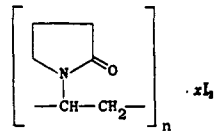
POVIDONE-IODINE

Therapeutic Function: Topical antiinfective

Chemical Name: 1-Ethenyl-2-pyrrolidinone homopolymer compound with iodine

Common Name: PVP-I

Structural Formula:



Chemical Abstracts Registry No.: 25655-41-8

Trade Name	Manufacturer	Country	Year Introduced
Betadine	Purdue Frederick	U.S.	1957
Betadine	Sarget	France	1970
Efodine	Fougera	U.S.	1978
Vagidine	Beecham	U.S.	1981
Clinidine	Clinipad	U.S.	1982
Mallisol	Mallard	U.S.	1983
ACU-Dyne	Acme	U.S.	—
Batticon	Trommsdorff	W. Germany	—
Betadine Ginecologico	Chinoin	Italy	—
Betaisodona	Mundipharma	Austria	—
Braunol	Braun	W. Germany	—
Chem-O-Dine	Remedia	S. Africa	—
Difexon	Bago	Argentina	—
Disadine	Stuart	U.K.	—
Isodine	Purdue Frederick	U.S.	—
Jodobac	Bode	W. Germany	—
Jodocur	Farm. Milanese	Italy	—
Neojodin	Iwaki	Japan	—
Nutradine	Restan	S. Africa	—
Pevidine	Berk	U.K.	—
Polydine	Fischer	Israel	—
Povadyne	Chaston	U.S.	—
Proviodine	Rougier	Canada	—
Summer's Eve	Fleet	U.S.	—
Topionic	Rius	Spain	—

Raw Materials

Polyvinylpyrrolidone
Iodine

Manufacturing Process

12 g of dry polyvinylpyrrolidone having a K value of 90 (water content about 2 to 3%) was added to 6 g of solid iodine crystals in a glass bottle containing a few pebbles and beads. This was rolled for 3 days on a roller mill with occasional manual stirring to loosen the material caked on the sides of the bottle. Analysis showed that the thus-obtained product contained 35.4% total iodine and 31.91% available iodine. The material was heat-treated at 95°C for 64 hours in a closed glass bottle with occasional stirring. On completion of this treatment, analysis showed that the material contained 35.3% total iodine, 25.7% available iodine, according to U.S. Patent 2,706,701.

References

Merck Index 7595
PDR pp. 880, 888, 1432
DOT 7 (4) 149 (1971)
I.N. p. 793
REM p. 1164
Beller, H. and Hosmer, W.A.; U.S. Patent 2,706,701; April 19, 1955; assigned to General Aniline & Film Corporation
Hosmer, W.A.; U.S. Patent 2,826,532; March 11, 1958; assigned to General Aniline & Film Corporation
Siggia, S.; U.S. Patent 2,900,305; August 18, 1959; assigned to General Aniline & Film Corporation

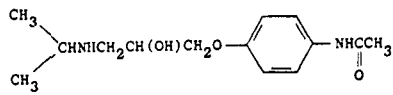
PRACTOLOL

Therapeutic Function: Antiarrhythmic

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

Common Name: 1-(4-Acetamidophenoxy)-3-isopropylamino-2-propanol

Structural Formula:



Chemical Abstracts Registry No.: 6673-35-4

Trade Name	Manufacturer	Country	Year Introduced
Eraldin	I.C.I.	U.K.	1970
Eraldin	I.C. Pharma	Italy	1972
Dalzic	Rhein/Pharma	W. Germany	1973
Eraldine	I.C.I. Pharma	France	1973
Cardiol	Orion	Finland	—
Pralon	Farmos	Finland	—

Raw Materials

4-Acetamidophenol
Epichlorohydrin
Isopropylamine

Manufacturing Process

The 1-(4-acetamidophenoxy)-2,3-epoxypropane used as starting material may be obtained as follows. To a solution of 4.5 parts of 4-acetamidophenol and 1.5 parts of sodium hydroxide in 50 parts of water at 15°C, there is added 3.5 parts of epichlorohydrin. The mixture is stirred for 16 hours at ambient temperature, filtered and the solid residue is washed with water. There is thus obtained 1-(4-acetamidophenoxy)-2,3-epoxypropane, MP 110°C.

A mixture of 2 parts of 1-(4-acetamidophenoxy)-2,3-epoxypropane and 10 parts of isopropylamine is stirred at ambient temperature for 16 hours. The resulting solution is

evaporated to dryness under reduced pressure and the residue is crystallized from butyl acetate. There is thus obtained 1-(4-acetamidophenoxy)-3-isopropylamino-2-propanol, MP 134° to 136°C.

References

Merck Index 7597
OCDS Vol. 2 pp. 106, 108 (1980)
DOT 6 (5) 188 (1970)
I.N. p. 794
Howe, R. and Smith, L.H.; U.S. Patent 3,408,387; October 29, 1968; assigned to Imperial Chemical Industries Limited, England

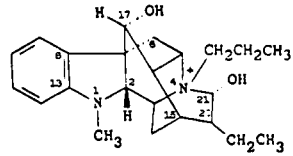
PRAJMALINE BITARTRATE

Therapeutic Function: Antiarrhythmic

Chemical Name: 17R,21α-Dihydroxy-4-propylajmalanium

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 2589-47-1; 35080-11-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Neo-Gilurtymal	Giulini	W. Germany	1973
Neo-Aritmina	Byk-Gulden	Italy	1979

Raw Materials

Ajmaline
Sodium bicarbonate
Allyl bromide
Tartaric acid

Manufacturing Process

1 g of ajmaline was dissolved in 4 cc of chloroform, and 1 cc of allyl bromide was added to the resulting solution. The reaction mixture thus obtained was allowed to stand for 24 hours at room temperature. Thereafter, the clear reaction solution was briefly cooled to a temperature below 0°C, whereby crystallization set in. The crystals were filtered off and were then recrystallized from a mixture of absolute methanol and absolute ether. The purified colorless crystalline product was identified to be N-(b)-allyl-ajmalinium-bromide having a melting point of 252°C to 254°C.

75 g of N-(b)-n-propyl-ajmalinium-bromide were suspended in 3 liters of an aqueous saturated solution of sodium bicarbonate, and the suspension was admixed with 3 liters of chloroform. The resulting mixture was vigorously stirred for six to eight hours. Thereafter, the chloroform phase was separated and evaporated to dryness. 68 g of a yellow syrup remained as a

residue. The aldehyde base was dissolved in about 150 cc of acetone and, while stirring and cooling on an ice bath, the solution was slowly admixed with a solution of 25 g of tartaric acid in 2 liters of acetone. The fine white precipitate formed thereby was separated by vacuum filtration, washed with ether and dried. The raw product, weighing 80 g, was recrystallized once from a mixture of ethanol and ether, yielding 50 g of N-(b)-n-propyl-ajmalinium hydrogen tartrate having a melting point of 149°C to 152°C (decomposition).

References

Merck Index 7598
Kleeman & Engel p. 744
I.N. p. 794
Keck, J.; U.S. Patent 3,414,577; December 3, 1968; assigned to Boehringer Ingelheim G.m.b.H. (Germany)

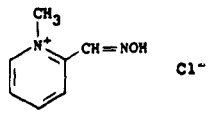
PRALIDOXIME CHLORIDE

Therapeutic Function: Cholinesterase reactivator (antidote for nerve gas)

Chemical Name: 2-[(Hydroxyimino)methyl]-1-methylpyridinium chloride

Common Name: 2-PAM chloride

Structural Formula:



Chemical Abstracts Registry No.: 51-15-0; 495-94-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Contrathion	Specia	France	1961
Protopam	Ayerst	U.S.	1964
Combo Pen	Rodana Res. Corp.	U.S.	—

Raw Materials

2-Pyridinealdoxime
α-Picoline
Nitrosyl chloride
Dimethyl sulfate
Methyl chloride
Sodium hydroxide

Manufacturing Process

As described in U.S. Patent 3,123,613, the preparation of the intermediate product, 2-pyridinealdoxime methomethylsulfate, is as follows. 1 kg of 2-pyridinealdoxime is dissolved in 6 liters of acetone and filtered until clear. 2 kg (2 equivalents) of freshly distilled dimethyl sulfate are added and the solution mixed. In about 30 minutes crystals start to appear, after which a cooling bath is used to keep the temperature at about 30° to 35°C until the reaction is nearly complete (about 2 hours).

The mixture is allowed to stand at room temperature overnight, the crystals filtered off and washed on a filter with acetone. The product is obtained as colorless needles, which melt at 111° to 112.5°C. The methylsulfate is not stable indefinitely. For preparation of pure chloride salt it is desirable to use methylsulfate which gives no titratable acidity with sodium hydroxide using bromophenol blue as indicator.

10 g of 2-pyridinealdoxime methomethylsulfate are then dissolved in 6 cc of concentrated hydrochloric acid, and 60 cc of isopropanol is added with stirring. Crystals appear almost instantly. After 2 hours standing at room temperature, the crystals are separated by filtration and washed with acetone. The product had a melting point of 227° to 228°C and the yield was 85%.

An alternative route is described in U.S. Patent 3,155,674.

(A) Preparation of 1-Methyl-2-Picolinium Chloride: 98 ml of α-picoline is dissolved in 200 ml of methanol, cooled and 85 ml (at -68°C) of methyl chloride is added. The solution is charged to an autoclave, sealed and the nitrogen pressure of 300 psig is established. The mixture is heated at 120° to 130°C for 2 hours, cooled and opened. The resulting solution is then evaporated to dryness in vacuo, yielding a residue of 110 g. This residue is then dissolved in 50 ml of water and extracted with two 50 ml portions of ether. The aqueous phase is then diluted to 150 ml with water and an assay for ionic chloride is performed which indicates the presence of chloride ion equivalent to 721 mg/ml of 1-methyl-2-picolinium chloride.

(B) Preparation of 2-(Hydroxyiminomethyl)-1-Methyl Pyridinium Chloride: An aqueous solution of 15 ml of 1-methyl-2-picolinium chloride having a concentration of 477 mg/ml is covered with 50 ml of benzene in an atmosphere of nitrogen and cooled to below 10°C. An aqueous solution of sodium hydroxide is added dropwise and the mixture is stirred for 5 minutes and allowed to stratify. The aqueous phase is then drawn off and the benzene solution is added slowly to a solution of 3 ml of nitrosyl chloride in 175 ml of benzene containing 0.5 ml of dimethyl formamide at about 10°C in an atmosphere of nitrogen with good agitation. The mixture is then stirred for 1.5 hours and then extracted with four 5 ml of portions of water. The aqueous extracts are then concentrated in vacuo, 30 ml of isopropanol is added and the concentration is repeated. 20 ml of isopropanol is then added to the concentrated mixture, and the mixture is cooled to room temperature and filtered, yielding 3.04 g of crude 2-(hydroxyiminomethyl)-1-methyl pyridinium chloride, melting at 202° to 214°C with decomposition. The filtrate is then further concentrated to a 7 g residue which is crystallized from absolute alcohol and yields 0.9 g of 2-(hydroxyiminomethyl)-1-methyl pyridinium chloride melting at 221° to 225°C with decomposition.

References

Merck Index 7599
Kleeman & Engel p. 744
PDR p. 648
I.N. p. 794
REM p. 901
Bloch, L.P.; U.S. Patent 3,123,613; March 3, 1964; assigned to Campbell Pharmaceuticals, Inc.
Ellin, R.I., Easterday, D.E. and Kondritzer, A.A.; U.S. Patent 3,140,289; July 7, 1964; assigned to the U.S. Secretary of the Army
McDowell, W.B.; U.S. Patent 3,155,674; November 3, 1964; assigned to Olin Mathieson Chemical Corporation

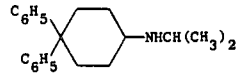
PRAMIVERIN

Therapeutic Function: Antispasmodic

Chemical Name: N-(1-Methylethyl)-4,4-diphenylcyclohexanamine

Common Name: Primaverine; propaminodiphen

Structural Formula:



Chemical Abstracts Registry No.: 14334-40-8; 14334-41-9 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Sistalgin	Bracco	Italy	1974
Sistalgin	Cascan	W. Germany	1976

Raw Materials

4,4-Diphenyl-cyclohexen-(2)-one
Isopropylamine
Hydrogen

Manufacturing Process

20 g 4,4-diphenyl-cyclohexen-(2)-one, 10 g isopropylamine, and 50 ml tetrahydrofuran are agitated for 10 hours in a bomb tube at 200°C. Subsequently, the reaction mixture is cooled, and the tetrahydrofuran and the excess isopropylamine are distilled off. The remaining Schiff base is dissolved in methanol and after the addition of 2 g platinum oxide, the base is hydrogenated at normal pressure and room temperature until a quantity of hydrogen corresponding to 2 mols has been absorbed.

The mixture is filtered off from the catalyst, made acidic with dilute hydrochloric acid, and the methanol is removed under vacuum. The remaining aqueous solution is made alkaline with solution of sodium hydroxide and extracted with ether. After drying and concentrating the ether extract, there is obtained 17 g 1-isopropylamino-4,4-diphenyl-cyclohexane, boiling point 164°C to 165°C/0.05 mm. The hydrochloride melts at 230°C.

References

Merck Index 7602
Kleeman & Engel p. 745
DOT 11 (8) 320 (1975)
I.N. p. 795
Unger, R., Sommer, S., Schorscher, E. and Encakel, H.J.; U.S. Patent 3,376,312; April 2, 1968; assigned to E. Merck A.G. (Germany)

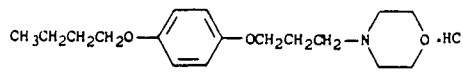
PRAMOXINE HYDROCHLORIDE

Therapeutic Function: Topical anesthetic

Chemical Name: 4-[3-(4-Butoxyphenoxy)propyl] morpholine hydrochloride

Common Name: Pramocaine hydrochloride; proxazocain hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 637-58-1; 140-65-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Tronothane	Abbott	U.S.	1954
Tronothane	Abbott	France	1956
Proctofoam	Reed Carnrick	U.S.	1975
Prax	Ferndale	U.S.	1980
Analpram	Ferndale	U.S.	–
Anusol	Parke Davis	U.S.	–
F.E.P.	Boots	U.S.	–
Fleet Relief	Fleet	U.S.	–
Otic-HC	Hauck	U.S.	–
Pramosone	Ferndale	U.S.	–
Tronolane	Ross	U.S.	–
Zone-A	U.A.D. Labs	U.S.	–

Raw Materials

Hydroquinone monobutyl ether
Potassium hydroxide
γ-Morpholinopropyl chloride
Hydrogen chloride

Manufacturing Process

About 5.6 g of potassium hydroxide is dissolved in about 150 cc of refluxing ethanol, and then about 16.6 g of hydroquinone monobutyl ether is added to the alcoholic solution. When the hydroquinone is dissolved, about 16.3 g of γ-morpholinopropyl chloride (dissolved in a small amount of ethanol) is added to the refluxing solution. The solution is refluxed for about 24 hours and then cooled. The product is recovered by filtering the reaction mixture and then removing the solvent by vacuum distillation. The oily residue is acidified and shaken with ether. The acidic phase is made strongly alkaline with 40% sodium hydroxide, and the oil which separates is extracted into ether. The ethereal phase is dried, and the solvent removed by vacuum distillation. The product distills at 183° to 184°C at a pressure of 2.8 mm. The hydrochloride salt of the foregoing base is prepared by dissolving the base in ether and acidifying with hydrochloric acid and is found to have a MP of 181° to 183°C.

References

Merck Index 7603
Kleeman & Engel p. 745
PDR pp. 684, 875, 880, 928, 1316, 1565, 1808
OCDS Vol. 1 p. 18 (1977)
I.N. p. 795
REM p. 1057
Wright, H.B. and Moore, M.B.; U.S. Patent 2,870,151; January 20, 1959; assigned to Abbott Laboratories

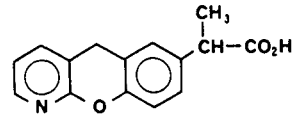
PRANOPROFEN

Therapeutic Function: Analgesic, antiinflammatory

Chemical Name: 2-(5H-[1]benzopyrano[2,3-b]-pyridin-7-yl)propionic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 52549-17-4

Trade Name	Manufacturer	Country	Year Introduced
Niflan	Yoshitomi	Japan	1981

Raw Materials

Ethyl 2-cyano-2-(5H-[1]benzopyrano[2,3-b]-pyridin-7-yl)propionate
Hydrogen chloride

Manufacturing Process

A mixture of 100 g of ethyl 2-cyano-2-(5H-[1]benzopyrano[2,3-b]-pyridin-7-yl)propionate, 500 ml of glacial acetic acid and 200 g of concentrated hydrochloric acid is refluxed for 48 hours. The reaction mixture is concentrated, and the residue is dissolved in hot water. The solution is adjusted to pH 2 to 3 by addition of 10% sodium hydroxide. The resulting crystalline precipitate is washed thoroughly with water, and recrystallized from aqueous dioxane to give 74 g of 2-(5H-[1]benzopyrano[2,3-b]-pyridin-7-yl)propionic acid as white crystals melting at 183°C to 183.5°C.

References

Merck Index 7604
DFU 2 (3) 217 (1977) (As Y-8004) & 2 (12) 829 (1977)
Nakanishi, M., Oe, T. and Tsuruda, M.; U.S. Patent 3,931,205; January 6, 1976; assigned to Yoshitomi Pharmaceutical Industries, Ltd.

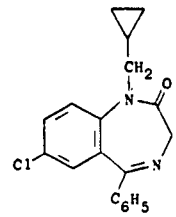
PRAZEPAM

Therapeutic Function: Tranquilizer

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

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 2955-38-6

Trade Name	Manufacturer	Country	Year Introduced
Demetrin	Goedecke	W. Germany	1973
Centrax	Parke Davis	U.S.	1977
Demetrin	Cosmopharm	Switz.	1978
Lysanxia	Substantia	France	1979
Prazene	Parke Davis	Italy	1980
Trepidan	Sigma Tau	Italy	1980
Centrax	Warner William	U.K.	1981
Demetrin	Parke Davis	France	1982
Reapam	Goedecke	W. Germany	—
Verstran	Warner-Chilcott	U.S.	—

Raw Materials

2-Amino-5-chlorobenzophenone
Cyclopropane carboxylic acid chloride
Phthalimidoacetyl chloride
Lithium aluminum hydride
Manganese dioxide
Hydrazine hydrate

Manufacturing Process

Preparation of 2-Cyclopropylcarbonylamido-5-Chlorobenzophenone: To 400.5 g (1.73 mols) of 2-amino-5-chlorobenzophenone dissolved in 220 g (2.18 mols) of triethylamine and 3.5 liters of tetrahydrofuran is added cautiously 181 g (1.73 mols) of cyclopropanecarboxylic acid chloride. The reaction is refluxed 2½ hours and allowed to cool to room temperature. The solvent is then removed under vacuum to obtain 2-cyclopropylcarbonylamido-5-chlorobenzophenone as a residue which is dissolved in 1 liter of methylene chloride, washed twice with 5% hydrochloric acid, and then twice with 10% potassium hydroxide. The methylene chloride solution is then dried over anhydrous magnesium sulfate, filtered and the solvent removed under vacuum. The residue is recrystallized from 1,500 ml of methanol, charcoal-treating the hot solution to give 356 g of 2-cyclopropylcarbonylamido-5-chlorobenzophenone, MP 105° to 105.5°C (69% yield).

Preparation of 2-Cyclopropylmethylamino-5-Chlorobenzhydrol: To a slurry of 94.8 g (2.47 mols) of lithium aluminum hydride in 1.2 liters of tetrahydrofuran is added with stirring a solution of 356 g (1.18 mols) of 2-cyclopropylcarbonylamido-5-chlorobenzophenone in 1.8 liters of tetrahydrofuran. The addition takes 80 minutes while maintaining gentle refluxing, and the reaction mixture is then refluxed overnight and allowed to cool to room temperature over a period of 3 days. The complex formed in the reaction mixture is then hydrolyzed with water.

During the hydrolysis, 500 ml of tetrahydrofuran is added to facilitate stirring. At a point where the flocculant white precipitate settles quickly when stirring is interrupted, the mixture is filtered, the filter cake washed with solvent, the combined filtrates dried over magnesium sulfate, filtered and the solvent removed under vacuum to obtain 2-cyclopropylmethylamino-5-chlorobenzhydrol as a residue. The residue is recrystallized from 1,300 ml of Skelly B, giving 315 g of 2-cyclopropylmethylamino-5-chlorobenzhydrol, MP 85° to 85.5°C (93% yield).

Preparation of 2-Cyclopropylmethylamino-5-Chlorobenzophenone: To a solution of 315 g (1.09 mols) of 2-cyclopropylmethylamino-5-chlorobenzhydrol in 4 liters of benzene is added 453.6 g (5.22 mols) of manganese dioxide, freshly prepared according to the method of Attenburrow et al, *J.C.S.* 1952, 1104. The mixture is then refluxed for 1¼ hours, filtered, and the filtrate evaporated under vacuum. The reddish residue is recrystallized from 510 ml of 90% acetone-10% water, giving 181 g of pure 2-cyclopropylmethylamino-5-chlorobenzophenone, MP 79° to 80°C (58% yield). Upon concentration of the mother liquor a second crop of 2-cyclopropylmethylamino-5-chlorobenzophenone weighing 34.1 g and melting at 76.5°-78°C are obtained.

Preparation of 2-(N-Phthalimidoacetyl-N-Cyclopropylmethyl)-Amino-5-Chlorobenzophenone: To a solution of 36.0 g (0.126 mol) of 2-cyclopropylmethylamino-5-chlorobenzophenone in 500 ml of tetrahydrofuran is added 50.7 g (0.252 mol) of phthalimidoacetyl chloride. The resulting solution is refluxed for 16 to 24 hours, the solvent removed under vacuum, the residual oil crystallized from 200 ml of ethanol and recrystallized from 500 ml of 80% ethanol-20% tetrahydrofuran giving 44.7 g of 2-(N-phthalimidoacetyl-N-cyclopropylmethyl)-amino-5-chlorobenzophenone, MP 163° to 164°C (75% yield).

Preparation of 1-Cyclopropylmethyl-5-Phenyl-7-Chloro-1H-1,4-Benzodiazepine-2(3H)-one: To a solution of 39.5 g (0.0845 mol) of 2-(N-phthalimidoacetyl-N-cyclopropylmethyl)amino-5-chlorobenzophenone in a mixture of 423 ml of chloroform and 423 ml of ethanol is added 9.52 g (0.1903 mol) of hydrazine hydrate and 9.52 ml of water. This solution is allowed to stand at room temperature. In 3 hours a precipitate begins to form in the solution. After standing 16 to 24 hours a voluminous pulpy white precipitate forms. The solvents are removed under vacuum while keeping the temperature under 40°C and the residue is partitioned between dilute ammonia water and ether.

The aqueous layer is separated and washed with ether, the ether extracted with 5% hydrochloric acid, the acidic solution is made basic with 10% sodium hydroxide and again extracted with ether. Since some spontaneous crystallization occurs in the ether, the solvent is removed without drying under vacuum and the residue is recrystallized from 35 ml of ethanol giving 18.0 g of 1-cyclopropylmethyl-5-phenyl-7-chloro-1H-1,4-benzodiazepine-2(3H)-one, MP 145° to 146°C (65% yield), according to U.S. Patent 3,192,199.

References

Merck Index 7608
Kleeman & Engel p. 747
PDR p. 1320
OCDS Vol. 2 p. 405 (1980)
DOT 2 (3) 119 (1966); 9 (6) 237 (1973); & 10 (5) 179 (1974)
I.N. p. 796
REM p. 1063
McMillan, F.H. and Pattison, I.; U.S. Patent 3,192,199; June 29, 1965
Wuest, H.M.; U.S. Patent 3,192,200; June 29, 1965

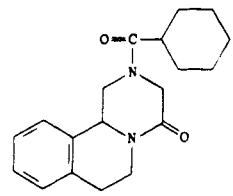
PRAZIQUANTEL

Therapeutic Function: Anthelmintic

Chemical Name: 2-(Cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 55268-74-1

Trade Name	Manufacturer	Country	Year Introduced
Cesol	Merck	W. Germany	1980
Biltricide	Bayer	W. Germany	1980
Cenaride	Merck Clevenot	France	1981
Biltricide	Bayer	France	1983
Biltricide	Miles	U.S.	1983
Droncit	Bayvet	U.S.	—

Raw Materials

2-Cyclohexylcarbonyl-4-oxo-2,3,6,7-tetrahydro-4H-pyrazino[2,1-a] isoquinoline
Hydrogen

Manufacturing Process

15 g of a nickel-aluminum alloy (1:1) is introduced in incremental portions and under agitation into 200 ml of 20% sodium hydroxide solution within 5 minutes; the mixture is maintained at 80°C for 45 minutes, then allowed to settle, decanted off, washed with water, and 1,000 ml of 1% (—)-tartaric acid solution is added thereto, adjusted to pH 5 with 1 N sodium hydroxide solution. The mixture is heated under agitation for 90 minutes to 80°C, decanted, and washed with water and methanol. The thus-obtained (—)-tartaric acid - Raney nickel catalyst is added to a solution of 2-cyclohexylcarbonyl-4-oxo-2,3,6,7-tetrahydro-4H-pyrazino-[2,1-a] isoquinoline. The reaction mixture is hydrogenated under normal pressure and at room temperature. After the catalyst has been filtered off and the solvent evaporated, 2-cyclohexylcarbonyl-4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a] isoquinoline, melting point 136°C to 138°C, is produced.

References

Merck Index 7609
Kleeman & Engel p. 748
PDR p. 1249
DOT 13 (3) 121 (1977) & 17 (10) 429 (1981)
I.N. p. 796
REM p. 1237
Seubert, J., Thomas, H. and Andrews, P.; U.S. Patent 4,001,411; January 4, 1977; assigned to Merck Patent G.m.b.H. (Germany)

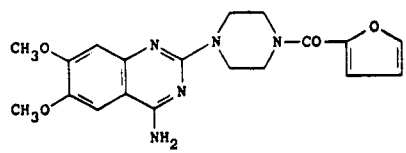
PRAZOSIN

Therapeutic Function: Antihypertensive

Chemical Name: 1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)piperazine

Common Name: Furazosin

Structural Formula:



Chemical Abstracts Registry No.: 19216-56-9; 19237-84-4 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Hypovase	Pfizer	U.K.	1974
Minipress	Pfizer	U.S.	1976
Minipress	Pfizer	W. Germany	1977
Minipress	Pfizer	Italy	1978
Minipress	Pfizer	France	1979
Minipress	Pfizer Taito	Japan	1981
Adversuten	Arzneimittelwerk Dresden	E. Germany	–
Orbisan	Mack	W. Germany	–
Pratsiol	Orion	Finland	–
Prazac	Erco	Denmark	–
Sinetens	Carlo Erba	U.K.	–
Vasoflex	Alkaloid	Yugoslavia	–

Raw Materials

2,4-Dichloro-6,7-dimethoxyquinazoline
Piperazine
Ammonia
2-Furoyl chloride

Manufacturing Process

Preparation of 2-Chloro-4-Amino-6,7-Dimethoxyquinazoline: To 800 ml of a solution of anhydrous ammonia in tetrahydrofuran at room temperature is added 30 g of 2,4-dichloro-6,7-dimethoxyquinazoline [F.H.S. Curd et al, *J. Chem. Soc.*, p 1759 (1948)]. The mixture is stirred for 44 hours. The precipitate (29 g, MP 267° to 268°C) is filtered and recrystallized from methanol to yield 19 g of 2-chloro-4-amino-6,7-dimethoxyquinazoline, MP 302°C (dec.).

Preparation of 2-(1-Piperazinyl)-4-Amino-6,7-Dimethoxyquinazoline: To 5 g of 2-chloro-4-amino-6,7-dimethoxyquinazoline, is added 20 g of a 25% solution of piperazine in ethanol. The mixture is heated at 160°C for 16 hours in a pressure bottle. The solvent is then evaporated and the residue is recrystallized from methanol/water.

Preparation of 2[4-(2-Furoyl)-Piperazinyl]-4-Amino-6,7-Dimethoxyquinazoline: To 0.10 mol 2-(1-piperazinyl)-4-amino-6,7-dimethoxyquinazoline in 300 ml methanol is added with vigorous stirring, 0.10 mol 2-furoyl chloride. After addition is complete, the mixture is stirred for 3 hours at room temperature. The solids are filtered to give the desired product, MP 278° to 280°C.

References

Merck Index 7610
Kleeman & Engel p. 748
PDR pp. 1420, 1421
OCDS Vol. 2 p. 382 (1980) & 3, 194 (1984)
DOT 11 (2) 67, 80 (1975)
I.N. p. 796
REM p. 844
Hess, H.-J.E.; U.S. Patent 3,511,836; May 12, 1970; assigned to Chas. Pfizer & Co., Inc.

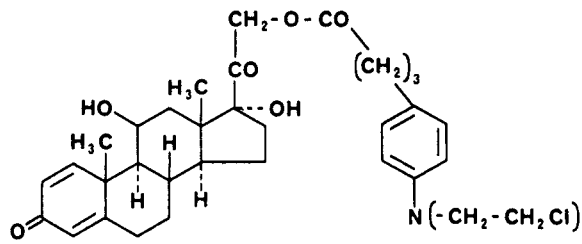
PREDNIMUSTINE

Therapeutic Function: Cancer chemotherapy

Chemical Name: Prednisolone 21-[4'-[p-bis(2-chloroethyl)amino] phenyl] butyrate

Common Name: Prednisolone chlorambucil ester

Structural Formula:



Chemical Abstracts Registry No.: 29069-24-7

Trade Name	Manufacturer	Country	Year Introduced
Stereocyt	Bellon	France	1978
Sterecyt	Leo	Switz.	1981
Mostarina	Abello	Spain	—

Raw Materials

p-[N-Bis(β-chloroethyl)amino] phenyl butyric acid
Thionyl chloride
Prednisolone

Manufacturing Process

p-[N-bis(β-chloroethyl)amino] phenyl butyric acid was dissolved in a mixture of 150 ml dry benzene and 8.04 ml dry pyridine. The solution was cooled in an ice bath, and a solution of thionyl chloride in 30 ml dry benzene was slowly added with stirring under anhydrous conditions.

The reaction mixture was then kept at room temperature for 1 hour and thereafter poured into a mixture of 5.0 N HCl and crushed ice. The benzene solution was immediately washed with water, with cold 1.0 N $NaHCO_3$ and finally with cold water. After drying over anhydrous sodium sulfate, the benzene was removed in vacuo. The residue is the p-[N-bis(β-chloroethyl)-amino] phenyl butyric anhydride which could be used without any further purification.

To a solution of 42.0 g of p-[N-bis(β-chloroethyl)amino] phenyl butyric anhydride in 500 ml dry pyridine was added 24.4 g of prednisolone. The reaction mixture was kept at room temperature for 24 hours under anhydrous condition. It was then poured into a mixture of concentrated HCl and crushed ice and extracted with ether-ethyl acetate (1:1).

The organic phase was washed several times with cold 1.0 N K_2CO_3 and finally water. After drying over $CaCl_2$ the solvent was removed in vacuo.

The residue is prednisolone 21-[4'-[p-bis(β-chloroethyl)amino] phenyl] butyrate which after crystallization from methanol/water had a melting point of 163°C to 164°C.

References

Merck Index 7612
DFU 1 (3) 137 (1976)
Kleeman & Engel p. 749
OCDS Vol. 3 p. 93 (1984)
DOT 16 (3) 84 (1980)

I.N. p. 797
Fox, H.J., Hogberg, K.B. and Konyves, I.; U.S. Patent 3,732,260; May 8, 1973; assigned to A.B. Leo

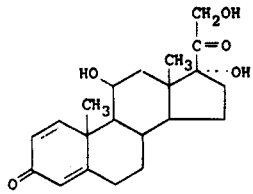
PREDNISOLONE

Therapeutic Function: Glucocorticoid

Chemical Name: 11β,17,21-Trihydroxypregna-1,4-diene-3,20-dione

Common Name: Metacortandralone; Δ^1-hydrocortisone

Structural Formula:



Chemical Abstracts Registry No.: 50-24-8

Trade Name	Manufacturer	Country	Year Introduced
Sterane	Pfizer	U.S.	1955
Meticortelone	Schering	U.S.	1955
Delta-Cortef	Upjohn	U.S.	1955
Hydeltra	MSD	U.S.	1955
Paracortol	Parke Davis	U.S.	1957
Sterolone	Rowell	U.S.	1957
Prednis	U.S.V. Pharm.	U.S.	1957
Ulacort	Fellows-Testagar	U.S.	1960
Cosilone	Person Covey	U.S.	1963
Adnisolone	Adams	Australia	–
Aprednislon	Arcana	Austria	–
Caberdelta	Caber	Italy	–
Cordrol	Vita Elixir	U.S.	–
Cortalone	Halsey	U.S.	–
Cortisolone	S.I.T.	Italy	–
Cotolone	Truxton	U.S.	–
Dacortin	Igoda	Spain	–
Decaprednil	Dorsch	W. Germany	–
Decortasmyl	Larec	Ecuador	–
Delta-Hycortol	Medica	Finland	–
Delta-Larma	Larma	Spain	–
Deltalone	D.D.S.A.	U.K.	–
Deltasolone	Knoll	Australia	–
Deltidrosol	Poli	Italy	–
Deltisolon	Ferring	Sweden	–
Domucortone	Medici Domus	Italy	–
Encortolone	Polfa	Poland	–
Fernisolon	Ferndale	U.S.	–
Ibisterolon	I.B.I.	Italy	–
Keteocort-H	Desitin	W. Germany	–
Neodelta	Amelix	Italy	–

Trade Name	Manufacturer	Country	Year Introduced
Normosona	Normon	Spain	–
Novoprednisolone	Novopharm	Canada	–
Panafcortelone	Glebe	Australia	–
Predartrina	Farmochimica	Italy	–
Prednicen	Central	U.S.	–
Predni-Coelin	Pfleger	W. Germany	–
Prednicort	Cortec	Denmark	–
Predni-Helvacort	Helvepharm	Switz.	–
Predni-H-Tablinen	Sanorania	W. Germany	–
Predniretard	Boots-Dacour	France	–
Prelone	Langley	Australia	–
Ropredlone	Robinson	U.S.	–
Scherisolon	Schering	W. Germany	–
Serilone	Serpero	Italy	–
Stermin	Schlicksup	U.S.	–
Vitacort	Vitarine	U.S.	–

Raw Materials

Bacterium *Corynebacterium simplex*
Hydrocortisone

Manufacturing Process

The following procedure is described in U.S. Patent 2,837,464: from a solution of 3 grams of yeast extract (Difco) in 3.0 liters of tap water containing 13.2 grams of potassium dihydrogen phosphate and 26.4 grams disodium hydrogen phosphate (pH of the solution, 6.9) 27 portions of 100 ml each are withdrawn, placed in 300 ml Erlenmeyer flasks and sterilized by autoclaving for 15 minutes at 15 pounds steam pressure (120°C). After autoclaving and cooling of the broth, one ml of suspension of *Corynebacterium simplex* (ATCC 6946) is placed in each flask. The flasks are then shaken on a shake table at 220 rpm and 28°C for 24 hours.

Into each of 27 Erlenmeyer flasks are placed 150 mg of Kendall's Compound F (hydrocortisone). The flasks and contents are then sterilized for 15 minutes at 15 pounds steam pressure (120°C). To each flask are then added 5.0 ml of ethanol. The 24-hour bacterial culture is then transferred aseptically and the resulting suspensions are shaken on a shake table at 220 rpm and 28°C for 48 hours. The pH at the end of the shake period is 7.0.

The contents of all the flasks are combined and extracted with a total of 9.0 liters of chloroform in 3 equal portions. The combined extracts are then concentrated to a residue which weighs 3.75 grams. The MP of the residue is 227°-232°C. From 2.75 grams of this crude material on sludging with 50 ml of acetone and cooling, there is recovered on filtration 1.35 grams of $\Delta^{1,4}$-pregnadiene-11β,17α,21-triol-3,20-dione, MP 237°-239°C (dec.). Additional product can be recovered from the mother liquor. Recrystallization from acetone raised the MP to 239°-241°C (dec.).

References

Merck Index 7613
Kleeman & Engel p. 750
PDR pp. 830, 1569, 1606
OCDS Vol. 1 p. 192 (1977) & 2, 178 (1980)
I.N. p. 797
REM p. 969
Nobile, A.; U.S. Patent 2,837,464; June 3, 1958; assigned to Schering Corporation
Oliveto, E.P. and Gould, D.H.; U.S. Patent 2,897,216; July 28, 1959; assigned to Schering Corporation

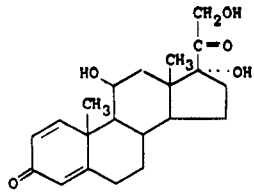
PREDNISOLONE ACETATE

Therapeutic Function: Glucocorticoid

Chemical Name: 11β,17,21-Trihydroxypregna-1,4-diene-3,20-dione 21-acetate

Common Name: —

Structural Formula:



(base)

Chemical Abstracts Registry No.: 52-21-1

Trade Name	Manufacturer	Country	Year Introduced
Sterane	Phipharmex	U.S.	1955
Nisolone	Ascher	U.S.	1962
Savacort	Savage	U.S.	1969
Econapred	Alcon	U.S.	1973
Pred Mild	Allergan	U.S.	1974
Pred Cor 100	Hauck	U.S.	1977
Alto-Pred	Alto	U.S.	—
Cortipred	Italsuisse	Italy	—
Deitacortilen	S.I.F.I.	Italy	—
Dermo-Nydol	Brichard	France	—
Durapred	Federal	U.S.	—
Hexacorton	Spirig	Switz.	—
Ibisterolon-Pommada	I.B.I.	Italy	—
Inflanefran	Allergan	W. Germany	—
Key-Pred	Hyrex	U.S.	—
Metimyd	Schering	U.S.	—
Meticortelone	Essex	Italy	—
Predate	Legere	U.S.	—
Predicort	Dunhall	U.S.	—
Prednifor	Vifor	Switz.	—
Prenema	Nortech	U.S.	—
Pricortin	Premedics	U.S.	—
Sigpred	Sig	U.S.	—
Ulacort	Fellows-Testagar	U.S.	—
Ultracortenol	Dispersa	Switz.	—

Raw Materials

Prednisolone
Acetic anhydride

Manufacturing Process

To a solution of 0.85 gram of 1,4-pregnadiene-11β,17α,21-triol-3,20-dione (prednisolone) in 5 ml of pyridine are added 3 ml of acetic anhydride. The reaction mixture is allowed to stand at room temperature overnight and is then diluted with ice water. The resulting precipitate is filtered from the mixture and recrystallized from acetone-hexane. There is recovered 0.45 gram of 1,4-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate, MP 235°-239°C. On recrystallization, the MP rose to 237°-239°C.

References

Merck Index 7613
Kleeman & Engel p. 750
PDR pp. 1033, 1633
OCDS Vol. 1 p. 192 (1977)
I.N. p. 798
REM p. 969
Nobile, A.; U.S. Patent 3,134,718; May 26, 1964; assigned to Schering Corporation

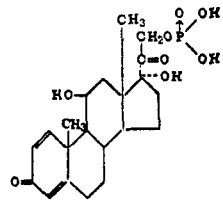
PREDNISOLONE PHOSPHATE SODIUM

Therapeutic Function: Glucocorticoid

Chemical Name: 11β,17,21-Trihydroxypregna-1,4-diene-3,20-dione 21-(dihydrogen phosphate)disodium salt

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 125-02-0

Trade Name	Manufacturer	Country	Year Introduced
Hydeltrasol	MSD	U.S.	1957
Inflamase	Cooper Vision	U.S.	1969
Optival	White	U.S.	1969
PSP-IV	Tutag	U.S.	1972
Alto-Pred	Alto	U.S.	–
Caberdelta	Caber	Italy	–
Codelsol	MSD	U.K.	–
Hydrosol	Rocky Mtn.	U.S.	–
Key-Pred S.P.	Hyrex	U.S.	–
Metreton	Schering	U.S.	–
Nor-Preds	North Amer. Pharm.	U.S.	–
Parisolon	Riker	U.S.	–
Predate S	Legere	U.S.	–
Prednesol	Glaxo	U.S.	–
Savacort	Savage	U.S.	–
Sodasone	Fellows-Testagar	U.S.	–
Solucort	Chibret	France	–
Solu-Pred	Myers-Carter	U.S.	–

Raw Materials

Prednisolone
Sodium iodide
Sodium hydroxide
Methane sulfonyl chloride
Phosphoric acid

Manufacturing Process

Preparation of Prednisolone 21-Methanesulfonate: Seventy liters of dry pyridine and 7.5 kg of prednisolone are charged to a 30-gallon jacketed glass-lined still. The mixture is agitated until complete solution is obtained. About 40 liters of pyridine are distilled at high vacuum while maintaining the batch temperature below 40°C. The solution is cooled to 0°C, and 2.2 liters of methanesulfonyl chloride are charged. The batch temperature is maintained between 0°C and +3°C during charging of the methanesulfonyl chloride. An atmosphere of flowing nitrogen is maintained in the still, and the mixture is agitated during the last stages of the addition. The mixture is then aged for one hour, and 15 gallons of ice water are added cautiously to the still while maintaining the temperature between 0° and 5°C.

The still contents are then transferred to a jacketed kettle equipped with an agitator, and 62 kg of cracked ice in 15 gallons of deionized water are added. The batch is aged one hour and a solution of 2 liters of concentrated (37%) hydrochloric acid in 4 gallons of deionized water is added. The batch is centrifuged and the centrifuge cake washed free of pyridine with deionized water. The centrifuge cake is then vacuum-dried at 50°C to a moisture content of about 1%, which requires about 3 days of drying. Yield about 7.77 kg (92%), according to U.S. Patent 2,932,657.

Preparation of Prednisolone 21-Iodide: To a 30-gallon jacketed glass-lined still 64.5 lb (31.0 liters) of dimethylformamide are charged by vacuum. The still contents are agitated as 7.74 kg of dry (less than 1% moisture) prednisolone 21-methanesulfonate are charged. Then 4.02 kg of sodium iodide are charged. The still contents are heated to 57° to 60°C by means of a steam jacket and held at this temperature for 30 minutes. The batch is cooled to 35°C and 12 gallons of deionized water are added at the rate of about 1 gallon per minute. In the event the solution becomes cloudy, addition of water is interrupted and the mixture agitated for five minutes before resumption of water addition. After all of the water is added, the batch is transferred to a 50 gallon kettle equipped with agitator and an additional 16.7 gallons of deionized water are added. The batch is cooled to 0° to 5°C and aged for one hour. The batch is filtered and the filter cake washed and vacuum dried at 30° to 35°C to a moisture content of less than 1%. Yield about 7.95 kg (96%), according to U.S. Patent 2,932,657.

Preparation of Prednisolone 21-Disodium Phosphate: Acetonitrile (50.0 ml) containing phosphoric acid (90%; 1.0 ml) was treated with triethylamine (3.0 ml) and the solution added to 11β,17α-dihydroxy-21-iodopregna-1,4-diene-3,20-dione (1.0 gram; powdered). The mixture was refluxed for 2.75 hours and the solvent was then evaporated under reduced pressure to give a yellow oil. The oil was taken up in methanol (25 ml) and titrated to pH 10.9 with sodium hydroxide in methanol (N) using a pH meter. The precipitate was filtered off and the filtrate evaporated to a gum under reduced pressure. The gum was taken up in methanol (5 ml), filtered through filter paper and acetone (100 ml) was added to the filtrate. The precipitate was filtered off, washed with acetone and dried at 100°C/1 mm for 0.75 hour giving a pale yellow solid, prednisolone disodium phosphate (0.74 gram), which was completely soluble in water, according to U.S. Patent 2,936,313.

References

Merck Index 7615
Kleeman & Engel p. 752
PDR pp. 1033, 1633
I.N. p. 798
REM p. 970
Sarett, L.H.; U.S. Patent 2,789,117; April 16, 1957; assigned to Merck & Co., Inc.
Christensen, B.G., Hirschmann, R.F. and Putter, I.; U.S. Patent 2,932,657; April 12, 1960; assigned to Merck & Co., Inc.
Elks, J. and Phillipps, G.H.; U.S. Patent 2,936,313; May 10, 1960; assigned to Glaxo Laboratories Limited, England

PREDNISOLONE STEAROYLGLYCOLATE

Therapeutic Function: Glucocorticoid

Chemical Name: 11β,17-Dihydroxy-21-[[[(1-oxoctadecyl)oxy] acetyl] oxy] pregna-1,4-diene-3,20-dione

Common Name: Prednisolone steaglate

Structural Formula: See prednisolone for formula of base

Chemical Abstracts Registry No.: 5060-55-9

Trade Name	Manufacturer	Country	Year Introduced
Deturgylone	Dausse	France	1970
Erbacort	Erba	Italy	–
Estilsona	Erba	Italy	–
Glistelone	Erba	Italy	–
Glitisone	Vis	Italy	–
Prenisol	Cifa	Italy	–
Rollsone	Bellon	France	–
Sintisone	Erba	Italy	–
Verisone	Tiber	Italy	–

Raw Materials

Prednisolone
Prednisolone-21-chloroacetate
Stearoyl-glycolyl chloride
Potassium stearate

Manufacturing Process

This material can be prepared, e.g., by reaction of prednisolone-21-chloroacetate in solvent with the sodium or potassium salt of the corresponding aliphatic or aromatic acid, or by reaction of prednisolone with the chloride of the corresponding acyl-glycolic acid, in the presence of a hydrochloric acid acceptor.

Alternative (A): 3 grams (0.0068 mol) prednisolone chloroacetate dissolved in 200 ml tetrahydrofuran and 10 ml H_2O are added with 2.7 grams (0.0084 mol) K stearate and 0.06 g NaI and heated to boiling, under stirring, for 36 hours, then evaporated in vacuum to dryness.

The residue is washed with H_2O to disappearance of the Cl-ion from the filtrate. Crystallization from diluted alcohol results in prednisolone-21-stearoyl-glycolate (MP 104°-105°C).

Alternative (B): 3.6 grams (0.01 mol) prednisolone and 4.32 grams (0.012 mol) stearoyl-glycolyl-chloride, separately dissolved in dry dioxane, are added with 0.89 ml (0.011 mol) dry pyridine. The mixture is kept at 60°C for 20 hours, then poured into water-ice and filtered. Crystallization from diluted ethanol results in prednisolone-21-stearoyl-glycolate (MP 104°-105°C).

References

Merck Index 7618
Kleeman & Engel p. 753
DOT 3 (1) 18 (1967)
I.N. p. 799

Giraldi, P.N. and Nannini, G.; U.S. Patent 3,171,846; March 2, 1965; assigned to Carlo Erba SpA, Italy

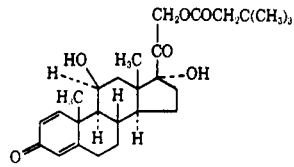
PREDNISOLONE TEBUTATE

Therapeutic Function: Glucocorticoid

Chemical Name: 21-(3,3-Dimethyl-1-oxobutoxy)-11β,17-dihydroxypregna-1,4-diene-3,20-dione

Common Name: Prednisolone-21-tert-butyl acetate

Structural Formula:



Chemical Abstracts Registry No.: 7681-14-3

Trade Name	Manufacturer	Country	Year Introduced
Hydeltra TBA	MSD	U.S.	1956
Codelcortone TBA	MSD	U.S.	–
Predate TBA	Legere	U.S.	–
Prednisol TBA	Pasadena	U.S.	–
Rodelta TBA	Rocky Mtn.	U.S.	–

Raw Materials

tert-Butyl acetyl chloride
Prednisolone

Manufacturing Process

A solution of about 10 parts of tertiary-butyl acetyl chloride in 45 parts of dry chloroform is added portionwise to a cold solution of 25 parts of $\Delta^{1,4}$-3,20-diketo-11β,17α,21-trihydroxy-pregnadiene (prednisolone) in 125 parts of anhydrous pyridine. The resulting solution is allowed to stand for about 15 hours at 0° to 5°C, and the reaction solution is poured into 750 parts of water. The resulting aqueous mixture is extracted four times with 250 parts of chloroform each extraction. The combined chloroform layers are washed with water, dilute aqueous hydrochloric acid solution, water, 5% aqueous sodium bicarbonate solution, and finally with water. The chloroform extract is dried over magnesium sulfate, and the chloroform is evaporated in vacuo to give a residual oil. This oil is triturated with alcohol until it crystallizes, and is then recrystallized from ethanol to give substantially pure $\Delta^{1,4}$-3,20-diketo-11β,17α,21-trihydroxy-pregnadiene 21-tertiary-butyl acetate.

References

Merck Index 7619
Kleeman & Engel p. 754
PDR pp. 1033, 1183
I.N. p. 798
REM p. 970
Sarett, L.H.; U.S. Patent 2,736,734; February 28, 1956; assigned to Merck & Co., Inc.

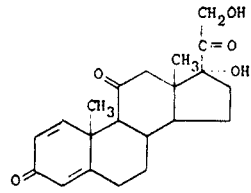
PREDNISONE

Therapeutic Function: Glucocorticoid

Chemical Name: 17α,21-Dihydroxy-pregna-1,4-diene-3,11,20-trione

Common Name: Deltacortisone

Structural Formula:



Chemical Abstracts Registry No.: 53-03-2

Trade Name	Manufacturer	Country	Year Introduced
Meticorten	Schering	U.S.	1955
Deltasone	Upjohn	U.S.	1955
Deltra	MSD	U.S.	1955
Paracort	Parke Davis	U.S.	1957
Lisacort	Fellows-Testagar	U.S.	1960
Servisone	Lederle	U.S.	1970
Orasone	Rowell	U.S.	1972
Wojtab	Philips Roxane	U.S.	1981
Adasone	Adams	Australia	–
Alto-Pred	Alto	U.S.	–
Colisone	Merck-Frosst	Canada	–
Cortan	Halsey	U.S.	–
Cortancyl	Roussel	France	–
Cortialper	Santos	Spain	–
Dacortin	Igoda	Spain	–
Decortin	Merck	W. Germany	–
Decortisyl	Roussel	U.K.	–
Decorton	Salfa	Italy	–
Deidrocortisone	Stip	Italy	–
Deltacortene	Lepetit	Italy	–
Delta Dome	Dome	U.S.	–
Delta Prenovis	Vister	Italy	–
Deltison	Ferring	Sweden	–
Erftopred	Erfto	W. Germany	–
Fernisone	Ferndale	U.S.	–
Hostacortin	Hoechst	W. Germany	–
Inocortyl	Liposeptine	France	–
Keteocort	Desitin	W. Germany	–
Keysone	Key	U.S.	–
Liquid Pred	Muro	U.S.	–
Marnisonal	Juan Martin	Spain	–
Marvidiene	Panther-Osfa	Italy	–
Me-Korti	Farmos	Finland	–
Nisone	Llorente	Spain	–
Nizon	Bosnalijek	Yugoslavia	–
Novoprednisone	Novopharm	Canada	–
Nurison	Nourypharma	Neth.	–
Panafcort	Protea	Australia	–
Parmenison	Kwizda	Austria	–
Pred-S	Saron	U.S.	–
Predniartrit	Maipe	Spain	–
Prednicen-M	Seymour	U.S.	–

Trade Name	Manufacturer	Country	Year Introduced
Prednifor	Vifor	Switz.	–
Prednilonga	Dorsch	W. Germany	–
Predni-Tablinen	Sanorania	W. Germany	–
Predni-Wolner	Wolner	Spain	–
Prednovister	Substancia	Spain	–
Predsol	Morgan	Italy	–
Predsone	Century	U.S.	–
Presone	Langley	Australia	–
Pronison	Galenika	Yugoslavia	–
Propred	Medac	Australia	–
Rectodelt	Trommsdorff	W. Germany	–
Ropred	Robinson	U.S.	–
Sarogesic	Saron	U.S.	–
Sone	Fawns & McAllan	Australia	–
Sterapred	Mayrand	U.S.	–
Supopred	Europa	Spain	–
Urtilone	Recherche Therap.	France	–
Wescopred	Saunders	Canada	–
Winpred	I.C.N.	Canada	–

Raw Materials

Bacterium *Corynebacterium simplex*
Cortisone

Manufacturing Process

From a solution of 30 grams of yeast extract (Difco) in 3.0 liters of tap water containing 13.2 grams of potassium dihydrogen phosphate and 26.4 grams of disodium hydrogen phosphate (pH of the solution 6.9) 27 portions of 100 ml each are withdrawn, placed in 300 ml Erlenmeyer flasks and sterilized by autoclaving for 15 minutes at 15 pounds steam pressure (120°C). After autoclaving and cooling of the broth one ml of a suspension of *Corynebacterium simplex* (ATCC 6946) is placed in each flask. The flasks are then shaken on a shake table at 220 rpm and 28°C for 24 hours.

Into each of 27 Erlenmeyer flasks are placed 150 mg of Kendall's Compound E (cortisone). The flasks and contents are then sterilized for 15 minutes at 15 pounds steam pressure (120°C). To each flask are then added 5.0 ml of ethanol. The 24-hour bacterial culture is then transferred aseptically and the resulting suspensions are shaken on a shake table at 220 rpm and 28°C for 48 hours. The final pH is 7.2.

The contents of all the flasks are combined and extracted with a total of 9.0 liters of chloroform in three equal portions. The combined extracts are then concentrated to a residue which is crystallized from acetone-hexane. There results 1.1 grams of $\Delta^{1,4}$-pregnadiene-17α, 21-diol-3,11,20-trione, MP 210°-215°C (dec.). Several additional recrystallizations raised the MP to 230°-232°C (dec.).

References

Merck Index 7621
Kleeman & Engel p. 755
PDR pp. 830, 993, 1268, 1573, 1606, 1723, 1837
OCDS Vol. 1 p. 192 (1977)
I.N. p. 799
REM p. 970
Djerassi, C., Rosenkranz, G. and Berlin, J.; U.S. Patent 2,579,479; December 25, 1951; assigned to Syntex SA, Mexico
Nobile, A.; U.S. Patent 2,837,464; June 3, 1958; assigned to Schering Corporation

Oliveto, E.P. and Gould, D.H.; U.S. Patent 2,897,216; July 28, 1959; assigned to Schering Corporation

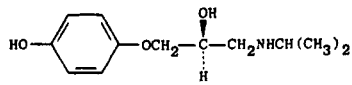
PRENALTEROL

Therapeutic Function: Adrenergic

Chemical Name: 4-[2-Hydroxy-3-[(1-methylethyl)amino] propoxy] phenol

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 57526-81-5

Trade Name	Manufacturer	Country	Year Introduced
Coleb	Astra	W. Germany	1981
Hyprenan	Astra	U.K.	1981
Varbian	Ciba	U.K.	1981

Raw Materials

4-Hydroxyphenoxypropylene oxide
Isopropylamine

Manufacturing Process

A solution of 100 g (1.7 mols) of isopropylamine in 60 cc of water was stirred into a solution of 4-hydroxyphenoxypropylene oxide. After the exothermic reaction has subsided, the reaction mixture was heated for two hours at 60°C. Thereafter, the aqueous ethanol was distilled off, and the solid residue was dissolved in aqueous hydrochloric acid comprising more than the theoretical stoichiometric molar equivalent of hydrochloric acid. The aqueous acid solution was extracted with ether and was then made alkaline with sodium hydroxide, whereby a solid crystalline precipitate was formed which was filtered off and dried over phosphorus pentoxide. The product was 1,1-(4'-hydroxyphenoxy)-2-hydroxy-3-isopropylamino-propane. Its hydrochloride had a melting point of 166°C to 169°C.

References

Merck Index 7639
DFU 4 (1) 46 (1979)
OCDS Vol. 3 p. 30 (1984)
DOT 17 (5) 199 (1981) & 18 (4) 190 (1982)
I.N. p. 801
Koppe, H., Engelhardt, A., Ludwig, G. and Zeile, K.; U.S. Patent 3,637,852; January 25, 1972; assigned to Boehringer Ingelheim G.m.b.H. (Germany)

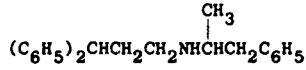
PRENYLAMINE

Therapeutic Function: Vasodilator (coronary)

Chemical Name: N-(1-Methyl-2-phenylethyl)-γ-phenylbenzenepropanamine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 390-64-7

Trade Name	Manufacturer	Country	Year Introduced
Synadrin	Hoechst	U.K.	1961
Segontin	Hoechst	Italy	1962
Segontin	Hoechst	W. Germany	1964
Segontine	Hoechst	France	1965
Agozol	Tableta	Rumania	–
Angiovigor	Violani-Farmavigor	Italy	–
Angorsan	Isola-Ibi	Italy	–
Cardional	Unipharm	Israel	–
Corditin-Same	Savoma	Italy	–
Coredamin	Meiji	Japan	–
Crepasin	Hoei	Japan	–
Daxauten	Woelm Pharma	W. Germany	–
Epocol	Teisan-Nagase	Japan	–
Eucardion	Vita	Italy	–
Falicor	Fahlberg-List	E. Germany	–
Herzcon	Sana	Japan	–
Incoran	I.T.A.	Italy	–
Irrorin	Alfa Farm.	Italy	–
Lactamine	Daisan	Japan	–
Newsantin	Sawai	Japan	–
NP 30	Sanken	Japan	–
Nyuple	Ohta	Japan	–
Onlemin	Ono	Japan	–
Plactamin	Morishita	Japan	–
Prectolact	Showa Yakuhin	Japan	–
Rausetin	Tanabe	Japan	–
Reocorin	Farmochimica	Italy	–
Roinin	Mohan	Japan	–
Seccidin	Nippon Kayaku	Japan	–
Wasangor	Wassermann	Italy	–

Raw Materials

1,1-Diphenyl-propylamine-(3)
Phenyl acetone
Hydrogen

Manufacturing Process

10.6 g of 1,1-diphenylpropylamine-(3) are hydrogenated by means of palladium with 6.7 g of phenyl acetone in 200 cc of methanol at 50°C. The calculated amount of hydrogen is taken up. The separated oily base is dissolved by heating with alcohol. After filtration water is added until turbidity sets in. 24.5 g of 2-(1',1'-diphenylpropyl-3'-amino)-3-phenyl-propane are obtained with a boiling point at 195°C to 198°C under a pressure of 0.5 mm of mercury, which after prolonged standing crystallizes out. Melting point about 38°C to 40°C. Hydrochloride (prepared in usual manner): melting point 188°C to 190°C.

References

Merck Index 7641
Kleeman & Engel p. 759
OCDS Vol. 1 p. 76 (1977)
I.N. p. 801
Ehrhart, G., Ott, H. and Lindner, E.; U.S. Patent 3,152,173; October 6, 1964; assigned to Farbwerke Hoechst A.G. (Germany)

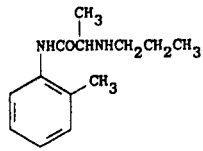
PRILOCAINE HYDROCHLORIDE

Therapeutic Function: Local anesthetic

Chemical Name: N-(2-methylphenyl)-2-(propylamino)-propanamide hydrochloride

Common Name: Propitocaine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 1786-81-8; 721-50-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Xylonest	Astra	W. Germany	1963
Citanest	Astra	U.K.	1974
Citanest	Astra	U.S.	1966
Citanest	Pierrel	Italy	1968
Citanest	Bellon	France	1973

Raw Materials

o-Toluidine
α-Bromopropionyl bromide
n-Propylamine

Manufacturing Process

One mol of ortho-toluidine is dissolved in 800 ml of glacial acetic acid. The mixture is cooled to 10°C whereupon 1.1 mols of α-bromopropionylbromide is added. The mixture is vigorously stirred for about a minute and a solution of sodium acetate (330 grams of $CH_3COONa \cdot 3H_2O$ in 1,380 ml of water) or another buffering or alkalizing substance or solution is added in one portion. The reaction mixture is then shaken for half an hour. The precipitate formed is filtered off, washed with water and dried. The product is sufficiently pure for further processing. Yield: 70-80% of theory. MP 133°-134°C.

One mol of α-bromopropio-ortho-toluidide is mixed with a solution of 3 mols of n-propylamine in 500 ml of water-free benzene and the reaction mixture is heated in an autoclave to 80°C for 8 hours. After cooling the reaction mixture is treated as described above. The base is obtained as a colorless oil. BP 159°-162°C/0.1 mm. Yield 55%. The base is then converted to the hydrochloride by reaction with HCl.

References

Merck Index 7646
DFU 8 (12) 1021 (1983)
Kleeman & Engel p. 760
OCDS Vol. 1 p. 17 (1977)
I.N. p. 802
REM p. 1053
Aktiebolaget Astra: Apotekarnes Kemiska Fabriker, Sweden; British Patent 839,943; June 29, 1960

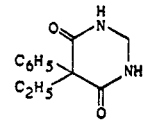
PRIMIDONE

Therapeutic Function: Anticonvulsant

Chemical Name: 5-Ethyldihydro-5-phenyl-4,6(1H,5H)-pyrimidinedione

Common Name: 2-Desoxyphenobarbital; primaclone

Structural Formula:



Chemical Abstracts Registry No.: 125-33-7

Trade Name	Manufacturer	Country	Year Introduced
Mysoline	I.C.I.	France	1953
Mysoline	Ayerst	U.S.	1954
Cyral	Gerot	Austria	—
Liskantin	Desitin	W. Germany	—
Majsolin	Pliva	Yugoslavia	—
Midone	Protea	Australia	—
Mylepsinum	ICI Pharma	W. Germany	—
Mysedon	Medica	Finland	—
Primidone	Schein	U.S.	—
Primoline	Darby	U.S.	—
Primron	Fujinaga	Japan	—
Prysoline	Abic	Israel	—
Resimatil	Labaz	W. Germany	—
Sertan	Chinoin	Hungary	—

Raw Materials

α,α-Phenylethylmalonic acid diamide
Formamide

Manufacturing Process

50 parts of α,α-phenylethylmalondiamide and 150 parts of formamide are boiled together under reflux for 2 hours. The mixture is then cooled to 0°C and filtered. The solid residue is washed with 50 parts of ethanol and then crystallized from 660 parts of an 80% ethanol water mixture. There is obtained 5-phenyl-5-ethylhexahydropyrimidine-4,6-dione, MP 281°-282°C.

References

Merck Index 7649
Kleeman & Engel p. 761
PDR pp. 631, 830, 1606
OCDS Vol. 1 p. 276 (1977)
I.N. p. 803
REM p. 1081
Boon, W.R., Carrington, H.C. and Vasey, C.H.; U.S. Patent 2,578,847; December 18, 1951; assigned to Imperial Chemical Industries Limited, England

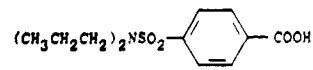
PROBENECID

Therapeutic Function: Antiarthritic

Chemical Name: 4-[(Dipropylamino)sulfonyl] benzoic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 57-66-9

Trade Name	Manufacturer	Country	Year Introduced
Benemid	MSD	U.S.	1952
Benemide	Theraplix	France	1954
Benecid	Kaken	Japan	–
Benuryl	I.C.N.	Canada	–
Colbenemid	MSD	U.K.	–
Panuric	Propan-Lipworth	S. Africa	–
Perdurine	Pharma-Union	Belgium	–
Probemid	Lefa	Spain	–
Probenicid	Lederle	U.S.	–
Probenemid	Merck-Banyu	Japan	–
Procid	Protea	Australia	–
Solpurin	Salfa	Italy	–
Urecid	Frosst	Australia	–
Uroben	Mitim	Italy	–

Raw Materials

p-Carboxybenzene sulfonyl chloride
Di-n-propylamine

Manufacturing Process

24.0 grams (0.11 mol) of p-carboxybenzenesulfonyl chloride was added in small portions to a suspension of 20.0 grams (0.146 mol) of di-n-propylamine in 100 milliliters of 10% sodium hydroxide with vigorous stirring at a temperature of 15°-25°C. Stirring was continued for 15 minutes after the final addition. The clear solution was treated with decolorizing carbon and filtered. The product was precipitated by the addition of an excess of hydrochloric acid. The crude product was purified by reprecipitation from bicarbonate solution and recrystallization from dilute alcohol. The yield was 20.0 grams (64%) melting at 194°-196°C.

References

Merck Index 7656
Kleeman & Engel p. 761
PDR pp. 705, 830, 993, 1142, 1150, 1606, 1999
OCDS Vol. 1 p. 135 (1977)
I.N. p. 804
REM p. 944
Miller, C.S.; U.S. Patent 2,608,507; August 26, 1952; assigned to Sharp & Dohme, Inc.

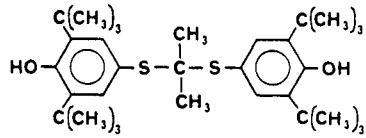
PROBUCOL

Therapeutic Function: Hypolipidemic

Chemical Name: Bis(3,5-di-tert-butyl-4-hydroxyphenyl) acetone mercaptole

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 23288-49-5

Trade Name	Manufacturer	Country	Year Introduced
Lorelco	Merrell Dow	U.S.	1977
Lurselle	Lepetit	France	1980
Lurselle	Lepetit	U.K.	1980
Lurselle	Dow-Lepetit	Switz.	1980
Lurselle	Merrell	W. Germany	1980
Lurselle	Lepetit	Italy	1982
Biphenabid	Merrell Dow	–	–
Lesterol	Lepetit	–	–

Raw Materials

2,6-Di-tert-butyl-4-mercaptophenol
Acetone

Manufacturing Process

Bis(3,5-di-tert-butyl-4-hydroxyphenyl) acetone mercaptole, melting at 125°C to 126°C is prepared by employing 2,6-di-tert-butyl-4-mercaptophenol and acetone as starting materials. In one representative procedure, the 2,6-di-tert-butyl-4-mercaptophenol (47.5 g, 0.2 mol) is dissolved in methanol (50 ml) heated at a temperature of 50°C. A catalytic amount of concentrated hydrochloric acid (1 ml) is added, followed by acetone (5.8 g, 0.1 mol). The temperature of the mixture rises to about 60°C, and is maintained at about 60°C to 65°C for 1.5 hours. The mixture is cooled, diluted with water and about 10 ml of aqueous sodium bicarbonate and extracted with ether. The ether extract is evaporated, and the product is obtained as a residue, which is recrystallized from ethanol and then from isopropanol to obtain the bis(3,5-di-tert-butyl-4-hydroxyphenyl) acetone mercaptole as a crystalline solid melting at about 125°C to 126°C.

In another representative procedure about 2.3 mols of 2,6-di-tert-butyl-4-mercaptophenol is dissolved in about 1,700 ml of methanol under a nitrogen atmosphere; about 100 ml of concentrated hydrochloric acid and 180 ml of acetone are added, and the mixture is stirred and maintained at a temperature of about 35°C to 50°C, for 1.5 hours. The mixture is then cooled to room temperature and filtered, and the bis(3,5-di-tert-butyl-4-hydroxyphenyl) acetone mercaptole product is collected as a colorless crystalline solid filter cake. The product is washed with water and aqueous sodium bicarbonate and purified by recrystallization from ethanol.

References

Merck Index 7657
DFU 2 (2) 128 (1977)
Kleeman & Engel p. 762
PDR p. 1229
OCDS Vol. 2 p. 126 (1980)
DOT 14 (1) 33 (1978)
I.N. p. 804
REM p. 864
Barnhart, J.W. and Shea, P.J.; U.S. Patent 3,862,332; January 21, 1975; assigned to The Dow Chemical Co.

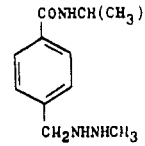
PROCARBAZINE HYDROCHLORIDE

Therapeutic Function: Cancer chemotherapy

Chemical Name: N-(1-Methylethyl)-4-[(2-methylhydrazino)methyl] benzamide HCl

Common Name: Ibenmethyzin

Structural Formula:



(base)

Chemical Abstracts Registry No.: 366-70-1; 671-16-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Natulan	Roche	France	1965
Natulan	Roche	W. Germany	1966
Natulan	Roche	U.K.	1966
Natulan	Roche	Italy	1967
Matulane	Roche	U.S.	1969
Natulan	Nippon Roche	Japan	1973

Raw Materials

4-Methylbenzoic acid
Methanol
1-Methyl-1,2-dicarbobenzoxyhydrazine
Sodium hydroxide
Hydrogen bromide
Thionyl chloride
Bromine
Sodium hydride
Isopropyl amine
Hydrogen chloride

Manufacturing Process

544 grams of 4-methylbenzoic acid was boiled with 550 ml of thionyl chloride until a clear solution was obtained. After the excess thionyl chloride was distilled off, the residue was fractionated, yielding 605 g of 4-methylbenzoyl chloride; BP 91°C/9 mm Hg, $n_D^{24} = 1.5532$. This was dissolved in 550 ml of absolute benzene and the so-formed solution added to a mixture of 248 ml of absolute methanol and 550 ml of absolute benzene. After the exothermic reaction had terminated, the reaction mixture was boiled for a further 20 hours, then concentrated in vacuo and the product, 4-methylbenzoic acid methyl ester, isolated by conventional means. It could be purified by distillation, and the purified product boiled at 91°C/9 mm Hg, MP 32°C.

574 grams of this ester were dissolved in 1200 ml of carbon tetrachloride and, while boiling and exposing to a UV lamp, treated dropwise with a solution of 109 ml of bromine in 400 ml of carbon tetrachloride. After all of the bromine had been dropped in, the mixture was heated for a further hour, concentrated in vacuo and the residue crystallized from low boiling petroleum ether, yielding as colorless fine crystals, 4-(bromo-methyl)-benzoic acid methyl ester, which melted at 52°C. For the reaction of this ester with 1-methyl-1,2-dicarbobenzoxy-hydrazine, the following procedure was followed.

309 grams of a 27% suspension of sodium hydride in an inert solvent was treated with 300 ml of dimethylformamide, and a solution of 1095 grams of 1-methyl-1,2-dicarbobenzoxy-hydrazine in dimethylformamide was added thereto. When all the material had been added and the hydrogen evolution had nearly come to a standstill, the mixture was heated for an hour at about 80°C in order to carry the formation of the sodium salt to completion. A mixture of 759 grams of 4-(bromo-methyl)-benzoic acid methyl ester in 700 ml of dimethylformamide was then dropped in, and finally the reaction mixture was heated for an hour at 80°C. After cooling, the reaction mixture was poured into 10 liters of ice water and the condensation products taken up in ether. The thereby obtained crude methyl ester ($n_D^{24} = 1.1558$) was used without further purification for the next step. It was dissolved in about 2,200 ml of dioxane, treated with a solution of 133 grams of sodium hydroxide in 870 ml of water, and the resulting mixture stirred for about 24 hours at room temperature. It was then poured into 10 liters of ice water and neutral materials were extracted with ether.

The aqueous phase was rendered acid with concentrated hydrochloric acid (weak Congo red) and the separated acid taken up in ether. The isolated crude acid was recrystallized from dibutyl ether, yielding colorless crystals of 4-[(2-methyl-1,2-dicarbobenzoxy-hydrazino)-methyl]-benzoic acid, which melted at 112°C. The so-obtained product was sufficiently pure for further reaction.

15 grams of 4-[(2-methyl-1,2-dicarbobenzoxy-hydrazino)methyl]-benzoic acid were boiled with an excess of thionyl chloride for 1 hour under reflux. The unconverted thionyl chloride was distilled off in vacuo, the residue twice dissolved each time in 75 ml of absolute benzene and then concentrated in vacuo. The so-obtained 4-[(2-methyl-1,2-dicarbobenzoxy-hydrazino)-methyl]-benzoyl chloride, a viscous light yellow oil, was dissolved in 50 ml of absolute benzene and with stirring mixed with a solution of 4.45 grams of isopropylamine in 100 ml of absolute benzene. By cooling, the temperature of the reaction mixture was kept below 30°C. After the mixing had been completed, the reaction mixture was maintained first at room temperature for 3 hours and then for ½ hour at 40°C. It was then cooled down and poured into about 100 ml of ice water. After the addition of a mixture of methylene chloride and ether (40 ml + 200 ml), the organic phase was separated and then washed with water, dilute hydrochloric acid, water, dilute sodium hydroxide and again with water.

The solvents were then evaporated, yielding 4-[(2-methyl-1,2-dicarbobenzoxyhydrazino)-methyl]-benzoic acid isopropylamide as a yellow oil, which crystallized upon triturating with ether; MP 90°-92°C. This product was then covered with 70 ml of a 33% solution of hydrogen bromide in glacial acetic acid, and then permitted to stand for 2 hours with occas-

ional swirling, whereupon a thick slurry of crystals was formed. The precipitate was filtered off, washed with 20 ml of glacial acetic acid and finally with ether, yielding crystals of 4-[(2-methyl-hydrazino)-methyl]-benzoic acid isopropylamide hydrobromide, which after recrystallization from methanol/ether melted at 216°-217°C (dec.).

87.5 grams of 4-[(2-methyl-hydrazino)-methyl]-benzoic acid isopropylamide hydrobromide (obtained as described above) were dissolved in 550 ml of water. To this solution, there were added 1,000 ml of methylene chloride and, while cooling with ice and stirring under nitrogen atmosphere, 1,200 grams of potassium carbonate portionwise. The methylene chloride layer was separated and the aqueous slurry extracted three times with 500 ml of methylene chloride in a nitrogen atmosphere. The united methylene chloride extracts were concentrated in vacuo. The residue was dissolved under nitrogen in 100 ml of methanol and treated, while cooling with ice, with 40 ml of a 45% methanolic hydrochloric acid solution, which induces immediate crystallization. The crystals were filtered off and recrystallized from methanol, yielding 4-[(2-methyl-hydrazino)-methyl]-benzoic acid isopropylamide hydrochloride melting at 223°-226°C.

References

Merck Index 7662
Kleeman & Engel p. 763
PDR p. 1491
OCDS Vol. 2 p. 27 (1980)
I.N. p. 805
REM p. 1153
Bollag, W., Gutmann, H., Hegedus, B., Kaiser, A., Langemann, A., Muller, M. and Zeller, P.; U.S. Patent 3,520,926; July 21, 1970; assigned to Hoffmann-La Roche Inc.

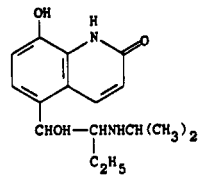
PROCATEROL

Therapeutic Function: Bronchodilator

Chemical Name: 8-Hydroxy-5-[1-hydroxy-2-[(1-methylethyl)amino]butyl]-2(1H)-quinolinone

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 72332-33-3

Trade Name	Manufacturer	Country	Year Introduced
Meptin	Otsuka	Japan	1981

Raw Materials

α-Bromobutyric acid bromide
Isopropylamine
8-Hydroxycarbostyril
Lithium aluminum hydride

Manufacturing Process

50 g of α-bromobutyric acid bromide, 50 g of anhydrous aluminum chloride and 400 ml of carbon disulfide were added to 20 g of 8-hydroxycarbostyril. The resulting mixture was heated at a temperature of 50°C for 13 hours and the carbon disulfide layer was removed by decantation. Crushed ice was added to the residue, and the precipitated crystals were filtered, washed with water and recrystallized from methanol to obtain 27 g of 5-(α-bromobutyryl)-8-hydroxycarbostyril having a melting point of 218°C to 219°C (with coloring and decomposition). To 5 g of the thus obtained 5-(α-bromobutyryl)-8-hydroxycarbostyril was added 100 ml of isopropylamine, and the mixture was heated at a temperature of 50°C for 4 hours followed by concentration to dryness. Crystals which formed upon addition of water were filtered, washed with water and then recrystallized from methanol to obtain 4.6 g of a methanol solvate of 5-(α-isopropylaminobutyryl)-8-hydroxycarbostyril having a melting point of 136°C to 137°C (with foaming and decomposition).

20 g of tetrahydrofuran was added to 1 g of 5-(α-isopropylaminobutyryl)-8-hydroxycarbostyril hydrochloride, and the resulting mixture was added dropwise to a suspension of 0.12 g of lithium aluminum hydride in 10 ml of tetrahydrofuran while stirring at room temperature. After completion of the addition, a small amount of water was added to the reaction mixture to decompose any excess of lithium aluminum hydride. The reaction mixture was then poured into 50 ml of ice-water and the aqueous layer of the resulting solution was separated and concentrated to dryness. The precipitated crystals were filtered, washed with acetone and dissolved in water. The solution was adjusted to pH of 8 with aqueous sodium hydroxide to precipitate crystals which were then filtered and recrystallized from ethanol to obtain 0.8 g of 5-(1-hydroxy-2-isopropylamino)butyl-8-hydroxycarbostyril monohydrate having a melting point of 141°C to 142°C (with cooling and decomposition).

References

Merck Index 7663
DFU 3 (2) 135 (1978)
OCDS Vol. 3 p. 184 (1984)
DOT 17 (6) 256 (1981)
Nakagawa, K., Yoshizaki, S., Tanimura, K. and Tamada, S.; U.S. Patent 4,026,897; May 3, 1977; assigned to Otsuka Pharmaceutical Co. (Japan)

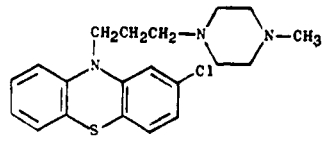
PROCHLORPERAZINE

Therapeutic Function: Antiemetic; antipsychotic

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

Common Name: Chlormeprazine

Structural Formula:



Chemical Abstracts Registry No.: 58-38-8; 84-02-6 (Maleate)

Trade Name	Manufactuer	Country	Year Introduced
Compazine	SKF	U.S.	1956
Tementil	Specia	France	1957
Anti-Naus	Protea	Australia	–
Combid	SKF	U.S.	–
Klometil	Farmos	Finland	–
Mitil	Lennon	S. Africa	–
Nibromin-A	Maruko	Japan	–
Normalmin	Sawai	Japan	–
Novamin	Shionogi	Japan	–
Pasotomin	Yoshitomi	Japan	–
Stemetil	May & Baker	U.K.	–
Vertigon	SKF	U.K.	–

Raw Materials

3-Chloro-10-[3-(di-N-2-chloroethyl)aminopropyl] phenthiazine hydrochloride
Monomethylpiperazine

Manufacturing Process

3-Chloro-10-[3-(di-N-2-chloroethyl)aminopropyl)]phenthiazine hydrochloride (1.8 g) is heated in a sealed tube for 4 hours at 140°C with a 290 g/l aqueous solution (9 cc) of monomethylpiperazine. The contents of the tube are treated with chloroform (40 cc). The aqueous layer is decanted and the chloroform layer is shaken with N hydrochloric acid (15 cc followed by 2 cc). The aqueous solution is treated with sodium hydroxide (d = 1.33, 10 cc) and chloroform (20 cc). After evaporation of the solvent, the base (1.5 g) is obtained. A solution of maleic acid (1 g) in ethanol (5 cc) is added and after recrystallization from water, 3-chloro-10-[3-(4'-methyl-1'-piperazinyl)propyl] phenothiazine dimaleate is obtained, melting point 228°C (inst.).

References

Merck Index 7665
Kleeman & Engel p. 764
PDR pp. 1606, 1706
OCDS Vol. 1 p. 381 (1977)
DOT 9 (6) 228 (1973)
I.N. p. 806
REM p. 809
Horclois, R.J.; U.S. Patent 2,902,484; September 1, 1959; assigned to Societe des Usines Chimiques Rhone-Poulenc, France

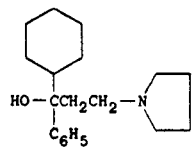
PROCYCLIDINE HYDROCHLORIDE

Therapeutic Function: Antiparkinsonism

Chemical Name: α-Cyclohexyl-α-phenyl-1-pyrrolidinepropanol hydrochloride

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 1508-76-5; 77-37-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Kemadrin	Burroughs Wellcome	U.S.	1956
Kemadrine	Wellcome	France	1965
Arpicolin	R.P. Drugs	U.K.	–
Kemadren	Gayoso Wellcome	Spain	–
Osnervan	Wellcome	W. Germany	–
Procyclid	I.C.N.	Canada	–

Raw Materials

Acetophenone
Pyrrolidine
Magnesium
Hydrogen chloride
Paraformaldehyde
Bromobenzene
Hydrogen

Manufacturing Process

1,1-Diphenyl-3-pyrrolidinopropan-1-ol (30 grams) was dissolved in glacial acetic acid (120 ml), Adams' platinum catalyst (6 grams) added, and the mixture shaken in an atmosphere of hydrogen until the equivalent of 3.4 molecules had been taken up per molecule of compound. Water was added, the catalyst removed by filtration, excess of ammonia added, and the liberated base extracted with ether. The ethereal extract was dried and evaporated and the residue recrystallized from light petroleum (BP 40°-60°C). The 1-cyclohexyl-1-phenyl-3-pyrrolidinopropan-1-ol (19.3 grams) so obtained had a melting point of 85.5°-86.5°C. The hydrochloride recrystallized from a mixture of ethanol and ethyl acetate, melted with decomposition at 226°-227°C according to U.S. Patent 2,891,890.

The starting material is prepared by the reaction of acetophenone, paraformaldehyde and pyrrolidine to give ω-pyrrolidinopropiophenone. That is in turn reacted with phenyl magnesium bromide to give 1,1-diphenyl-3-pyrrolidinpropan-1-ol.

References

Merck Index 7667
Kleeman & Engel p. 765
PDR p. 745
OCDS Vol. 1 p. 47 (1977)
DOT 18 (2) 88 (1982)
I.N. p. 806
REM p. 932

Bottorff, E.M.; U.S. Patent 2,826,590; March 11, 1958; assigned to Eli Lilly and Company
Harfenist, M. and Magnien, E.G.; U.S. Patent 2,842,555; July 8, 1958; assigned to Burroughs Wellcome & Co. (U.S.A.) Inc.
Adamson, D.W.; U.S. Patent 2,891,890; June 23, 1959; assigned to Burroughs Wellcome & Co. (U.S.A.) Inc.

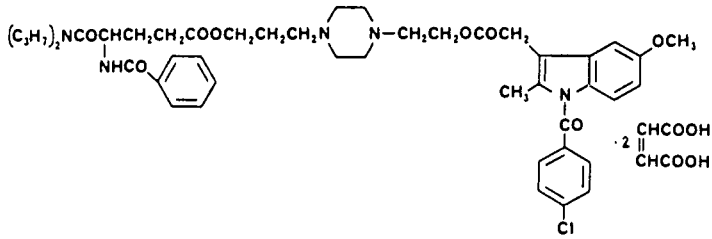
PROGLUMETACIN MALEATE

Therapeutic Function: Antiinflammatory

Chemical Name: N'-2-[1-(p-chlorobenzoyl)-5-methoxy-2-methyl-3-indoleacetoxy]-ethyl-N-3-(N-benzoyl-N',N'-di-n-propyl-DL-isoglutaminoyl)-oxypropyl piperazine dimaleate

Common Name: Protacine

Structural Formula:



Chemical Abstracts Registry No.: 57132-53-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Afloxan	Rotta	Italy	1981
Proxil	Rorer	Italy	1981

Raw Materials

N'-(2-Hydroxyethyl)-N-3-(N-benzoyl-N',N'-di-n-propyl-DL-isoglutaminoyl)-oxypropyl piperazine
1-(p-Chlorobenzoyl)-5-methoxy-2-methyl-3-indoleacetic acid
N',N'-Dicyclohexylcarbodiimide
Maleic acid

Manufacturing Process

To a titrated solution of 400 cc of ethyl acetate containing 0.1 mol of N'-(2-hydroxyethyl)-N-3-(N-benzoyl-N',N'-di-n-propyl-DL-isoglutaminoyl)-oxypropyl piperazine [obtained by dissolving 71.9 g (0.105 mol) of the corresponding di-oxalate in 500 cc of water, bringing this solution to a pH of between 9 and 10 with sodium bicarbonate and finally extracting the oily emulsion thus formed twice in succession with a total of 400 cc of ethyl acetate], there are added successively 35.8 g (0.1 mol) of 1-(p-chlorobenzoyl)-5-methoxy-2-methyl-3-indoleacetic acid and 20.6 g (0.1 mol) of N,N'-dicyclohexylcarbodiimide. This is left at room temperature for 24 hours, and after having filtered the N,N'-dicyclohexyl urea precipitate the organic phase is then washed with dilute HCl, a solution of sodium bicarbonate and a saturated solution of sodium chloride.

The ethyl acetate is dried with anhydrous sodium sulfate, filtered and dried off. The oily residue is dissolved in 600 cc of methanol; the di-oxalate is precipitated by the addition of a solution of oxalic acid in methanol. Yield 85%, melting point 190°C to 192°C (crystallized by methanol). Microcrystalline substance, creamy white color.

By the same method one can obtain the dimaleate. Yield, 83%; melting point, 146°C to 148°C (crystallized by ethanol). Microcrystalline pale cream colored substance.

References

Merck Index 7679
DFU 5 (3) 142 (1980)
DOT 17 (4) 157 (1981)
Makovec, F., Senin, P. and Rovati, L.; U.S. Patent 3,985,878; October 12, 1976; assigned to Rotta Research Laboratorium S.p.A.

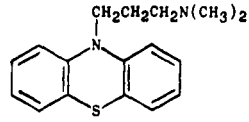
PROMAZINE HYDROCHLORIDE

Therapeutic Function: Tranquilizer

Chemical Name: N,N-Dimethyl-10H-phenothiazine-10-propanamine hydrochloride

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 53-60-1; 58-40-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Sparine	Wyeth	U.S.	1956
Atarzine	Saunders	Canada	–
Calmotal	S.I.T.	Italy	–
Eliranol	Wyeth	Italy	–
Frenil	Polfa	Poland	–
Neuroplegil	Gentili	Italy	–
Promanyl	Paul Maney	Canada	–
Promazettes	Barlow Cote	Canada	–
Promezerine	Barlow Cote	Canada	–
Protactyl	Wyeth	W. Germany	–
Savamine	Banyu	Japan	–
Sediston	Serono	Italy	–
Starazine	Star	Finland	–
Talofen	Pierrel	Italy	–
Tranquazine	Anthony	U.S.	–

Raw Materials

Phenothiazine
3-Dimethylamino-1-chloropropane
Sodium amide
Hydrogen chloride

Manufacturing Process

30 grams of phenothiazine, 120 grams of xylene and 7 grams of sodamide (80%) are mixed and heated under reflux. 23 grams of 3-dimethylamino-1-chloropropane, diluted with its own weight of xylene, is then added little by little during one hour, while maintaining the temperature of the reaction mixture; heating under reflux is then continued for a further hour. After cooling, the mixture is taken up in 400 cc of water and rendered slightly acid with hydrochloric acid. The xylene is decanted, the aqueous layer is rendered strongly alkaline with caustic soda and the base which separates is extracted with ether. On rectification of the ether extract, there is obtained N-(3'-dimethyl-amino-propyl)-phenothiazine which boils at 208°-210°C under 3 mm. The hydrochloride of this base melts at 181°C (Maquenne block).

References

Merck Index 7688
Kleeman & Engel p. 768
PDR p. 1989
OCDS Vol. 1 p. 377 (1977)
I.N. p. 810
REM p. 1090

Charpentier, P.; U.S. Patent 2,519,886; August 22, 1950; assigned to Societe des Usines Chimiques Rhone-Poulenc, France

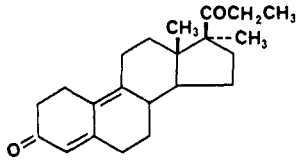
PROMEGESTONE

Therapeutic Function: Progestin

Chemical Name: 17α,21-Dimethyl-19-nor-$\Delta^{4,9}$-pregnadiene-3,20-dione

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: –

Trade Name	Manufacturer	Country	Year Introduced
Surgestone	Cassenne	France	1983

Raw Materials

17α-Methyl-19-nor-$\Delta^{5(10)}$-pregnene-3,20-dione
Bromine
Pyridine

Manufacturing Process

16.3 cc of a solution of 29% of bromine in methanol were added with agitation under a nitrogen atmosphere to a solution of 8.50 g of 17α-methyl-19-nor-$\Delta^{5(10)}$-pregnene-3,20-dione in 85 cc of pyridine cooled to 0°C and the mixture was stirred for 30 minutes at 0°C. The temperature was allowed to return to room temperature and the mixture was stirred for 16 hours.

The mixture was added to 850 cc of water-ice mixture and 82 cc of hydrochloric acid were added thereto. The mixture was extracted with methylene chloride and the combined extracts were washed with water until the wash waters were neutral, were dried over magnesium sulfate and distilled to dryness to obtain 8.480 g of crude product which is purified by crystallion from isopropyl ether to obtain 5.810 g of 17α-methyl-19-nor-$\Delta^{4,9}$-pregnadiene-3,20-dione melting at 106°C.

The mother liquors from the purification of the product were combined and evaporated to dryness. The residue was fractionated by chromatography over silica gel (Kieselgel) and elution with a 7:3 mixture of benzene-ethyl acetate. The first fractions were discarded and the ensuing fraction was evaporated to obtain colorless crystals. The product was purified by mixing with five volumes of boiling isopropyl ether and the crystals formed after cooling were recovered by vacuum filtration, were washed twice with two volumes of isopropyl ether and dried in a ventilated atmosphere to obtain 17α,21-dimethyl-19-nor-$\Delta^{4,9}$-pregnadiene-3,20-dione melting at 152°C.

References

DFU 3 (6) 469 (1978)
DOT 19 (7) 416 (1983)
I.N. p. 810
Warnant, J. and Farcilli, A.; U.S. Patents 3,679,714; July 25, 1972; and 3,761,591; Sept. 25, 1973; both assigned to Roussel UCLAF

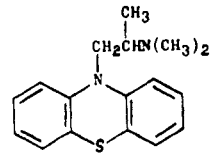
PROMETHAZINE HYDROCHLORIDE

Therapeutic Function: Antihistaminic

Chemical Name: N,N,α-trimethyl-10H-phenothiazine-10-ethanamine hydrochloride

Common Name: Proazamine hydrochloride

Structural Formula:



(base)

Chemical Abstracts Registry No.: 58-33-3; 60-87-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Phenergan	Wyeth	U.S.	1951
Ganphen	Tutag	U.S.	1971
Remsed	Endo	U.S.	1973
Lemprometh	Lemmon	U.S.	1974
Bromethacon	Alcon	U.S.	1981
Baymethazine	Bay	U.S.	1982
Atosil	Bayer	W. Germany	–
Avomine	May & Baker	U.K.	–
Diphergan	Polfa	Poland	–
Dorme	A.V.P.	U.S.	–
Fargan	Farmitalia	Italy	–
Fellozine	Fellows-Testagar	U.S.	–
Fenazil	Sella	Italy	–
Fenergan	Rhodia Iberica	Spain	–
Hiberna	Yoshitomi	Japan	–
Lenazine	Lennon	S. Africa	–
Lergigan	Recip	Sweden	–
Mopergan	Wyeth	U.S.	–
Pelpica	P.C.B.	Belgium	–
Perduretas	Medea	Spain	–
Phencen	Central	U.S.	–
Pipolphen	Nakataki	Japan	–
Progan	Adams	Australia	–
Promet	Legere	U.S.	–
Promethapar	Parmed	U.S.	–
Promethazine	Lederle	U.S.	–
Promine	Laser	U.S.	–
Prorex	Hyrex	U.S.	–

Trade Name	Manufacturer	Country	Year Introduced
Prothazine	Knoll	Australia	–
Prothia	Kanto	Japan	–
Prothiazine	Novis	Israel	–
Provigan	Reid-Provident	U.S.	–
Pyrethia	Shionogi	Japan	–
Quadnite	Reid-Provident	U.S.	–
Rivozine	Rivopharm	Switz.	–
Sayamol	Cinfa	Spain	–
V-Gan	Hauck	U.S.	–
Zipan	Savage	U.S.	–

Raw Materials

Phenothiazine
1-Dimethylamino-2-propyl chloride
Sodium amide
Hydrogen chloride

Manufacturing Process

30 grams of phenothiazine, 120 grams of xylene, and 7 grams of sodamide (85%) are mixed and heated under reflux. A solution of 23 grams of the base obtained by the action of sodium hydroxide on the hydrochloride of 1-dimethylamino-2-chloropropane, in 25 grams of xylene, is then added little by little during one hour, while maintaining the temperature of the reaction mixture; heating under reflux is then continued for a further hour. After cooling, the mixture is taken up in 400 cc of water and rendered slightly acid with hydrochloric acid. The xylene is decanted, the aqueous layer is rendered strongly alkaline with caustic soda and the base which separates is extracted with ether. The ethereal extract is rectified, the fraction which boils at 190°-192°C under 3 mm being recovered. This is diluted with acetone or ethyl acetate and dry hydrochloric acid is added. The hydrochloride of N-(2'-dimethylamino-2'-methyl-ethyl)-phenothiazine separates, according to U.S. Patent 2,530,451.

References

Merck Index 7691
Kleeman & Engel p. 769
PDR pp. 861, 993, 1033, 1959, 1968, 1989
OCDS Vol. 1 pp. 373, 377 (1977)
I.N. p. 811
REM p. 1129
Charpentier, P.; U.S. Patent 2,530,451; November 21, 1950; assigned to Societe des Usines Chimiques Rhone-Poulenc, France
Berg, S.S. and Ashley, J.N.; U.S. Patent 2,607,773; August 19, 1952; assigned to Societe des Usines Chimiques Rhone-Poulenc, France

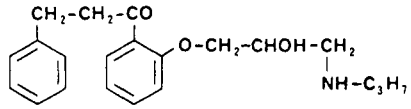
PROPAFENONE HYDROCHLORIDE

Therapeutic Function: Antiarrhythmic

Chemical Name: 2'-(2-Hydroxy-3-propylaminopropoxy)-3-phenylpropiophenone hydrochloride

Common Name: Fenoprain

Structural Formula:



(base)

Chemical Abstracts Registry No.: 34183-22-7; 54063-53-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Rytmonorm	Knoll	W. Germany	1978
Rytmonorm	Knoll	Italy	1983
Rytmonorm	Knoll	Switz.	1983
Baxarytmon	Helopharm	W. Germany	—
Normorytmin	Knoll	W. Germany	—

Raw Materials

2'-Hydroxy-3-phenylpropiophenone
n-Propylamine
Epichlorohydrin
Hydrogen chloride

Manufacturing Process

2'-(2,3-epoxypropoxy)-3-phenylpropiophenone — 24.8 g of the sodium salt of 2'-hydroxy-3-phenylpropiophenone were mixed with 40 cm^3 of 1-chloro-2,3-epoxypropane (epichlorohydrin) and the mixture heated on a boiling water bath while stirring, using a reflux condenser. The initially pasty-to-solid mixture liquefied after about 2 hours, sodium chloride separating out. Thereafter it was heated for a further 2 hours while stirring, using a reflux condenser. The mixture was then allowed to cool and subsequently freed, by filtration, from the sodium chloride formed. The filtrate was concentrated in vacuo, and the excess 1-chloro-2,3-epoxypropane thus separated from the desired 2'-(2,3-epoxypropoxy)-3-phenylpropiophenone. The latter remained as a yellowish oil which solidified in the cold, but did not crystallize. Purification of the intermediate product, by distillation in vacuo, was not necessary, particularly as the substance only boiled at a temperature of 280°C/12 mm Hg and at the same time decomposed.

2'-(2-hydroxy-3-propylaminopropoxy)-3-phenylpropiophenone hydrochloride — The above product was treated with 20 cm^3 of n-propylamine and the mixture warmed on a water bath for approximately 4 hours, while stirring, using a reflux condenser. Thereafter, the excess n-propylamine was distilled off. On cooling, the residue solidified to give a viscous yellow mass. 20 cm^3 of 1M aqueous hydrochloric acid were added to it, and the whole was boiled for 1 hour under reflux, while stirring. The mixture was then poured into a suitable vessel and allowed to crystallize at room temperature. The crude product was drained thoroughly by suction and subsequently crystallized from a mixture of acetone/methanol (80:20, v/v).

Approximately 25 g (66.2% of theory) of a white crystalline substance were obtained. The melting point of the hydrochloride was 173°C to 174°C.

References

Merck Index 7698
DFU 2 (5) 325 (1977)
Kleeman & Engel p. 770
I.N. p. 812
Sachse, R.; British Patent 1,307,455; February 21, 1973; assigned to Helopharm W. Petrick & Co. K.G.