol to give a cream solid (119 g, 80%), MP 117° to 118°C. Recrystallization gives 1-(4-methylphenyl)-1-(2-pyridyl)-3-pyrrolidonopropan-1-ol, MP 119° to 120°C.

1-(4-Methylphenyl)-1-(2-pyridyl)-3-pyrrolidinopropan-1-ol (10.0 g) is heated in a steam bath for 30 minutes with 85% aqueous sulfuric acid (30 cc). The solution is then poured onto crushed ice, excess of ammonia solution added and the liberated oil extracted with light petroleum (BP 60° to 80°C). The extract is dried over anhydrous sodium sulfate and the solvent evaporated to leave an amber syrup (8.8 g) consisting of the cis and trans isomers of 1-(4-methylphenyl)-1-(2-pyridyl)-3-pyrrolidinoprop-1-ene as described in US Patent 2,712,023. The isomers may be separated by base exchange chromatography. The 4-methyl-ω-pyrrolidinopropiophenone required as the starting product for

the preparation of the carbinol is prepared by the Mannich reaction (Blicke, Organic Reactions, 1942, vol 1, p 303; Adamson & Billinghurst, Journal of the Chemical Society, 1950,1039) from 4-methylacetophenone and pyrrolidine. The hydrochloride has a MP of 170°C with decomposition.

References

Merck Index 9552
Kleeman and Engel p. 929
PDR pp. 731, 830, 993, 1569, 1606, 1999
OCDS Vol. 1 p. 78 (1977)
I.N. p. 983
REM p. 1130
Adamson, D.W.; US Patent 2,712,020; June 28, 1955; assigned to Burroughs Wellcome and Co. (USA.) Inc.
Adamson, D.W.; US Patent 2,712,023; June 28,1955; assigned to Burroughs Wellcome and Co. (USA.) Inc.

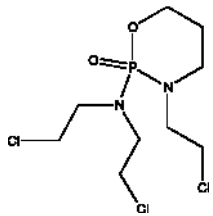
TROFOSFAMIDE

Therapeutic Function: Cancer chemotherapy

Chemical Name: N,N,3-Tris(2-chloroethyl)-tetrahydro-2H-1,3,2-oxaphosphorin-2-amine-2-oxide

Common Name: Trophosphamide

Structural Formula:



Chemical Abstracts Registry No.: 22089-22-1

Trade Name	Manufacturer	Country	Year Introduced
Ixoten	Asta	W. Germany	1973
Ixoten	Schering	Italy	1975

Raw Materials

N,N-Bis(β-chloroethyl)phosphoric acid amide dichloride
N-(2-Chloroethyl)-N-(3-hydroxypropyl)amine hydrochloride
Triethylamine

Manufacturing Process

259 g (1 mol) of N,N-bis-(2-chloroethyl)-phosphoric acid amide dichloride, 209 g (1.2 mols) of N-(2-chloroethyl)-N-(3-hydroxypropyl)-amine hydrochloride (crude), 1,000 cc of ethylene dichloride and 344 g (3.4 mols) of triethylamine are the reactants. N,N-bis-(2-chloroethyl)-phosphoric acid amide dichloride is dissolved in the methylene dichloride. N-(2-chloroethyl)-N-(3-hydroxypropyl)-amine hydrochloride is suspended in this solution and triethylamine is added thereto dropwise with stirring. The temperature of the solution rises to boiling, After the termination of the addition, the mixture is heated to boiling for another 6 hours. Thereafter, the reaction mixture is cooled down and allowed to stand overnight at about 0°C. The precipitated triethylamine hydrochloride is filtered off with suction. The resulting solution is evaporated, the residue (about 370 g) is triturated with about 3.2 liters of ether and is heated to boiling for a short period of time.

The ethereal solution is decanted from the insolubles (about 90 g). The solution is rendered to pH 6.5 to 7 by the addition of ethereal hydrochloric acid and then is filtered over charcoal and thereafter is evaporated. During evaporation, the temperature should not rise above 40°C. The residue is dissolved in ether and in an amount corresponding to half of its weight (240 g of residue, dissolved in 120 cc of ether), the ethereal solution is cooled to -5°C and is inoculated. After standing for 25 hours, 140 g have been separated by crystallization. After separation by filtration with suction, the mother liquor is diluted with ether to 5 times its volume, the solution is filtered over charcoal, is again evaporated and the residue is again dissolved in a volume corresponding to half of the weight of the residue. Another cooling to -5°C and inoculation produces further 18 g of the desired compound. MP: 50° to 51°C. Total yield: 161 g (50% of the theoretical).

References

Merck Index 9571
Kleeman and Engel p. 930
OCDS Vol. 3 p. 161 (1984)
DOT 9 (12) 502 (1973) and 13 (3) 118 (1977)
I.N. p. 985
Asta-Werke AG Chemische Fabrik, Germany; British Patent 1,188,159; April 15, 1970 Arnold, H., Brock, N., Bourseaux, F. and Bekel, H.;US Patent 3,732,340; May 8, 1973; assigned to Asta-Werke AG Chemische Fabrik

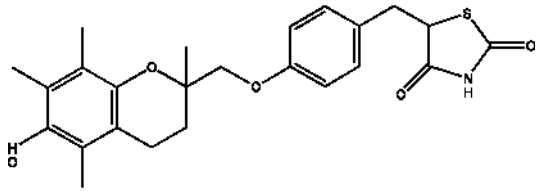
TROGLITAZONE

Therapeutic Function: Hypoglycemic

Chemical Name: 2,4-Thiazolidinedione, 5-((4-((3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy)phenyl)methyl)-

Common Name: Romglizone; Ronglitazone; Troglitazone

Structural Formula:



Chemical Abstracts Registry No.: 97322-87-7

Trade Name	Manufacturer	Country	Year Introduced
Noscal	Sankyo Company, Ltd.	Japan	-
Prelay	Sankyo	USA	-
Rezulin	Parke-Davis Pharmaceuticals, Ltd.	-	-
Romozin	Glaxo Wellcome	-	-

Raw Materials

Ethyl-3-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)phenyl]-2-chloropropionate
Thiourea
Hydrochloric acid
Acetic acid

Manufacturing Process

A mixture of 70 g of ethyl-3-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)phenyl]-2-chloropropionate, 13.12 g of thiourea and 80.2 ml of sulpholane was reacted for 80 min, under a nitrogen stream at 115°-120°C. Subsequently, a 656.2 ml acetic acid, 218.7 ml conc. hydrochloric acid and 109.4 ml water was added to this and the resulting mixture was further heated for 12 h at 85°-90°C. The reaction mixture was cooled to room temperature and 196.8 g of sodium bicarbonate was added and once the evolution of carbondioxide had ceased, the solvent was distilled off applying high vacuum. A 10:1 by volume mixture of benzene and ethyl acetate was added to the residue and the crude product was washed with a mixture of equal volumes of a saturated aq. sodium bicarbonate solution water. The organic layer was dried over anhydrous sodium sulphate and the solvent was distilled off. The resulting crude product was quickly eluted from a silica gel column with 50% ethylacetate-hexane to furnish 40 g of the required 5-{4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl-methoxy)benzyl)thiazolidine-2,4-dione (Troglitazone) with a HPLC purity of about 67-70%. The elution of column was continued further to yield 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl-methoxy)benzyl]-2-iminothiazolidine-4-one with HPLC purity of about 70%.

References

Vyas K. et al.; US Patent No. 5,700,820; Dec. 23, 1997; Assigned: Dr.Reddy's Research Foundation, Hyderabad, India

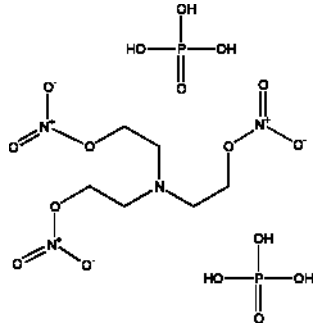
TROLNITRATE DIPHOSPHATE

Therapeutic Function: Coronary vasodilator

Chemical Name: Ethanol, 2,2',2''-nitrilotris-, trinitrate (ester), phosphate (1:2) (salt)

Common Name: Angitrit; Bentonyl; Duronitrin; Metamine; Nitrotamin; Nitroduran; Ortin; Vasomed

Structural Formula:



Chemical Abstracts Registry No.: 588-42-1

Trade Name	Manufacturer	Country	Year Introduced
Angitrit	Ranbaxy Unichem Co. Ltd	-	-
Duronitrin	AstraZeneca SpA	-	-
Duronitrin	Ethnor	-	-
Etamin	Zeria	-	-
Metamine	Elliot-Marion	-	-
Metamine	Pfizer	-	-
Nitrin	Andrews	-	-
Nitrocardiol	Miluy	-	-
Ortin	Wild	-	-
Sedalis	Kayaku	-	-

Raw Materials

Nitric acid
Triethanol amine
Phosporic acid
Sulfuric acid
Sodium bicarbonate

Manufacturing Process

To a mixture of 1940 g of nitric acid and 2590 g of sulfuric acid at 0-5°C was added dropwise 600 g of triethanol amine. The mixture was neutralized by addition of sodium bicarbonate. The reaction mixture was extracted with

ether. To the dried over sodium sulfate extract was added phosporic acid. A yield of triethanolamine trinitrate biphosphate 1500-1600 g, melting point 107-109°C.

References

Metadier M.J.; FR Patent No. 984,523; February 28, 1951

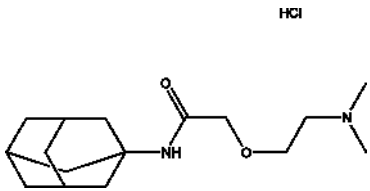
TROMANTIDINE HYDROCHLORIDE

Therapeutic Function: Antiviral

Chemical Name: 2-(2-(Dimethylamino)ethoxy)-N-tricyclo(3.3.1.1^{3,7})dec-1-ylacetamide monohydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 41544-24-5; 53783-83-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Viru-Merz	Merz	W. Germany	1973
Viruserol	Zyma	Italy	1972

Raw Materials

Sodium
Chloroacetyl chloride
Adamantane
Dimethylaminoethanol

Manufacturing Process

Adamantane is first reacted with chloroacetyl chloride to give chloroacetylaminoadamantane.

2.3 g Na (0.1 g-atom) were dissolved in 75 ml dimethylamino-ethanol. Then the excess alcohol was distilled off completely and the sodium salt developed was dried in a vacuum. After drying, the salt was dissolved in about 200 ml xylene. To thissolution.22.8 g (0.1 mol) chloroacetylaminoadamantane were

added, heated for 10 hours under reflux in a 250-ml round-bottomed flask with a reflux cooler, and the sodium chloride developed subsequently filtered off.

Next the xylene was distilled away, the liquid residue dissolved in about 80 ml carbon tetrachloride and the hydrochloride precipitated through introduction of hydrochloric acid gas. The hydrochloride was dissolved in about 100 ml acetone and the solvent subsequently distilled away, whereby excess hydrochloric acid passed over with it. This operation was repeated until no excess acid was present.

A large excess of petroleum ether was added in a 500 ml three-necked flask provided with a stirrer and reflux cooler, to a concentrated acetonic solution of the hydrochloride and stirred for at least 1 hour, whereby the desired substance was deposited in a crystalline form. Finally, the substance was filtered away and dried in a desiccator. 14 g of the substance (15% of theory) were obtained.

References

Merck Index 9574
Kleeman and Engel p. 930
DOT 10 (3) 105 (1974)
I.N. p. 985
Scherm, A. and Peteri, D.; US Patent 3,705,194; December 5, 1972; assigned to Merz and Co., Chemische Fabrik

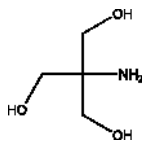
TROMETHAMINE

Therapeutic Function: Antacid

Chemical Name: 2-Amino-2-hydroxymethyl-1,3-propanediol

Common Name: Trometamol

Structural Formula:



Chemical Abstracts Registry No.: 77-86-1

Trade Name	Manufacturer	Country	Year Introduced
Trisaminol	Bellon	France	1964
In Tham-E	Abbott	US	1965
Tham	Otsuka	Japan	1969

Trade Name	Manufacturer	Country	Year Introduced
Thamesol	Baxter	Italy	1970
Addex-Tham	Pharmacia	Sweden	-
Alcaphor	Bellon	France	-
Apiroserum	Ibys	Spain	-
Basionic	Smith Kline-R.I.T.	Belgium	-
Buffer	Pages Maruny	Spain	-
Thamacetat	Bellon	France	-
Trizma	Sigma	US	-

Raw Materials

Nitromethane
Formaldehyde
Hydrogen

Manufacturing Process

Nitromethane is reacted with formaldehyde to give tris(hydroxymethyl)nitromethane in an initial step. This intermediate may be reduced by catalytic hydrogenation (US Patent 2,174,242) or by electrolytic reduction (US Patent 2,485,982).

References

Merck Index 9575
DOT 1 (4) 139 (1965)
I.N. p. 986
REM p. 836 Hass, H.B. and Vanderbilt, B.M.; US Patent 2,174,242; September 26,1939; assigned to Purdue Research Foundation
McMillan, G.W.; US Patent 2,485,982; October 25, 1949; assigned to Commercial Solvents Corporation

TROPICAMIDE

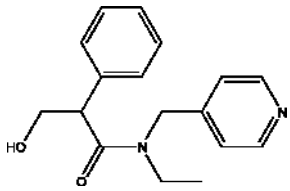
Therapeutic Function: Anticholinergic (ophthalmic)

Chemical Name: N-Ethyl-α-(hydroxymethyl)-N-(4-pyridinylmethyl) benzeneacetamide

Common Name: N-Ethyl-N-(γ-picolyl)tropamide

Chemical Abstracts Registry No.: 1508-75-4

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Mydriacyl	Alcon	US	1959
Mydriaticum	MSD-Chibret	France	1960
Mydrin	Santen	Japan	-
Mydrum	Ankerwerk	E. Germany	-
Tropimil	Farmigea	Italy	-
Tryptar	Armour	US	-
Visumidriatic	I.S.F.	Italy	-

Raw Materials

Ethyl amine
Acetyltropic acid chloride
γ-Chloromethyl pyridine hydrochloride
Hydrogen chloride

Manufacturing Process

A solution of 82 parts by weight of γ-chloromethyl-pyridine-hydrochloride in 60 parts of water is added dropwise, at 0° to 5°C, to 250 parts by weight of a 50% aqueous ethyl amine solution. The mixture is stirred for 1 hour at 60°C, whereupon it is cooled down and separated in the cold with solid potassium hydroxide. The oil formed is separated off, dried over potassium hydroxide and distilled. The ethyl-(γ-picolyl)-amine formed boils over at 103° to 104°C under a pressure of 13 mm Hg. Its dihydrochloride melts at 198° to 200°C.

To a mixture of 48.7 parts by weight of ethyl-(γ-picolyl)-amine and 36 parts by weight of dry pyridine in 220 parts by weight of dry chloroform is slowly added, while stirring and cooling with ice water, crude acetyltropic acid chloride prepared from 60 parts by weight of tropic acid. To complete the reaction, the mixture is stirred for one additional hour at 23°C. Thereupon the chloroform solution is diluted with 200 parts by weight of ether and agitated with 3 N hydrochloric acid. The weakly Congo acid solution is heated for 1 hour in a steam bath, the acetyl group of the reaction product being thereby split off, and the mixture is filtered over charcoal.

Upon adding concentrated ammonia in excess, the condensation product separates and is taken up in chloroform. The chloroform solution is dried and distilled, the tropic acid N-ethyl-N-(γ-picolyl)-amide being thereby obtained in the form of a thick oil, which crystallizes after prolonged time and which then melts at 96° to 97°C.

References

Merck Index 9585
Kleeman and Engel p. 932
DOT 16 (3) 89 (1980)
I.N. p. 986
REM p. 918
Rev-Bellet, G. and Spiegelberg, H.; US Patent 2,726,245; December 6, 1955; assigned to Hoffmann-LaRoche Inc.

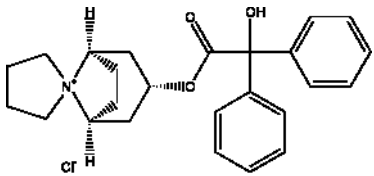
TROSPIUM CHLORIDE

Therapeutic Function: Anticholinergic, Spasmolytic

Chemical Name: Spiro(8-azoniabicyclo[3.2.1]octane-8,1'-pyrrolidinium), 3-((hydroxydiphenylacetyl)oxy)-, chloride, (1α,3β,5α)- chloride

Common Name: Uraplex; Trospium chloride

Structural Formula:



Chemical Abstracts Registry No.: 10405-02-4

Trade Name	Manufacturer	Country	Year Introduced
Keptan	Muller	-	-
Keptan	Sanofi-Synthelabo	-	-
Spasmex	Nikken	-	-
Spasmex	Pfleger	-	-
Spasmex	Lek	-	-
Trospi	Medac	-	-
Uraplex	Alfa Wassermann spa	-	-
Uraplex	MADAUS AG	-	-

Raw Materials

Nortropine
Basic ion exchanger
1,4-Dibromobutane
Acetyl mandelic acid chloride

Manufacturing Process

12.7 g of nortropine and 21.6 g 1,4-dibrombutane are heated, with stirring,

for 14 hours at 38-40°C in 200 ml 70% ethanol in the presence of a strongly basic ion exchanger. The reaction mixture is filtered, the filtrate brought to a pH of 4-5 by addition of dilute hydrochloric acid, then evaporated to dryness in a vacuum. The residue crystallized from ethanol-ether. Azoniaspiro-(3α-hydroxy-nortropan-8,1'-pyrrolidine) chloride is obtained in a yield of about 51%; melting point 294-297°C.

2.17 g azoniaspiro-(3α-hydroxy-nortropan-8,1'-pyrrolidine) chloride and 4.24 g acetyl mandelic acid chloride are heated in a vacuum (12 mm Hg) for 6n hours at 100°C. After the addition of 40 ml water, the reaction mixture is repeatedly extracted, the aqueous phase adjusted to pH 6.7-6.8 and continuously extracted with chloroform for 24 hours. After the addition of 20 ml concentrated hydrochloric acid, the residue of the chloroform extract is left to stand for 15 hours at room temperature. The hydrochloric acid is then removed in a vacuum, the residue taken up in absolute ethanol, filtered through aluminum oxide. The filtrate evaporated to dryness and the residue crystallized from methanol-acetone. Azoniaspiro(3α-benziloyloxy-nortropan-8,1'-pyrrolidine)-chloride is obtained in a yield of about 20%; melting point 197-198°C.

References

Peleger R.; GB Patent No. 1,058,542; March 1965

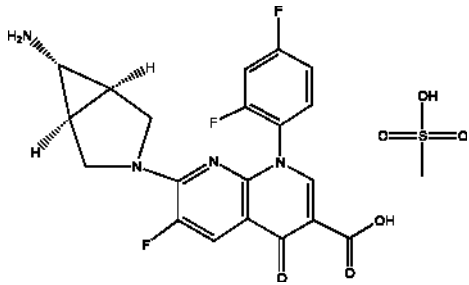
TROVAFLOXACIN MESYLATE

Therapeutic Function: Antibacterial

Chemical Name: 1,8-Naphthyridine-3-carboxylic acid, 1,4-dihydro-7-(6-amino-3-azabicyclo(3.1.0)hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-4-oxo-, (1α,5α,6α)-, monomethanesulfonate

Common Name: Trovafloxacin mesilate

Structural Formula:



Chemical Abstracts Registry No.: 147059-75-4; 147059-72-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Trovan	Pfizer	USA	-
Turvel	Roerig Farmaceutici	-	-

Raw Materials

N-Benzylmaleimide
Bromonitromethane
1,2-Dimethyl-1,4,5,6-tetrahydropyrimidine
Ethyl-7-chloro-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid

Manufacturing Process

N-Benzylmaleimide (500 g, 2.67 mole), 90% bromonitromethane (831 g, 5.34 mole), powdered molecular sieves 200 mesh (2020 g) and toluene (12 dm^3) were stirred under nitrogen at -10°C. 1,2-Dimethyl-1,4,5,6-tetrahydropyrimidine (616 g, 5.49 mole) was added slowly over about 3 h maintaining the reaction temperature at <-8°C throughout the addition. After completion of the addition, the reaction mixture was stirred for 1.5 h at 25°C, filtered under a nitrogen atmosphere in a sealed pressure filter to remove sieves and resulting tar, and the sieves were washed with toluene (2 L). The combined filtrates were washed with 2 N dilute hydrochloric acid (3 times 750 cm^3), treated with carbon (50 g) at 70°C, 1 h filtered, concentrated, and triturated with 2-propanol (about 4 dm^3) to obtain crystals of the (1α,5α,6α)-3-N-benzyl-6-nitro-2,4-dioxo-3-azabicyclo[3.1.0]hexane (223 g, 34%) melting point 116°-118°C.

Tetrahydrofuran (350 cm^3), sodium borohydride (14.1 g) and (1α,5α,6α)-3-N-benzyl-6-nitro-2,4-dioxo-3-azabicyclo[3.1.0]hexane (35.0 g, mmol) obtained above were stirred under nitrogen for 0.25 h and then treated dropwise with boron trifluoride-THF complex containing 21.5% BF_3 (44.9 cm^3) so that the exotherm was controlled to <40°C. After addition was completed, the reaction mixture was stirred for 3 h at 40°C, quenched slowly with water/THF 1:1 (70 cm^3) to avoid excessive foaming, and stirred for 0.5 h at 50°C to ensure that the quench of unreacted diborane generated in situ was completed. The quench formed a salt slurry which was filtered and washed with THF (140 cm^3); the combined filtrate was partially concentrated, diluted with water (350 cm^3) and further concentrated to remove most of the THF, and extracted with ethyl acetate (140 cm^3). The resulting ethyl acetate solution was concentrated to afford the (1α,5α,6α)-3-N-benzyl-6-nitro-3-azabicyclo[3.1.0]hexane as a clear oil (30.6 g, 97%).

(1α,5α,6α)-3-N-Benzyl-6-nitro-3-azabicyclo[3.1.0]hexane (30.9 g, 142 mmol) obtained above, 2-propanol (310 cm^3), water (30 cm^3), and 10% Pd on carbon, 50% water content (12.3 g) were hydrogenated at 50 psi and 50°C for 18-24 h in a Parr shaker. The Pd catalyst was filtered off, and the resulting pale yellow filtrate was azeotropically distilled at constant volume to remove water. The resulting solution was treated with triethylamine (46 g, 456 mmol) and heated to reflux. Benzaldehyde (15.0 g, 141 mmol) was added dropwise over 15 min. The reaction mixture was heated at reflux for 4 h to form (1α,5α,6α)-6-benzylidenylamino-3-azabicyclo[3.1.0]hexane in situ. The resulting orange solution was cooled to 40°-50°C, and ethyl 7-chloro-1-(2,4-

difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (42.45 g, 111 mmol; see United Kingdom Patent Publication No. GB 2,191,776) and triethylamine (13.1 g, 130 mmol) were added. The resulting slurry was heated at reflux for 16-18 h, cooled to 20°C and stirred for 5 h. The slurry was filtered, and the compound was isolated as a white solid (75.5% yield based on (1α,5α,6α)-3-N-benzyl-6-nitro-2,4-dioxo-3-azabicyclo[3.1.0]hexane; 96.6% based on ethyl 7-chloro-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid). The ethyl (1α,5α,6α)-7-(6-benzylidenylamino-3-azabicyclo[3.1.0]hex-3yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate was recrystallized from acetonitrile, melting point 148°-155°C decomp.

Tetrahydrofuran (250 cm^3), ethyl (1α,5α,6α)-7-(6-benzylidenylamino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (25.05 g, 47 mmol) obtained above, and water (250 cm^3) were treated with 97% methanesulfonic acid (13.3 g, 138 mmol) and heated to reflux for 24 h. The resulting solution was cooled to 45°C, treated with activated carbon (2.5 g) for 1 h and filtered. The resulting filtrate was concentrated under vacuum to approximately 25% of its original volume to provide a white crystal slurry, cooled to 15°-25°C, granulated for 4 h and filtered to yield the trovafloxacin methanesulfonate salt (mesylate) (16.86 g, 70.0%). Melting point 253°-256°C decomp.

References

Norris T. et al.; US Patent No. 6,359,137 B1; March 19, 2002; Assigned: Pfizer Inc., New York, NY (US)

TROXERUTIN

Therapeutic Function: Topical venotonic

Chemical Name: Flavone, 3,5-dihydroxy-3',4',7-tris(2-hydroxyethoxy)-, 3-(6-O-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranoside)

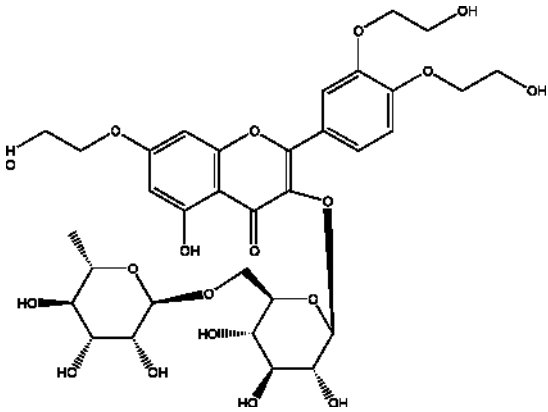
Common Name: Trioxyethylrutine; Troxerutin

Chemical Abstracts Registry No.: 7085-55-4

Trade Name	Manufacturer	Country	Year Introduced
Venoruton	Novartis Co.	-	-
Venoruton	Zyma Co.	-	-
Venoruton Forte	Novartis Co.	-	-
Venoruton Forte	Zyma Co.	-	-
Troxerutin-ratiopharm	Ratiopharm	-	-
Troxerutin	Leciva	-	-
Troxerutin	Interpharma (IPP)	-	-

Trade Name	Manufacturer	Country	Year Introduced
Troxerutin	Yangzhou Pharmaceutical Co.	-	-
Venoruton	ZYF Pharm Chemical	-	-
Gefasschutz-Kapseln	Karner	-	-

Structural Formula:



Raw Materials

Rutin
Caustic soda
Ethylene chlorohydrin

Manufacturing Process

In a nitrogen atmosphere 120 g of caustic soda (3 moles) in solution are added to 610 g of rutin (1 mol) suspended in 2 litres of water, the mixture being vigorously agitated by a mechanical stirrer, 241.5 g of ethylene chlorohydrin being then introduced at 55°C for 10 min. When all the chlorohydrin has been thus added the temperature is progressively raised to 75°C and maintained at this level for 2 hours. After cooling, in a nitrogen atmosphere, the pH value adjusted to 5 by the addition of dilute hydrochloric acid. The solution is kept in an ice box for 24 hours and then filtered to remove any impurities. At reduced pressure the solution is evaporated until dry, the residue taken up in 3 litres of boning methanol which dissolves the tri-(β-hydroxyethyl)rutin formed and leaves the sparingly soluble sodium chloride behind. The tri-(β-hydroxyethyl)rutin is recovered from its methanolic solution either by evaporation and refrigeration, or by evaporation precipitation with absolute ethanol. In either case tri-(β-hydroxyethyl)rutin obtained is in the form of small very hygroscopic crystals which contain alcohol of crystallization.These crystals are quickly shaken washed in a little cold absolute ethanol and then dried in vacuum at 100°C. 680 g of anhydrous tri-(β-hydroxyethyl)rutin are thus obtained in the form of a yellow powder which melts at 156°C.

References

GB Patent No. 833,174; April 21, 1960; Assigned to Zyma S.A., a Swiss Corporation, of Route Etraz, Nyon Canton of Vaud, Switzerland

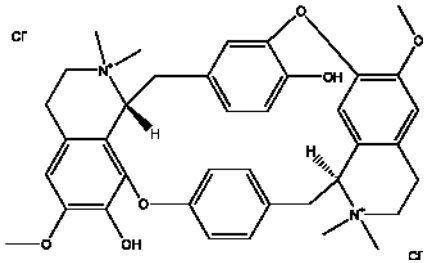
TUBOCURARINE CHLORIDE

Therapeutic Function: Muscle relaxant

Chemical Name: 7',12'-Dihydroxy-6,6'-dimethoxy-2,2',2'-trimethyl-tubocuraranium chloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 6533-76-2

Trade Name	Manufacturer	Country	Year Introduced
Mecostrin	Squibb	US	1946
Amelizol	Yoshitomi	Japan	-
Curarin	Asta	W. Germany	-
Introcortin T	Squibb	Italy	-
Jexin	Duncan Flockhart	UK	-
Metubine	Lilly	US	-
Relvene	Pharmascience	US	-
Tubadil	Endo	US	-
Tubocuran	N.D. and K.	Denmark	-

Raw Materials

Chondrodendron tomentosum plant
Picric acid
Hydrogen chloride

Manufacturing Process

The initial step involves extraction of the stems and bark of the plant

Chondrodendron tomentosum with water as the solvent.

Producing substantially pure d-tubocurarine chloride essentially comprises treating with picric acid the quaternary-base fraction of a crude curare of the curarine type, hydrolyzing the resulting picrate in an emulsion of hydrochloric acid and a water-immiscible organic solvent for picric acid, recovering crystalline d-tubocurarine chloride from the aqueous phase, dissolving the d-tubocurarine chloride in a minimum of hot water, allowing the solution to stand at room temperature until the bulk of the d-tubocurarine chloride precipitates, adding sufficient concentrated hydrochloric acid to bring the HCl content up to about 6% and refrigerating the solution.

References

Merck Index 9608
Kleeman and Engel p. 934
I.N. 988
REM p. 924
Bashour, J.T.; US Patent 2,409,241; October 15,1946; assigned to E.R. Squibb and Sons

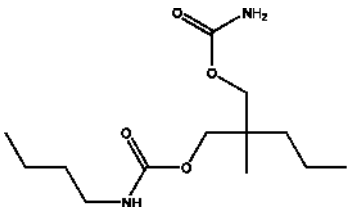
TYBAMATE

Therapeutic Function: Tranquilizer

Chemical Name: Butylcarbamic acid 2-[[(aminocarbonyl)oxy]methyl]-2-methylpentyl ester

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 4268-36-4

Trade Name	Manufacturer	Country	Year Introduced
Solacen	Wallace	US	1965
Tybatran	Robins	US	1967
Effisax	Maggioni	Italy	-
Nospan	Johnsons	Sweden	-

Raw Materials

Sulfuric acid	Diethylmethyl propylmalonate
Phosgene	Lithium aluminum hydride
Butylamine	Urethane

Manufacturing Process

Diethylmethyl propylmalonate is reacted with $LiAlH_4$, then H_2SO_4 to give 2-methyl-2-propyl-1,3-propanediol. That is reacted with phosgene in toluene to give the chlorocarbonate which is in turn reacted with butylamine to give N-butyl-2-methyl-2-propyl-3-hydroxy-propyl carbamate.

22.1 parts of N-butyl-2-methyl-2-propyl-3-hydroxy-propyl carbamate and 9.8 parts of urethane are dissolved in 300 parts of anhydrous xylene in a suitable vessel equipped with an efficient distillation column. Xylene is distilled to remove traces of water from the mixture. 2.3 parts of aluminum isopropylate are added and distillation is continued until substantially the theoretical quantity of ethanol has been distilled at about 78°C. The reaction mixture is then freed from xylene by distillation under reduced pressure. Approximately 100 parts of water are added and the mixture again freed of solvent by distillation under reduced pressure. 100 parts of trichloroethylene are added, the solution filtered to remove insoluble matter and the solution freed of solvent by evaporation. The residual oil is purified by molecular distillation at a pressure of about 0.01 mm. 8.7 parts (35% of theoretical yield) of purified N-butyl-2-methyl-2-propyl-1,3-propanediol dicarbamate are obtained.

References

Merck Index 9628
Kleeman and Engel p. 935
OCDS Vol. 2 p. 22 (1980)
DOT 3 (3) 101 (1967)
I.N. p. 989
REM p. 1074
Berger, F.M. and Ludwig, B.J.; US Patent 2,937,119; May 17,1960; assigned to Carter Products, Inc.

TYLOXAPOL

Therapeutic Function: Bronchodilator

Chemical Name: 4-(1,1,3,3-Tetramethylbutyl)phenol polymer with formaldehyde and ethylene oxide

Common Name: -

Chemical Abstracts Registry No.: 25301-02-4

Raw Materials

α,α,γ,γ-Tetramethylbutylphenol
Formaldehyde
Ethylene oxide

Manufacturing Process

Srep 1: Into a 3-necked flask equipped with thermometer, mechanical agitator, and reflux condenser was charged the following: 412 g of α,α,γ,γ-tetramethylbutylphenol, 162 g of a 37% aqueous solution of formaldehyde, and 27.6 g of water. The mixture was agitated and heated to a temperature of 90°C. At this point, 246 g of oxalic acid and 0.92 g of Twitchell's reagent dissolved in 10 g of water were added. While being agitated, the reaction mixture was refluxed for 6 hours. 200 g of water and 384 g of toluene were added, and refluxing was continued for an hour.

Agitation was stopped and the contents of the flask were removed to a separatory funnel. The aqueous and resinous layers were separated and the solvent was removed from the resinous layer by vacuum distillation. After the removal of the solvent, heating at a reduced pressure of 1.5 to 2.5 mm and at a temperature of 245° to 250°C was continued for 4 1/2 hours. The condensate then had a viscosity of 4.0 poises when measured as a 60% solution in toluene and, on cooling, solidified to a brittle mass.

Step 2: A mixture of 118 parts of the product of Step 1, having hydroxyl number of 260, 2 parts of solid NaH, and 100 parts of toluene was heated to 125° to 150°C in an autoclave. Ethylene oxide was added slowly over a period of 2 1/2 hours until 261 parts of ethylene oxide were absorbed. This corresponds to 11 mols of ethylene oxide per mol of phenol in the product of Step 1. The toluene was then removed by steam distillation and the water by vacuum distillation at 10°C. The product was obtained as a viscous paste having a corrected hydroxyl number of 97. It was readily soluble in water and had marked detergent properties.

References

Merck Index 9632
I.N. p. 990
REM p. 869
Bock, L.H. and Rainey, J.L.; US Patent 2,454,541; assigned to Rohm and Haas Company

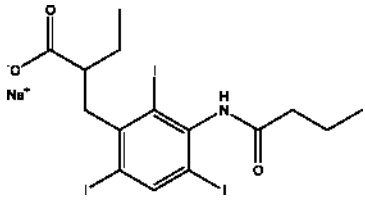
TYROPANOATE SODIUM

Therapeutic Function: Diagnostic aid (radiopaque medium)

Chemical Name: α-Ethyl-2,4,6-triiodo-3-[(1-oxobutyl)amino] benzenepropanoic acid monosodium salt

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 7246-21-1

Trade Name	Manufacturer	Country	Year Introduced
Bilopaque	Winthrop	US	1972
Bilopaque	Winthrop	W. Germany	1977
Tyropaque	Torii	Japan	1979

Raw Materials

α-Ethyl-β-(aminophenyl)propionic acid
Butyric anhydride
Iodine monochloride
Sodium hydroxide

Manufacturing Process

A solution of 5.0 g of α-ethyl-β-(aminophenyl)propionic acid in 100 ml of water containing 5 ml of concentrated hydrochloric acid was added over a period of ½ hour to a stirred solution of 3.2 ml of iodine monochloride in 25 ml of water and 25 ml of concentrated hydrochloric acid heated to 60°C. After addition was complete, the heating was continued for ½ hour longer at 60° to 70°C. A black oil separated which gradually solidified. The mixture was then cooled and sodium bisulfite was added to decolorize. Recrystallization of the product from methanol gave about 8 g of α-ethyl-β-(2,4,6-triiodo-3-aminophenyl)-propionic acid, MP 147° to 150°C. The product could be further purified by precipitation of its morpholine salt from ether solution and regeneration of the free amino acid by treatment of a methanol solution of the morpholine salt with sulfur dioxide. The pure amino acid had the MP 155° to 156.5°C (corr).

A mixture of 57.1 g (0.1 mol) of α-ethyl-β-(3-amino-2,4,6-triiodophenyl)propionic acid, 250 ml of butyric anhydride and 1 ml of 70% perchloric acid was heated at 105°C for 5 hours. After cooling, the reaction mixture was poured onto ice, diluted to a volume of 3 liters with water, and heated on a steam bath with addition of solid sodium carbonate to keep the mixture basic. After all the excess butyric anhydride had been hydrolyzed, the mixture was made acid with dilute hydrochloric acid, the aqueous layer decanted from the resulting gummy solid, and the latter was then washed several times with water. The product was dissolved in acetic acid, decolorized with activated charcoal, and the solution while hot diluted with water to the

point of turbidity. The product was collected by filtration and dried, giving 40 g of α-ethyl-β-(3-dibutyramido-2,4,6-triiodophenyl)propionic acid, MP 166° to 169.5°C (corr.) when recrystallized from acetic acid. Reaction with sodium hydroxide gives the final product.

References

Merck Index 9636
I.N. p. 991
REM p. 1270
Archer, S. and Hoppe, J.O.; US Patent 2,895,988; assigned to Sterling Drug, Inc.