C

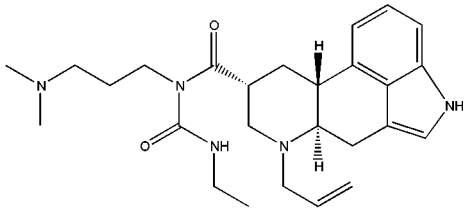
CABERGOLINE

Therapeutic Function: Prolactin inhibitor

Chemical Name: 1-((6-Allylergolin-8β-yl)carbonyl)-1-(3-(dimethylamino) propyl)-3-ethylurea

Common Name: Cabergoline

Structural Formula:



Chemical Abstracts Registry No.: 81409-90-7

Trade Name	Manufacturer	Country	Year Introduced
Destinex	Farmitalia Carlo Erba	Italy	-
Cabergoline	Pharmacia and Upjohn	-	-

Raw Materials

6-Methyl-8β-carboxy-ergoline
N-(3-Dimethylaminopropyl)-N-ethyl carbodiimide
Sodium hydroxide

Manufacturing Process

A mixture of 6-(2-propenyl)-8β-carboxy-ergoline and N-(3-dimethylaminopropyl)-N-ethyl carbodiimide in tetrahydrofuran were refluxed, with stirring and under nitrogen, for 24 h. The resultant solution was evaporated in vacuo to dryness and the residue taken up with chloroform and

5% sodium hydroxide solution. The organic phase was separated, dried over anhydrous sodium sulfate and evaporated in vacuo. The residue was chromatographed on silica (eluant chloroform with 1% methanol) to give the title compound N-(3-(dimethylamino)propyl)-N-((ethylamino)carbonyl)-8β-carboxamide-6-(2-propenyl)ergoline.

References

Salvati P. et al; US Patent No. 4,526,892; July 2, 1985; Assigned: Farmitalia Carlo Erba, S.p.A., Milan, Italy

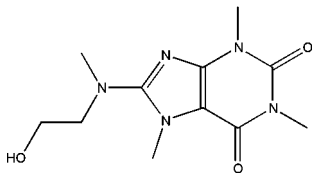
CAFAMINOL

Therapeutic Function: Nasal decongestant

Chemical Name: 3,7-Dihydro-8-[(2-hydroxyethyl)methylamino]-1,3,7-trimethyl-1H-purine-2,6-dione

Common Name: Methylcoffanolamine

Structural Formula:



Chemical Abstracts Registry No.: 30924-31-3

Trade Name	Manufacturer	Country	Year Introduced
Rhinoptil	Promonta	W. Germany	1974
Rhinetten	Arzneimittelwerk Dresden	E. Germany	-

Raw Materials

8-Chlorocaffeine
beta-N-Methylaminoethanol

Manufacturing Process

21 g 8-chlorocaffeine and 15 g beta-N-methylaminoethanol are heated to 140°-160°C for 30 minutes. Then the temperature is increased for 15-20 minutes to 165°-170°C. On cooling a colorless mass of crystals results. This is boiled with 50-60 ml ethanol and crystallized. Colorless crystals result which

are soluble in water up to about 6%; pH of the aqueous solution is 6.9. The yield is 19 g while the MP is 162°-164°C.

References

Merck Index 1603
I.N. p. 173
Klosa, J.; US Patent 3,094,531; June 18,1963; assigned to Delmar Chemicals Ltd. (Canada)

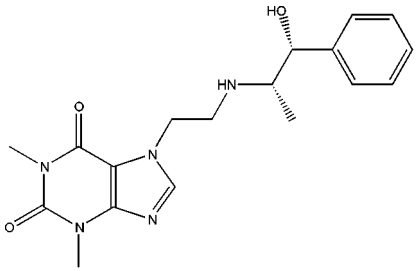
CAFEDRINE

Therapeutic Function: Analeptic

Chemical Name: Theophylline, 7-(2-(beta-hydroxy-alpha-methylphenethyl-amino)ethyl)-

Common Name: Cafedrine; Kafedrin; Norephedrinoethyltheophylline

Structural Formula:



Chemical Abstracts Registry No.: 78396-34-6

Trade Name	Manufacturer	Country	Year Introduced
Praxinor	Merck Lipha Sante	-	-
Cafedrine	Merck	-	-
Cafedrine	Shanghai Lancheng Corporation	-	-
Cafedrine	Gennapharm, Inc.	-	-
Akrinor	Adcock Ingram Ltd.	-	-
Akrinor	AWD Pharma GmbH and Co. KG	-	-
Bifort	Finadiet	-	-

Raw Materials

7-(2-Bromethyl)theophylline
1-Norphedrine

Manufacturing Process

7.5 g 7-(2-bromethyl)theophylline, 11.3 g 1-norphedrine and 12.5 ml isopropanol were refluxed with stirring for 6 hours. Then 30 ml ethanol and HCl in ethanol to pH 5-6 were added. The mixture stood for 2 days. 9.6 g of 7-(2-(beta-hydroxy-alpha-methylphenethylamino)ethyl)theophylline hydrochloride was filtered off and dried. MP 243°-244°C.

In practice it is usually used as free base.

References

Kohlstaedt E. et al.; D. B. Patent No. 1,095,285; 25 Sept. 1956; Assigned to Chemiewerk Homburg Zweigniedererlassung der Deutschen Gold- und Silber-Scheideanstalt vormals Roessler Franffurt/Main

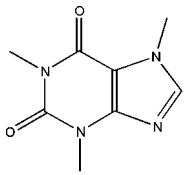
CAFFEINE

Therapeutic Function: Neurotropic, Central stimulant

Chemical Name: 3,7-Dihydro-1,3,7-trimethyl-1H-purine-2,6-dione

Common Name: Cafeina; Caféine; Caffeine; Coffein; Guaranine; Kafeiyin; Kaffein; Koffein; Mateina; Methyltheobromine; Thein

Structural Formula:



Chemical Abstracts Registry No.: 58-08-2

Trade Name	Manufacturer	Country	Year Introduced
Caffedrine	Thompson Med.	-	-
Caffeine	Prolab	-	-
Koffein	Prolab	-	-
Vivarin	GlaxoSmithKline Consumer Healthcare, L.P.	USA	-

Raw Materials

Theophylline
Dimethyl sulfoxide
Dimethyl sulfate

Manufacturing Process

Caffeine was synthesized by the reaction N-chloromethylation of theophylline by action dimethylsulphate in dimethylsulfoxide.

References

DBP 834105 (Boehringer Ing.; Anm. 1949)

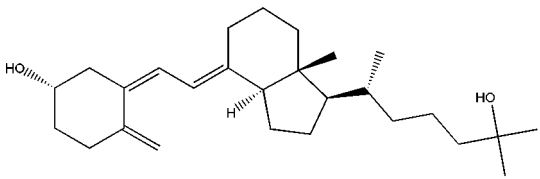
CALCIFEDIOL

Therapeutic Function: Calcium regulator

Chemical Name: 9,10-Secocholesta-5,7,10(19)-triene-3,25-diol

Common Name: 25-Hydroxyvitamin D_3; 25-Hydroxycholecalciferol

Structural Formula:



Chemical Abstracts Registry No.: 19356-17-3

Trade Name	Manufacturer	Country	Year Introduced
Dedrogyl	Roussel	France	1976
Delakmin	Roussel	W. Germany	1978
Calderol	Upjohn	US	1980
Didrogyl	Roussel Maestretti	Italy	1980
Dedrogyl	Hoechst	Switz.	1982
Hidroferol	Juventus	Spain	-
Calderol	Organon	US	-

Raw Materials

Cholesta-5,7-diene-3β,25-diol

Manufacturing Process

A solution of 125 mg of cholesta-5,7-diene-3β,25-diol in 125 ml of benzene and 10 ml of absolute ethanol is placed in a photo reactor equipped with a quartz lamp well cooled with water and a nitrogen inlet. The reaction mixture is cooled to about 16°C, and purged with N_2. A Hanovia 8A36, 100-watt lamp, centered in the lampwell 2.5 cm from the internal surface of the reaction mixture, is turned on for 15 minutes, including the 5-6 minutes required for the lamp to reach full brilliance. The lamp is a typical actinic energy source suitable for the irradiation step in the known synthesis of Vitamin D, and can be replaced by any such available lamp. The specific lamp used is a 100-watt high-pressure quartz mercury-vapor lamp, producing approximately 11.5 watts total radiated energy distributed over the range of 220-1400 nm. A fast stream of water is necessary to keep the outlet water temperature below 20°C. The reaction mixture is concentrated to dryness in a rotary evaporator below room temperature. The semisolid residue is triturated with 5 ml of 35% ethyl acetate-65% Skellysolve B hexanes mixture and filtered and another 5 ml of the same solvent is used for wash. The solid contains unreacted starting material and the liquor contains the product. The liquor is poured onto a 40 g column containing TLC grade Florisil, 150-200 mesh packed wet with 35% ethyl acetate-Skellysolve B hexanes, and the products are eluted with the same solvent mixture collecting 10 ml fractions. The fractions containing the product, located by spotting on a TLC plate, are combined and evaporated to dryness below room temperature to give an oily residue. A few drops of absolute ether are added and removed under vacuum to give 25-hydroxyprecholecalciferol as a fluffy foam; yield 60 mg.

A solution of about 300 mg of 25-hydroxyprecholecalciferol prepared as described above in 5 ml of chloroform is heated for 3.5 hours at 70°-75°C under N_2 in a sealed flask. The solvent is evaporated and the residue is chromatographed through a 60 g column containing TLC grade Florisil, 150-200 mesh packed wet with 35% ethyl acetate in Skellysolve B hexanes. The column is eluted with the same solvent mixture, collecting 10 ml fractions. The fractions which crystallize on trituration with aqueous methanol are combined and recrystallized twice from aqueous methanol to give 25-hydroxycholecalciferol hydrate; yield 120 mg, MP 81°-83°C (sinters 75°C).

A solution of 20 mg of 25-hydroxycholecalciferol hydrate, prepared as described above, in 20 ml of methylene chloride is dried with 200 mg of anhydrous sodium sulfate. The solution is filtered and the filtrate is evaporated to yield 25-hydroxycholecalciferol essentially anhydrous as an amorphous oil.

References

Merck Index 1610
Kleeman and Engel p. 133
PDR p. 1285
OCDS Vol. 3 p. 101 (1984)

DOT 13 (6) 225 (1977)
I.N. p. 174
Babcock, J.C. and Campbell, J.A.; US Patent 3,833,622; September 3, 1974; assigned to The Upjohn Company
Saimond, W.G.; US Patent 4,001,096; January 4, 1977; assigned to The Upjohn Company

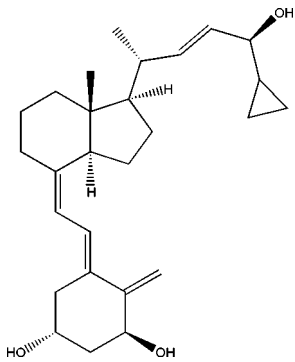
CALCIPOTRIOL

Therapeutic Function: Antipsoriatic

Chemical Name: 9,10-Secochola-5,7,10(19),22-tetraene-1,3,24-triol, 24-cyclopropyl-, (1α,3β,5Z,7E,22E,24S)-

Common Name: Calcipotriene; Calcipotriol; Dovonex; MC 903

Structural Formula:



Chemical Abstracts Registry No.: 112965-21-6

Trade Name	Manufacturer	Country	Year Introduced
Psorcutan	KOHLPHARMA	-	-

Raw Materials

(1S,3R)-Bis-(tert-butyldimethylsilyloxy)-(20S)-formyl-9.10-secopregna-(5E,7E,10(19))triene
(Cyclopropyl)(triphenylphosphoranylidene)ketone
Cerium (III) chloride
Cyclopropyl magnesium bromide
Anthracene
Sodium borohydride
Triethylamine
Tetrabutylammonium fluoride

Manufacturing Process

(1S,3R)-Bis-(t-butyldimethylsilyloxy)-(20S)-formyl-9,10-secopregna(5E,7E,10(19))triene (Calverley Tetrahedron 43.4609 (1967) and (cyclopropyl)(triphenylphoshoranylidene)ketone are stirred in dimethyl sulfoxide under nitrogen. The reaction mixture is then diluted at room temperature with ethyl acetate and washed with common salt solution. The organic phase is dried on sodium sulfate and filtered. After removal of the solvent, the residue is filtered with toluene through silica gel. Evaporation of the solvent and gradient chromatography (toluene/hexane (1:1)-toluene) of the residue on silica gel yield (5E,7E,22E),(1S,3R)-1,3-bis-(t-butyldimethylsilyloxy)-24-cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-24-one.

(5E,7E,22E),(1S,3R)-1,3-Bis-(t-butyldimethylsilyloxy)-24-cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-24-one in tetrahydrofuran and methanol are mixed with a 0.4 M methanol $CeCl_3 \cdot 7H_2O$ solution. Sodium borohydride is added by portions under nitrogen with ice cooling. The suspension is stirred with ice cooling and then put into ice/common salt solution. The aqueous phase is extracted with ethyl acetate, the organic phase is washed neutral with water and dried on sodium sulfate. Filtration and removal of the solvent yield oil. By chromatography on silica gel with ethyl acetate/hexane (1:9). The (5E,7E,22E),(1S,3R,24S)-1,3-bis-(t-butyldimethylsilyloxy)-24-cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-24-ol is obtained.

(5E,7E,22E),(1S,3R,24S)-1,3-Bis-(t-butyldimethylsilyloxy)-24-cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-24-ol is dissolved in toluene and after addition of anthracene and 1 drop of triethylamine it is radiated at room temperature with a high pressure mercury vapor lamp (Heraeus TQ 150) through Pyrex glass. The reaction mixture is concentrated by evaporation and the residue a mixture of (5Z,7E,22E),(1S,3R,24S)-1,3-bis-(t-butyldimethylsilyloxy)-24-cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-24-ol and anthracene - is directly reacted with tetrabutylammonium fluoride.

(5Z,7E,22E),(1S,3R,24S)-1,3-Bis-(t-butyldimethylsilyloxy)-24-cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-24-ol in tetrahydrofuran is kept with a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran under nitrogen. For working up, the cooled reaction mixture is poured into cold sodium bicarbonate solution and then extracted with ethyl acetate. After drying of the organic phase on sodium sulfate, filtration and evaporation of the solvent yields a resin-like residue. Chromatography on silica gel with ethyl acetate/hexane (2:1) yields (5Z,7E,22E),(1S,3R,24S)-24-cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1,3,24-triol.

References

Kircsch G. et al.; US Patent No. 5,665,716; Sept. 9, 1997; Assigned to Schering Aktiengesellscaft, Berlin, Germany

CALCITONIN

Therapeutic Function: Calcium regulator

Chemical Name: Complex hormone of molecular weight about 4,500

Common Name: Thyrocalcitonin

Structural Formula: H-L-Cys-L-Ser-L-Asp(NH_2)-L-Leu-L-Ser-L-Thr-L-Cys-L-Val-L-Leu-Gly-L-Lys-L-Leu-L-Ser-L-Glu(NH_2)-L-Glu-L-Leu-L-His-L-Lys-L-Leu-L-Glu(NH_2)-L-Thr-L-Tyr-L-Pro-L-Arg-L-Thr-L-Asp(NH2)-L-Thr-Gly-L-Ser-Gly-L-Thr-L-Pro-NH_2 (Disulfide bridge: 1-7)

Chemical Abstracts Registry No.: 9007-12-9

Trade Name	Manufacturer	Country	Year Introduced
Calcitar	Yamanouchi	Japan	1978
Cibacalcin	Ciba Geigy	Switz.	1978
Elcitonin	Toyo Jozo	Japan	1981
Calcimar	Armour	US	-
Calcitonin-Sandoz	Sandoz	Switz.	-
Calsyn	Armour	UK	-
Calsynar	Armour	UK	-
Miacalcic	Sandoz	Switz.	-
Staporos	Roussel	France	-

Raw Materials

C-cell-rich thyroid gland carcinoma

Manufacturing Process

The process for the manufacture of human calcitonin in pure form from C-cell rich medulla carcinoma of the thyroid gland or from C-cell metastasis material is one wherein medullar carcinoma of the thyroid gland or C-cell metastasis material, which has been defatted, for example with acetone or ether, and which may have been first purified with alcohol or with aqueous trichloroacetic acid, is extracted one or more times with a solvent system containing water and an alkanol having at most 5 carbon atoms, at a pH of from about 1 to 6, and the extracted product subjected to gel chromatography using aqueous formic acid as eluant. The calcitonin may be separated into its constituents by countercurrent distribution, for example by Craig distribution using a solvent system advantageously containing n-butanol and acetic acid.

References

Merck Index 1611
DFU 8 (2) 105 (1983)
PDR p. 1809
DOT 14 (4) 139 (1978)
I.N. p. 174
REM p. 979
Ciba-Geigy A.G.; British Patent 1,270,595; April 12, 1972

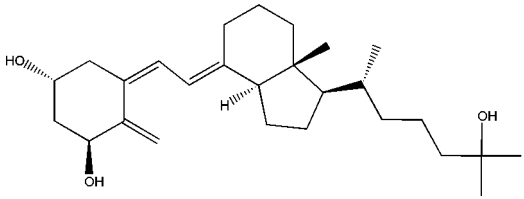
CALCITRIOL

Therapeutic Function: Calcium regulator

Chemical Name: 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol

Common Name: 1α,25-Dihydroxycholecalciferol; 1α,25-Dihydroxyvitamin D_3

Structural Formula:



Chemical Abstracts Registry No.: 32222-06-3

Trade Name	Manufacturer	Country	Year Introduced
Rocaltrol	Roche	US	1978
Rocaltrol	Roche	W. Germany	1980
Rocaltrol	Roche	UK	1980
Rocaltrol	Roche	Switz.	1980
Rocaltrol	Roche	Italy	1981

Raw Materials

1α,25-Diacetoxyprecholecalciferol
Potassium hydroxide

Manufacturing Process

1α,25-Dihydroxyprecholecalciferol: A solution of 1α,25-diacetoxyprecholecalciferol (0.712 g, 1.42 mmols), potassium hydroxide (2.0 g, 35.6 mmols) and methanol (40 ml) was stirred at room temperature under argon for 30 hours. The reaction mixture was concentrated under reduced pressure. Water (50 ml) was added to the residue and the mixture was extracted with methylene chloride (3 x 100 ml). The combined organic extracts were washed with saturated sodium chloride solution (3 x 50 ml), dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to give 0.619 g of 1alpha,25-dihydroxyprecholecalciferol as a thick oil.

1α,25-Dihydroxycholecalciferol: A solution of 1α,25-dihydroxyprecholecalciferol [0.619 g in dioxane (30 ml)] was heated under reflux for 30 minutes under an atmosphere of argon. The reaction mixture was concentrated under reduced

pressure and the residue was purified with a Waters Associates liquid chromatograph model 202 using a 8 foot * 3/8 inch Porasil A column and a 5:1 mixture of ethyl acetate-n-hexane as the eluent to give 0.474 g (80% yield based on 1α,25-diacetoxyprecholecalciferol) of pure 1α,25-dihydroxycholecalciferol. Recrystallization from methyl formate afforded 0.340 g of 1α,25-dihydroxcholecalciferol as colorless crystals, MP 113°-114°C.

References

Merck Index 1612
Kleeman and Engel p. 134
PDR p. 1498
OCDS Vol. 3 p. 103 (1984)
DOT 16 (5) 149 (1980)
I.N. p. 175
REM p. 1012
Uskokovic, M.R., Narwid, T.A., Iacobelli, J.A. and Baggiolini, E.; US Patent 3,993,675; November 23, 1976; assigned to Hoffmann-La Roche, Inc.

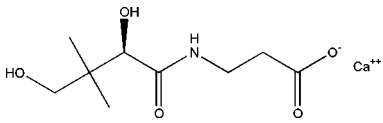
CALCIUM PANTOTHENATE

Therapeutic Function: Vitamin

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

Common Name: Calcium D-panthothenate; Calcium pantothenate

Structural Formula:



Chemical Abstracts Registry No.: 137-08-6

Trade Name	Manufacturer	Country	Year Introduced
Calcium D-Pantothenate	Arocor Holdings Inc.	-	-
Calcium pantothenate	Mallinckrodt Baker, Inc.	-	-
Calcium pantothenate	Epochem Co., Ltd.	-	-
Detro Calcium Pantothenate	Shandong Xinfa Parmaceutical Co., Ltd.	-	-
Calcium pantothenate	ICN	-	-
Calcium pantothenate	Natura Sanat BV	-	-

Trade Name	Manufacturer	Country	Year Introduced
Calcium pantothenate	Pharmeta BV	-	-
Calcipan T	Spencer Pharma	-	-
Calcipan	M/s. Fisons, Karachi	-	-
Calcipan	Tabros Pharma	-	-
Calpan	Pharm Chemical	-	-
Calpan	Metagenics, Inc.	-	-
Cal Pan	Fertrell Company products	-	-
Calpanate	Hangzhou Minsheng Bio-Tech Co., Ltd.	-	-
Kerato Biciron (N)	S and K PHARMA	-	-
Pantogen	Pantogen	-	-
Pantonate	Oasis	-	-
Eagle Pantonate	Eagle Pharmaceuticals	-	-
Pantothen	Linz	-	-
Pantothen-Streuli	Streuli	-	-

Raw Materials

Isobutyraldehyde
Sodium cyanide
β-Alanine
Brucine
Formaldehyde
Sodium methoxide
Diethylamine

Manufacturing Process

A mixture of 288 g (4 mols) of isobutyraldehyde, 288 g of methanol was cooled to 10°C and 170 g (2 mols) of 36.6% formalin containing 8.5 g (3% based on isobutyraldehyde) of sodium hydroxide was added dropwise over a 55 minute period to produce alpha,alpha-dimethyl-beta-hydroxy-propionaldehyde. The mixture was stirred for an additional 2 hours at 10-15°C and then contacted with acetic acid to neutralize the catalyst. The excess isobutyraldehyde and methanol were stripped off at a kettle temperature of 50°C at 25 mm. To the residual α,α-dimethyl-beta-hydroxypropionaldehyde a mixture of 260 ml of methanol and 2 g (0.75%) sodium cyanide was added and the solution cooled to 10°C before adding 59.4 g (2.2 mols) of hydrogen cyanide dropwise over a 35 minute period to produce α,γ-dihydroxy-β,β-dimethylbutyronitrile. The mixture was stirred at 10°C for one hour period and then contacted with acetic acid to neutralize the catalyst before stripping off the excess methanol to a kettle temperature of 45°C at 18 mm. The crude cyanohydrin was then hydrolysed by heating with 4 mols of concentrated hydrochloric acid at 80°C for 2 hours, then diluting with an equal volume of water and heating at 100°C for an additional 8 hours. The aqueous mixture was extracted continuously with ethylene dichloride. The solvent was

removed, and pantolactone (B. P. 131°C/19 mm, M.P. 61-77°C, 96.5% purity by saponification) was obtained by distillation in 71.5% yield based on formaldehyde and 55% efficiency based on isobutyraldehyde.

26 grams of racemic pantolactone (0.2 mol) and 1.1 grams of sodium methoxide (0.02 mol) contained in 30 ml of methanol, were added to 78.8 grams of 1-brucine (0.2 mol) contained in 156 ml of methanol. The resulting mixture was refluxed for 1.5 hours and allowed to stand at room temperature overnight. After centrifuging, washing with methanol and drying, 65.4 grams of D-(-)-pantolactone 1-brucine (62% of theory based upon all of the racemic pantolactone) melting at 203° to 206°C were obtained. Upon chilling the mother liquor, 13.46 grams of additional complex melting at 175° to 177°C were obtained.

D-(-)-Pantolactone was obtained from the complex in the following manner. The 65.4 grams of complex obtained above were treated with 65 ml of chloroform and 5.35 grams of sodium hydroxide contained in 35 ml of water for one hour at room temperature. The aqueous layer was extracted 6 times with 20 ml portions of chloroform in order to remove the brucine. The sodium pantoate contained in the aqueous layer was relactonized by treatment with 11 ml of concentrated hydrochloric acid. Extraction of the crude D-(-)-pantolactone yielded 15.29 grams. This material was then recrystallized from 7 ml of methyl isobutyl ketone and 7 ml hexane thereby yielding 9.77 grams of D-(-)-pantolactone (37% of theory). The α_{D25} was -44.8°.

Into a vessel equipped with an agitator and reflux condenser are placed approximately 52 parts by weight of α-hydroxy-β,β-di-methyl-γ-butyrolactone, approximately 36 parts by weight of β-alanine, about 40 parts by weight of diethylamine and about 100 parts by weight of anhydrous methanol. The mixture is stirred and refluxed for about 12 hours until the reaction is complete as evidenced by the dissolution of the β-alanine. To this resulting mass is gradually added 8 parts by weight of calcium metal nodules or pellets and refluxing continued until the metal is dissolved. The diethylamine and alcohol are distilled off until the residue becomes viscous. The viscous residue is dried under vacuum at 100°C. The solid residue recovered, as biologically assayed, indicated a 91% yield of calcium pantothenate.

References

Lynn J.W.; US Patent No. 2,863,878; Dec. 9, 1958; Assigned to Unione Carbide Corporation, a corporation of New York

Bckmann C.O. et al.; US Patent No. 2,967,869; Jan. 10, 1961; Assigned to Nopco Chemical Company Harrison, N.J., a corporation of New Jersey

Lekberg R.D. et al.; US Patent No. 2,809,213; Oct. 8, 1957; Assigned to Chemik Laboratorics Inc., a corporation of Illinois

CALFACTANT

Therapeutic Function: Lung surfactant

Chemical Name: Calfactant

Common Name: Infasurf

Structural Formula: Mixture of phospholipids

Chemical Abstracts Registry No.: 183325-78-2

Trade Name	Manufacturer	Country	Year Introduced
Infasurf	Forest Pharmaceuticals, Inc.	USA	-

Raw Materials

Calf lungs
Aqueous solution NaCl (0.15 M)

Manufacturing Process

Calfactant is purified surfactant phospholipids extracted from calf lungs and purified by gel permeation chromatography. Calfactant include phospholipids, neutral lipides, and hydrophobic surfactant - three biophysically active proteins SP-A, SP-B, and SP-C. It contained no preservatives.

References

Egan E.A. et al.; US Patent No. 6,458,759; Oct. 1, 2002; Assigned: Ony, Inc. (Amherst, NY)
http://www.fda.gov/cder/foi/label/1998/20521lbl.pdf
http://www.infasurf.com/Infasurf_pi.pdf

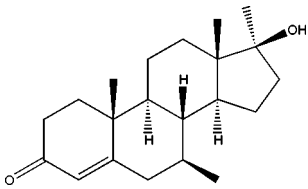
CALUSTERONE

Therapeutic Function: Antineoplastic

Chemical Name: 17β-Hydroxy-7β,17-dimethylandrost-4-en-3-one

Common Name: 7,17-Dimethyltestosterone

Structural Formula:



Chemical Abstracts Registry No.: 17021-26-0

Trade Name	Manufacturer	Country	Year Introduced
Methosarb	Upjohn	US	1973
Riedemil	Upjohn	US	-

Raw Materials

6-Dehydro-17-methyltestosterone
Methyl magnesium bromide

Manufacturing Process

As described in US Patent 3,029,263, one possibility is a multistep synthesis starting from 3β,17β-dihydroxy-17α-methyl-5-androstene.

Alternatively, as described in US Patent 3,341,557, 6-dehydro-17-methyltestosterone may be used as the starting material. A mixture of 0.4 g of cuprous chloride, 20 ml of 4M methylmagnesium bromide in ether and 60 ml of redistilled tetrahydrofuran was stirred and cooled in an ice bath during the addition of a mixture of 2.0 g of 6-dehydro-17-methyltestosterone, 60 ml of redistilled tetrahydrofuran and 0.2 g of cuprous chloride. The ice bath was removed and stirring was continued for four hours. Ice and water were then carefully added, the solution acidified with 3 N hydrochloric acid and extracted several times with ether. The combined ether extracts were washed with a brine-sodium carbonate solution, brine and then dried over anhydrous magnesium sulfate, filtered and then poured over a 75-g column of magnesium silicate (Florisil) packed wet with hexanes (Skellysolve B). The column was eluted with 250 ml of hexanes, 0.5 liter of 2% acetone, two liters of 4% acetone and 3.5 liters of 6% acetone in hexanes.

Four 250-ml fractions were collected followed by 150 ml fractions. The residues from fractions 8 to 16 were combined and rechromatographed over a 125-g column of magnesium silicate. The solumn was eluted with 6% acetone in hexanes which was collected in 150 ml portions. Fractions 18 to 29 were combined and dissolved in acetone, decolorized with charcoal, and recrystallized from acetone. One gram of a crystalline mixture of the 7epimers of 7,17-dimethyltestosterone was obtained melting at 120° to 140°C.

References

Merck Index 1701
Kleeman and Engel p. 138
OCDS Vol. 2 p. 154 (1980)
DOT 10 (3) 85 (1974)
I.N.p. 177
REM p. 1001
Campbell, J.A. and Babcock, J.C.; US, Patents 3,029,263; April 10, 1962 and 3,341,557; September 12, 1967; both assigned to The Upjohn Company

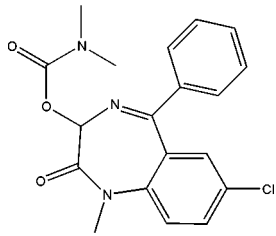
CAMAZEPAM

Therapeutic Function: Anxiolytic

Chemical Name: 3-N,N-Dimethylcarbamoyloxy-1-methyl-7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 36104-80-0

Trade Name	Manufacturer	Country	Year Introduced
Albego	Simes	Italy	1977
Albego	Boehringer Ingelheim	W. Germany	1978
Albego	Inpharzam	Switz.	1978
Albego	Farmasimes	Spain	-
Limpidon	Crinos	Italy	-

Raw Materials

7-Chloro-5-phenyl-1-methyl-3-hydroxy-1,3-dihydro-2H-1,4-benzodiazepine-2-one
Phenyl chlorocarbonate
Dimethylamine

Manufacturing Process

A suspension of 100 g of 7-chloro-5-phenyl-1-methyl-3-hydroxy-1,3-dihydro-2H-1,4-benzodiazepin-2-one in 700 ml of anhydrous pyridine, kept stirred between 0°C and +5°C, is slowly treated, during 20 to 30 minutes, with 54.5 ml phenyl chlorocarbonate. The temperature is gradually allowed to rise to 20°-25°C and stirring is maintained at this temperature during 24 hours.

2 l of water are then slowly added (during about 30 minutes) and stirring is maintained during 1 hour. The precipitate which has been formed is collected on a filter, washed thoroughly with water, dried in a vacuo at 50°C and recrystallized by dissolving it at 60°C in 1,400 ml dioxane, the solution thus

obtained being evaporated under reduced pressures to one-half of its volume, and 1,700 ml of ligroin (BP 80°C to 120°C) being added thereto.

7-chloro-5-phenyl-1-methyl-3-phenoxycarbonyloxy-1,3-dihydro-2H-1,4-benzodiazepin-2-one is thus obtained, with a melting point of 162°C to 164°C.

A suspension of 45 g 3-phenoxycarbonyloxy-1-methyl-7-chloro-5-phenyl-1,3-dihydro-2H-1,4benzodiazepin-2-one in 450 ml methanol is treated with stirring, with 43 ml of a solution of dimethylamine in methanol (containing 31 g dimethylamine in 100 ml). Stirring is maintained at 20°C to 25°C during 5 hours. The reaction mixture is filtered, and the filtrate is diluted with 450 ml water. The precipitate thus formed, is 3-(N,N-dimethylcarbamoyloxy)-1-methyl-7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one, which is collected on a filter, dried and recrystallized from ethyl acetate, and has a melting point of 173°C to 174°C.

References

Merck Index 1703
DFU 1 (10) 458 (1976)
Kleeman and Engel p. 139
DOT 11 (5) 182 (1975); 13 (12) 521 (1977)
I.N. p. 177
Ferrari, G. and Casagrande, C.; US Patent 3,799,920; March 26, 1974; assigned to Siphar SA

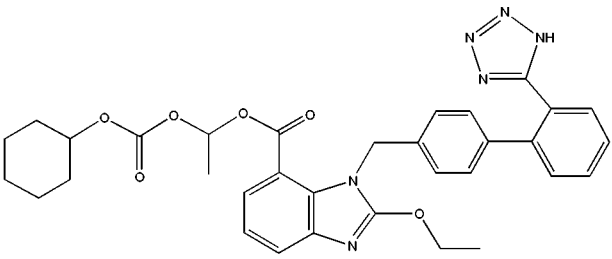
CANDESARTAN CILEXETIL

Therapeutic Function: Antihypertensive

Chemical Name: 1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-((2'-(1H-tetrazol-5-yl)(1,1'-biphenyl)-4-yl)methyl)-, 1-(((cyclohexyloxy)carbonyl)oxy)ethyl ester

Common Name: Candesartan cilexetil

Structural Formula:



Chemical Abstracts Registry No.: 145040-37-5

Trade Name	Manufacturer	Country	Year Introduced
Amias	Microlab	-	-
Amias	AstraZeneca	-	-
Amias	Takeda	USA	-
Atacand	Astra Merck, Inc.	-	-
Atacand	AstraZeneca	-	-

Raw Materials

3-Nitrophthalic acid
Sulfuric acid
Potassium carbonate
Sodium azide
Sodium hydroxide
Trimethyltin azide
Trityl chloride
4-(2-Cyanophenyl)benzyl bromide
Cyclohexyl 1-iodoethyl carbonate
Stannous dichloride dihydrate

Manufacturing Process

3-Nitrophthalic acid (35 g) in 300 ml ethanol and 20 ml concentrated sulfuric acid was heated under reflux for 24 hours. The solvent was evaporated in vacuo and the residue was poured into 700 ml cold water. The mixture was extracted with ethyl acetate. The aqueous layer was made acidic with hydrochloric acid and the mixture was extracted with methylene chloride. After evaporation of methylene chloride was obtained 29 g (74%) ethyl 2-carboxy-3-nitrobenzoate.

A mixture of 23.9 g ethyl 2-carboxy-3-nitrobenzoate and 12 ml thionyl chloride in 150 ml benzene were heated under reflux for 3 hours. The reaction mixture was concentrated to dryness. The resultant acid chloride (26 g) was dissolved in 20 ml. The solution was added to a mixture of sodium azide (9.75 g) in 20 ml DMF with stirring. The reaction mixture was poured into 200 ml a mixture of ether-hexane (3:1). The organic layer was washed with water and evaporated. The residue was dissolved in 200 ml tert-butanol and the solution was heated gradually with stirring, followed by heating under reflux for 2 hours. The reaction mixture was concentrated to give an oily ethyl 2-butoxycarbonylamino-3-nitrobenzoate (30 g).

To a solution of ethyl 2-butoxycarbonylamino-3-nitrobenzoate (29 g) in 50 ml THF was added, while stirring under ice-cooling, sodium hydride (60% dispersion in mineral oil, 2.8 g). After 20 min to the mixture were added 18 g 4-(2-cyanophenyl)benzyl bromide and 0.36 g potassium iodide. After heating for 10 hours under reflux the solvent was evaporated and the residue was partitioned between 250 ml water and 200 ml ether. The organic layer was washed with water, dried and concentrated to give yellow syrup. The syrup was dissolved in a mixture of 60 ml trifluoroacetic acid and 40 ml methylene chloride and the solution was stirred for 2 hour at room temperature. The reaction mixture was concentrated to dryness and to residue was added 200 ml ethyl ether to give crystals of ethyl 2-[(2'-cyanobiphenyl-4-yl)methylamino]nitrobenzoate (22.1 g, 85%), M.P. 118-119°C.

To a solution of 10.4 g ethyl 2-[(2'-cyanobiphenyl-4-yl)methylamino] nitrobenzoate in 50 ml ethanol was added 28.1 g stannous dichloride dihydrate and the mixture was stirred for 2 hours at 80°C. The solvent was

evaporated. To the ice-cooling mixture of the residue in 300 ml ethyl acetate was added dropwise 2 N NaOH (500 ml). The aqueous layer was extracted with ethyl acetate (200 ml x 2). The organic layers were combined and evaporated to dryness. Product was purified by column chromatography on silica gel. Recrystallization from ethyl acetate-hexane gave colorless crystals ethyl-3-amino-2-[[(2'-cyanobiphenyl-4-yl)methyl]amino]benzoate (7.3 g, 79%), M.P. 104-105°C.

Acetic acid (0.2 g) was added to a solution of ethyl-3-amino-2-[[(2'-cyanobiphenyl-4-yl)methyl]amino]benzoate (1 g) in ethylorthocarbonate (5 ml). The mixture was stirred at 80°C for 1 hours. The reaction mixture was concentrated. The solution was washed with an aqueous solution of $NaHCO_3$ and water. The solvent was evaporeted to give crystals. Recrystallization from ethyl acetate-benzene afforded colorless crystals 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-ethoxybenzimidazole-7-carboxylate (0.79 g, 69%), M.P. 131-132°C.

A mixture of 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-ethoxybenzimidazole-7-carboxylate (0.7 g) and trimethyltin azide (0.7 g) in toluene (15 ml) was heated under reflux for 4 days. The reaction mixture was concentrated, and to the residue were added methanol (20 ml) and 1 N HCl (10 ml). The solution was stirred at room temperature for 30 minutes and adjusted to pH 3-4 with 1 N NaOH. After removal of the solvent, the residue was partitioned between chloroform and water. The organic layer was evaporated to dryness to dive a syrup. The syrup was purified by column chromatography on silica gel to give crystals. Recrystallization from ethyl acetate-benzene afforded colorless crystals ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]-methyl]benzimidazole-7-carboxylate (0.35 g, 45%), M.P. 158-159°C.

Ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]-methyl]benzimidazole-7-carboxylate (0.24 g) was stirred with 1 N NaOH (1.5 ml) in ethanol (4 ml) for 1 hours at 80°C. The reaction mixture was concentrated, and the concentrate was exrtacted with water and ethyl acetate. The aqueous layer was adjusted to pH 3-4 with 1 N HCl to give crystals. Recrystallization from ethyl acetate-benzene afforded colorless crystals of 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]-methyl]benzimidazole-7-carboxylic acid (0.15 g, 67%), M.P. 183-185°C.

To a solution of 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]-methyl]benzimidazole-7-carboxylic acid (2.07 g) in methylene chloride (10 ml) were added trityl chloride (1.59 g) and triethylamine (0.8 ml). The mixture was stirred at room temperature for 1 hour. The mixture was washed with water and concentrated to dryness. The residue was purified by column chromatography on silica gel to give crystals. Recrystallization from ethyl acetate-benzene afforded colorless crystals 2-ethoxy-1-[[2'-(N-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]-methyl]benzimidazole-7-carboxylic acid (2.12 g, 66%), M.P. 168-170°C.

To a solution 2-ethoxy-1-[[2'-(N-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]-methyl]benzimidazole-7-carboxylic acid (0.5 g) in DMF (5 ml) were added potassium carbonate (0.12 g) and cyclohexyl 1-iodoethyl carbonate (0.26 g). The mixture was stirred at room temperature for 1 hour. To the mixture was added water and the mixture was extracted with ethyl acetate. The organic layer was washed with water and dried. After removal of the solvent, the

residue was dissolved in methanol (10 ml) and to solution was added 1 N HCl (2 ml). The mixture was stirred at room temperature for 1 hour. After removal of the solvent, the residue was purified by column chromatography on silica gel to give colorless powder (0.21 g), M.P. 103-106°C. The mixture was stirred for 3 hours at room temperature. To the powder (1 g) obtained as above was added ethanol (6 ml). The mixture was stirred for 3 hours at room temperature and allowed to stand under ice-cooling. The mixture was then stirred for 1 hour at temperature not higher than 10°C. Resultant crystals were collected and washed with cold ethanol. The crystals were dried at 25°C for 9 hours under reduced pressure, then at 35°C for further 18 hours to obtain white powdery crystal 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-benzimidazole-7-carboxylate (0.94 g, M.P. 158-166°C).

References

Naka T., Nishikawa K., Kato T.; US Patent No. 5,196,444; 03.23.1993; Assigned to Takeda Chemical Industries, Ltd.

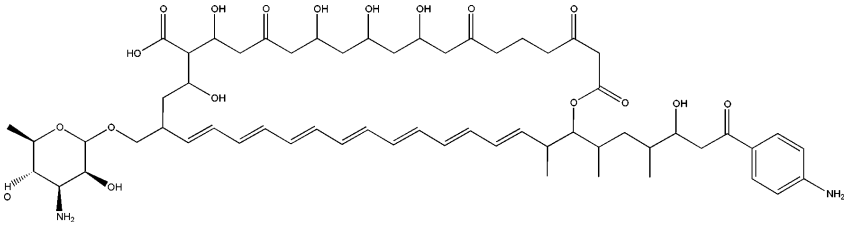
CANDICIDIN

Therapeutic Function: Topical antifungal

Chemical Name: Heptaene macrolide antibiotic

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 1403-17-4

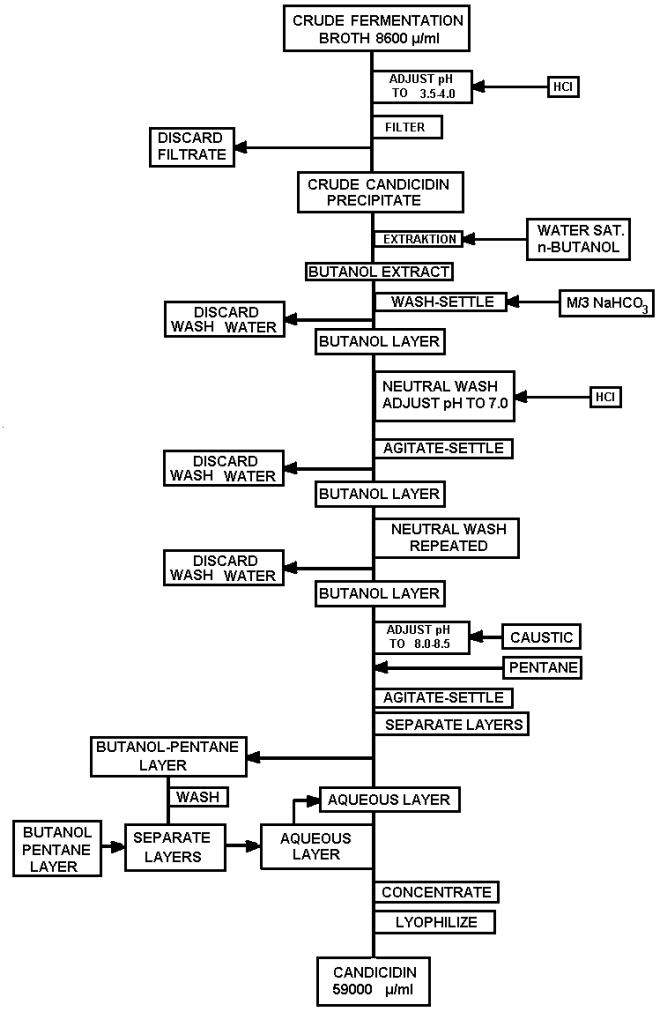
Trade Name	Manufacturer	Country	Year Introduced
Candeptin	Schmidt	US	1964
Candimon	Averst	US	-
Prostatin	Schmidt	US	-
Vanobid	Merrell Dow	US	-

Raw Materials

Yeast-glucose medium
Streptomyces Griseus No. 3570 bacterium

Manufacturing Process

Hubert Lechevalier et al were the first to describe "Candicidin, a New Antifungal Antibiotic," in Mycologia XLV, No. 2, 155-171, March-April 1953. They produced candicidin by growing a culture of the organism streptomyces griseus No. 3570 on a yeast-glucose medium, isolating a "crude candicidin" from the resulting broth and purifying it. An improved extraction and purification method is described in US Patent 2,872,373 and is shown in the flow diagram below.



Another extraction and separation process is described in US Patent 2,992,162.

References

I.N. p. 178
REM p. 1226
Siminoff, P.; US Patent 2,872,373; February 3, 1959; assigned to S.B. Penick and Company, Inc.
Waksman, S.A. and Lechevalier, H.A.; US Patent 2,992,162; July 11, 1961; assigned to Rutgers Research and Educational Foundation

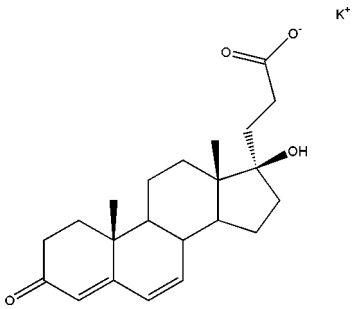
CANRENOATE POTASSIUM

Therapeutic Function: Aldosterone antagonist, Diuretic

Chemical Name: 17-Hydroxy-3-oxo-17α-pregna-4,6-diene-21 carboxylic acid potassium salt

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 2181-04-6; 976-71-6 (Canrenone base)

Trade Name	Manufacturer	Country	Year Introduced
Spiroctan	Boehringer Mannheim	Switz.	1968
Soldactone	Diethelm	Switz.	1968
Osyrol	Hoechst	W. Germany	1968
Soludactone	Searle	France	1971
Venactone	Lepetit	Italy	1978
Spiroctan-M	MCP Pharm.	UK	1981
Soldacton	Dainippon	Japan	1981

Trade Name	Manufacturer	Country	Year Introduced
Aldactone	Boehringer Mannheim	W. Germany	-
Aldatense	Searle	France	-
Aldatense	SPA	Italy	-
Phanurane	Specia	France	-
Sincomen	Schering	W. Germany	-
Soldactone	Searle	US	-

Raw Materials

17α-Carboxyethyl-17β-hydroxyandrost 4-en-3-one lactone
Chloranil

Manufacturing Process

The lactone is prepared as follows: A solution of 5 parts of 17α-carboxyethyl-17β-hydroxyandrost-4-en-3-one lactone and 5 parts of chloranil in 400 parts of xylene containing a trace of p-toluenesulfonic acid is heated at the boiling point of the solvent under reflux overnight. The solution is then cooled and filtered through approximately 200 parts of silica gel. The gel is successively washed with 5%, 10%, and 15% ethyl acetate-benzene solutions, and the washings comprising 15% ethyl acetate are thereupon purified by chromatography on a further quantity of silica gel, using benzene and ethyl acetate as developing solvents. From the 15% ethyl acetate eluate there is obtained pure 17α-carboxyethyl-17β-hydroxyandrost-4,6-dien-3-one lactone, melting at 148° to 151°C. The product solidifies above this melting point and melts again at 165°C.

References

Merck Index 1726
Kleeman and Engel p. 507
OCDS Vol. 2 p. 174 (1980)
DOT 12 (2)45 (1976)
I.N. p. 178
Cella, J.A.; US Patent 2,900,383; August 18, 1959; assigned to G.D. Searle and Co.

CAPECITABINE

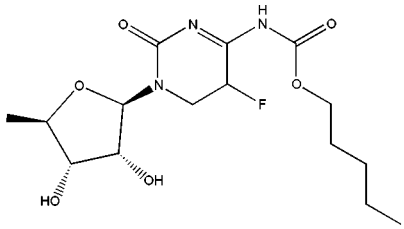
Therapeutic Function: Antitumor

Chemical Name: 5'-Deoxy-5-fluoro-N4-(4-(n-pentyloxy)carbonyl)cytidine

Common Name: Capecitabine

Chemical Abstracts Registry No.: 154361-50-9; 158798-73-3

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Xeloda	Hoffmann - La Roche Inc.	USA	-

Raw Materials

2',3'-Bis-O-(tert-butyldimethylsilyl)-5'-deoxy-5-fluorocytidine
n-Pentylchloroformate
Tetrabutylammonium fluoride

Manufacturing Process

5-Deoxy-5-fluoro-N^4-((n-pentyloxy)carbonyl)cytidine may be prepared according to US Patent No. 6,114,520.

From 2',3'-bis-O-(tert-butyldimethylsilyl)-5'-deoxy-5-fluorocytidine and n-pentylchloroformate in dichloromethane and pyridine may be obtained 2',3'-bis-O-(tert-butyldimethylsilyl)-5'-deoxy-5-fluoro-N^4-((pentyloxy)carbonyl) cytidine.From 2',3'-bis-O-(tert-butyldimethylsilyl)-5'-deoxy-5-fluoro-N^4-((pentyloxy)carbonyl)cytidineand tetrabutylammonium fluoride in tetrahydrofuran at room temperature for 2 hours may be prepared the product which by hydrolyses may be converted to 5-deoxy-5-fluoro-N^4-((pentyloxy)carbonyl)cytidine. Purification of the product may be carried out by silica gel chromatography (using dichloromethane:methanol = 20:1 as an eluent).

References

Hattory K. et al.; US Patent No. 6,114,520; Sep. 5, 2000; Assigned to Hoffmann-La, RocHe Inc.
Fujii M. et al.; US Patent No. 4,966,891, Oct. 30, 1990; Assigned to Hoffmann-La, RocHe Inc.

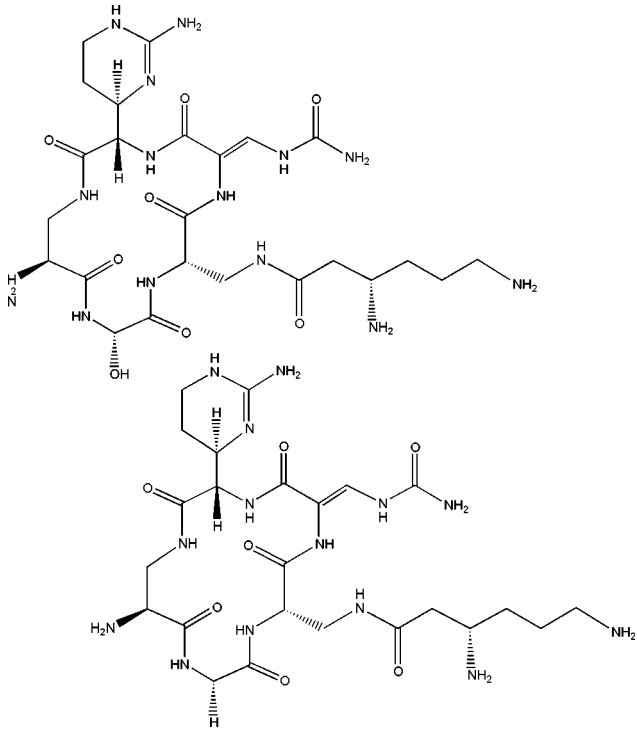
CAPREOMYCIN

Therapeutic Function: Antibacterial, Antitubercular

Chemical Name: Mixture of Capreomycin I A with Capreomycin I B and small quantities of Capreomycin II A and II B

Common Name: Capreomicina, Capreomycin, Capromycin

Structural Formula:



Chemical Abstracts Registry No.: 11003-38-6

Trade Name	Manufacturer	Country	Year Introduced
Capastat	Dista	-	-
Capastat	Eli Lilly	-	-

Raw Materials

Culture of NRRL 2773
Vegetative culture medium (Soluble starch, Peptones, Beef extract, Sodium chloride, Yeast extract, water)

Manufacturing Process

Preparation of Capreomycin

A culture of NRRL 2773 is produced by growing the organism on a nutrient agar slant having the following composition: Tomato paste 20 g, Pre-cooked oatmeal 20 g, Agar 15 g and tap water up to 1 L. The slant is inoculated for 10 days at about 30°C. The culture growth on the slant is covered with 6 ml of nutrient broth, and the slant is scraped gently to remove the organisms to provide an aqueous suspension.

Employing aseptic techniques, the inocolum obtained is used to inoculate a 2 L Erlenmeyer flask containing a 500 ml portion of a sterilized vegetative culture medium having the following composition: Soluble starch 10 g, Peptones 5 g, Beef extract 5 g, Sodium chloride 5 g, Yeast extract 2.5 g and tap water 1100 ml.

The incubation is carried out at 28°C for 48 hours; during which time the flasks are shaken at the rate of 250 cycles per minute on a rotary shaker having a 1-inch stroke. To produce a larger quantity of vegetative inocolum, 500 ml of the vegetative inocolum is added aseptically to a stainless steel 350-gallon fermentation tank containing 250 gallons of sterile medium having following composition (weight/volume): Glucose 1.5%, Yeast 1.5%, Antifoam ("Polyglycol No 2000" sold by Dow Chemical Co) 0.02%.

The inoculum is allowed to grow for 22 hours at 30°C. Throughout the growth period, the medium is aerated with sterile air at the rate of 17 cubic feet per minute and is agitated with 16-inch impeller rotating at 160 revolution per minute.

To a 1700-gallon stainless steel fermentor are added 1100 gallons of a medium having following composition (weight/volume): Glucose 2.5%, Molasses 1.0%, Peptones 4.0%, Calcium carbonate 0.2%, Hydrolyzed casein 0.6%, Antifoam ("Polyglycol No 2000" sold by Dow Chemical Co) 0.005%.

The medium after sterilization is inoculated with 100 gallons of the inoculum grown in the fermentation tank. The fermentation is carried on at 30°C for 5 days. The foam is controlled by the addition, when needed, of "Larex No 1" (an antifoam product sold by Swift and Co.). Throughout the fermentation, the medium is aerated with sterile air at the rate of 17 cubic feet per minute and is agitated with 22-inch impeller rotating at 140 revolution per minute. At the end of the fermentation, 240 pounds of "Dicalite 476" (a perlite filler product sold by Great Lakes Carbon Corporation) are added 1000 gallons or the antibiotic broth, and the mixture is stirred and filtered. The filter cake is washed with tap water and the filtrates are combined to provide a total volume of 1000 gallons. To 500 gallons of the combined liquids are added 132 pounds of "Darco G-60". The mixture is filtered, and the filtrate is discarded. The carbon filter cake is washed with 200 L of tap water, the wash water being discarded.

The washed carbon cake on which the capreomycin is adsorbed is washed with 200 L of 0.05 N aqueous hydrochloric acid. The acid wash is discarded. The washed carbon cake is eluted during a one-hour period with 400 L of an aqueous acetone containing 1.65 L of 11.7 N hydrochloric acid and 80 L of acetone. The filter cake is further eluted by washing the cake with 200 L of an aqueous acetone containing 825 ml of 11.7 N hydrochloric acid and 40 L of acetone during a 15-minute period. The combined eluates, having a total volume 575 L, are concentrated in vacuo to 52.5 L. The concentrate is added

with stirring to 525 L of acetone and the acetone mixture is permitted to stand overnight at room temperature, during which time an oily precipitate of capreomycin separates. The supernatant is decanted and discarded, and the oily precipitate which remains is dissolved in 20 L of distilled water. The aqueous solution is filtered. The filtrate is added to 240 L of methanol. The methanolic solution is acidified by the addition of 1 L of 10 N sulfuric acid, whereupon the precipitation of the capreomycin disulfate commences. The mixture is permitted to stand overnight. The supernant is removed by decantation and filtering. The precipitate is washed with 10 L of methanol, yield Capreomycin 2510 g.

References

Herr E.B. et al.; US Patent No. 3,143,468; 04.08.1964; Assigned to Eli Lilly and Company; W.S.
Marsh et al.; US Patent No. 2,633,445; 31.03.1953; Assigned to Ciba Pharm. Products

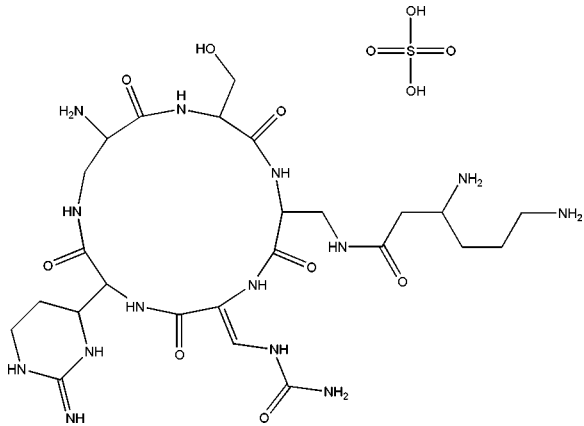
CAPREOMYCIN SULFATE

Therapeutic Function: Antitubercular

Chemical Name: Cyclic polypeptide antibiotic

Common Name: Caprolin

Structural Formula:



Chemical Abstracts Registry No.: 1405-37-4

Trade Name	Manufacturer	Country	Year Introduced
Capastat	Lilly	UK	1966

Trade Name	Manufacturer	Country	Year Introduced
Capastat	Serum Impfinst.	Switz.	1967
Ogostac	Lilly	W. Germany	1967
Capastat	Lilly	US	1971
Capastat	Lilly	Italy	1973
Capastat	Shionogi	Japan	-

Raw Materials

Glucose
Culture of NRRL 2773

Manufacturing Process

A culture of NRRL 2773 is produced by growing the organism on a nutrient agar slant having the following composition:

Oatmeal-Tomato Paste Agar

	Grams
Tomato paste	20
Precooked oatmeal	20
Agar	15

Tap water, added to make a final volume of 1 liter.

The slant is inoculated with spores of NRRL 2773 and is incubated for 10 days at about 30°C. The culture growth on the slant is covered with 6 ml of nutrient broth, and the slant is scraped gently to remove the organisms to provide an aqueous suspension. Employing aseptic techniques, the inoculum obtained from one 1-inch agar slant is used to inoculate a 2-liter Erlenmeyer flask containing a 500-ml portion of a sterilized vegetative culture medium having the following composition: soluble starch, 10 g; peptones, 5 g; beef extract, 5 g; sodium chloride, 5 g; yeast extract, 2.5 g; and tap water, 1,100 ml. The incubation is carried on at 28°C for 48 hours with shaking at 250 cycles per minute on a rotary shaker having a 1-inch stroke.

To produce a larger quantity of vegetative inoculum, 500 ml of the vegetative inoculum is added aseptically to a stainless steel 350-gallon fermentation tank containing 250 gallons of sterile medium having the following composition (weight/volume): glucose, 1.5%; yeast, 1.5%; and antifoam (Polyglycol No. 2000, Dow Chemical Co.), 0.02%. The inoculum is allowed to grow for about 22 hours at a temperature of 30°C. Throughout the growth period, the medium is aerated with sterile air at the rate of 17 cfm and is agitated with two 16-inch impellers rotating at 160 revolutions per minute. To a 1,700-gallon stainless steel fermentor are added 1,100 gallons of a medium having the following composition (weight/volume):

Peptone No. 159 Medium

	Percent
Glucose	2.5
Molasses	1.0
Peptones	4.0
Calcium carbonate	0.2
Hydrolyzed casein	0.6

Antifoam (Polyglycol No. 2000, Dow Chemical Co.) 0.005

The medium after sterilization is inoculated with 100 gallons of the inoculum grown in the fermentation tank. The fermentation is carried on at 30°C for about five days. The foam is controlled by the addition, when needed, of Larex No. 1 (an antifoam product, Swift and Co.). Throughout the fermentation, the medium is aerated by the addition of sterile air at the rate of 96 cfm and is agitated with two 22-inch impellers operated at 140 revolutions per minute. At the end of the fermentation, 240 lb of Dicalite 476 (a perlite filter product, Great Lakes Carbon Corporation) are added to 1,000 gallons of the antibiotic broth, and the mixture is stirred and filtered. The filter cake is washed with tap water and the wash water and the filtrate are combined to provide a total volume of 1,000 gallons.

To 500 gallons of the combined liquids are added 132 lb of Darco G-60. The mixture is stirred thoroughly and filtered, and the filtrate is discarded, The carbon filter cake is washed with 200 liters of tap water, the wash water being discarded. The washed carbon cake on which the capreomycin is adsorbed is further washed with 200 liters of 0.05 N aqueous hydrochloric acid. The acid wash is discarded. The washed carbon cake is eluted during a one-hour period with 400 liters of an aqueous acetone mixture containing 1.65 liters of 11.7 N hydrochloric acid and 80 liters of acetone. The filter cake is further eluted by washing the cake with 200 liters of an aqueous acetone mixture containing 825 ml of 11.7 N hydrochloric acid and 40 liters of acetone during a 15-minute period. The combined eluates, having a total volume of 575 liters, are concentrated in vacuo to 52.5 liters.

The concentrate is added with stirring to 525 liters of acetone and the acetone mixture is permitted to stand overnight at room temperature, during which time an oily precipitate of capreomycin separates. The supernatant is decanted and discarded, and the oily precipitate which remains is dissolved in 20 liters of distilled water. The aqueous solution is concentrated in vacuo to 12 liters to remove any residual acetone. The aqueous concentrate containing capreomycin is filtered to remove a small amount of a precipitate, which is discarded.

The filtrate containing the capreomycin is added to 240 liters of methanol with stirring. The methanolic solution of capreomycin is acidified by the addition of one liter of 10 N sulfuric acid, whereupon the precipitation of the sulfuric acid addition salt of capreomycin commences. The mixture is permitted to stand overnight for more complete precipitation. The supernatant is removed by decanting and filtering. The precipitate, consisting of the capreomycin disulfate, is washed with 10 liters of methanol and is dried in vacuo. Yield: 2,510 grams.

References

Merck Index 1732
Kleeman and Engel p. 141
PDR p. 1039
DOT 1 (1) 33 (1965)
I.N. p. 179
REM p. 1202
Herr, E.B., Jr., Hamill, R.L. and McGuire, J.M.; US Patent 3,143,468; August 4, 1964; assigned to Eli Lilly and Company

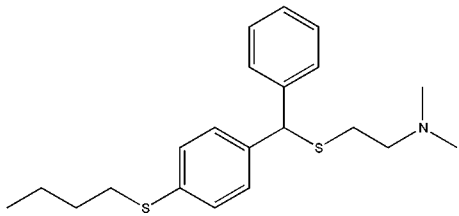
CAPTODIAMINE

Therapeutic Function: Sedative

Chemical Name: 2-[[[4-(Butylthio)phenyl]phenylmethyl]thio]-N,N-dimethylethanamine

Common Name: Captodiam; Captodramine

Structural Formula:



Chemical Abstracts Registry No.: 486-17-9; 904-04-1 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Covatine	Bailly	France	1958
Suvren	Ayerst	US	1958
Covatix	Lundbeck	Denmark	-

Raw Materials

Thiourea
Sodium hydroxide
Diethylaminoethyl chloride
4-Butylmercaptobenzhydryl chloride
Sodium

Manufacturing Process

p-Butylmercaptobenzhydryl chloride was boiled with thiourea in alcohol

thereby yielding p-butylmercaptobenzhydrylisothiouronium chloride which was then subjected to hydrolysis with dilute aqueous sodium hydroxide solution whereupon p-butylmercaptobenzhydryl mercaptan was formed.

p-Butylmercaptobenzhydryl mercaptan (28.5 g) was added to a solution of sodium (2.3 g) in absolute alcohol (75 ml), followed by the addition of a solution of diethylaminoethyl chloride (13.6 g) in toluene (50 ml). The mixture was boiled on a steam bath for 3 hours and the sodium chloride which separated out was removed by filtration. The filtrate was concentrated to one-third of its volume and dissolved in ether. The ether solution was shaken with 2N hydrochloric acid (100 ml), and the resulting middle oily layer was separated, dissolved in water and the resulting aqueous solution was washed with ether, then treated with aqueous sodium hydroxide solution to precipitate an oil. The latter was dissolved in ether, dried with anhydrous potassium carbonate, filtered and then treated with anhydrous hydrogen chloride whereupon the desired p-butylmercaptobenzhydryl 2-diethylaminoethyl sulfide hydrochloride precipitated as a white, crystalline substance which was filtered and dried in a desiccator. The melting point of the product was 124°C.

References

Merck Index 1746
Kleeman and Engel p. 141
OCDS Vol. 1 p. 44 (1977)
I.N. p. 179
Hubner, O.F. and Petersen, P.V.; US Patent 2,830,088; April 8, 1958

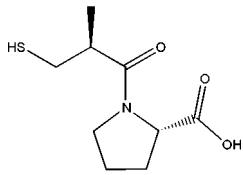
CAPTOPRIL

Therapeutic Function: Antihypertensive

Chemical Name: 1-(3-Mercapto-2-D-methylpropanoyl)-L-proline

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 62571-86-2

Trade Name	Manufacturer	Country	Year Introduced
Lopirin	Von Heyden	W. Germany	1980

Trade Name	Manufacturer	Country	Year Introduced
Capoten	Squibb	US	1981
Lopirin	Squibb	Switz.	1981
Capoten	Squibb	UK	1981
Capoten	Squibb	Italy	1981
Lopril	Squibb	France	1982
Captoril	Sankyo	Japan	1983
Dilabar	Vita	Spain	-
Isopresol	Elea	Argentina	-

Raw Materials

L-Proline
Benzyloxycarbonyl chloride
Ammonia
Trifluoroacetic acid
Isobutylene
Hydrogen
3-Acetylthiomethyl propanoic acid

Manufacturing Process

The first step is the manufacture of L-proline tert-butyl ester. L-proline (230 g) is dissolved in a mixture of water (1 l) and 5 N sodium hydroxide (400 ml). The solution is chilled in an ice bath, and under vigorous stirring, 5 N sodium hydroxide (460 ml) and benzyloxycarbonyl chloride (340 ml) are added in five equal aliquots during a half-hour period. After one hour stirring at room temperature, the mixture is extracted twice with ether and acidified with concentrated hydrochloric acid. The precipitate is filtered and dried. Yield is 442 g; MP 78°C to 80°C.

The benzyloxycarbonyl-L-proline thus obtained (180 g) is dissolved in a mixture of dichloromethane (300 ml), liquid isobutylene (800 ml) and concentrated sulfuric acid (7.2 ml). The solution is shaken in a pressure bottle for 72 hours. The pressure is released, the isobutylene is allowed to evaporate and the solution is washed with 5% sodium carbonate, water, dried over magnesium sulfate and concentrated to dryness in vacuo, to obtain benzyloxycarbonyl-L-proline tert-butyl ester, yield 205 g.

Benzyloxycarbonyl-L-proline tert-butyl ester (205 g) is dissolved in absolute ethanol (1.2 l) and hydrogenated at normal pressure with 10% Pd on carbon (10 g) until only a trace of carbon dioxide is observed in the hydrogen exit gas (24 hours). The catalyst is filtered off and the filtrate is concentrated in vacuo at 30 mm Hg. The residue is distilled in vacuo, to obtain L-proline tert-butyl ester, BP_{1mm} 50°C to 51°C.

The next step yields 1-(3-acetylthio-2-methylpropanoyl)-L-proline tert-butyl ester. L-proline tert-butyl ester (5.1 g) is dissolved in dichloromethane (40 ml) and the solution stirred and chilled in an ice bath. Dicyclohexylcarbodiimide (15 ml) is added followed immediately by a solution of 3-acetylthio-2-methylpropanoic acid (4.9 g) in dichloromethane (5 ml). After 15 minutes stirring in the ice bath and 16 hours at room temperature, the precipitate is filtered off and the filtrate is concentrated to dryness in vacuo. The residue is dissolved in ethyl acetate and washed neutral. The organic phase is dried over

magnesium sulfate and concentrated to dryness in vacuo. The residue 1-(3-acetylthio-2-methylpropanoyl)-L-proline tert-butyl ester is purified by column chromatography (silica gel-chloroform), yield 7.9 g.

Then, 1-(3-acetylthio-2-methylpropanoyl)-L-proline is produced. The 1-(3-acetylthio-3-methylpropanoyl)-L-proline tert-butyl ester (7.8 g) is dissolved in a mixture of anisole (55 ml) and trifluoroacetic acid (110 ml). After one hour storage at room temperature the solvent is removed in vacuo and the residue is precipitated several times from ether-hexane. The residue (6.8 g) is dissolved in acetonitrile (40 ml) and dicyclohexylamine (4.5 ml) is added. The crystalline salt is boiled with fresh acetonitrile (100 ml), chilled to room temperature and filtered, yield 3.8 g, MP 187°C to 188°C. This material is recrystallized from isopropanol $[\alpha]_D$-67° (C 1.4, EtOH). The crystalline dicyclohexylamine salt is suspended in a mixture of 5% aqueous potassium bisulfate and ethyl acetate. The organic phase is washed with water and concentrated to dryness. The residue is crystallized from ethyl acetate-hexane to yield the 1-(3-acetylthio-2-D-methylpropanoyl)-L-proline, MP 83°C to 85°C.

Finally, Captopril is produced. The thioester (0.85 g) is dissolved in 5.5 N methanolic ammonia and the solution is kept at room temperature for 2 hours. The solvent is removed in vacuo and the residue is dissolved in water, applied to an ion exchange column on the H^+ Cycle (Dowex 50, analytical grade) and eluted with water. The fractions that give positive thiol reaction are pooled and freeze dried. The residue is crystallized from ethyl acetate-hexane, yield 0.3 g. The 1-(3-mercapto-2-D-methylpropanoyl)-L-proline has a melting point of 103°C to 104°C.

References

Merck Index 1747
DFU 3 (11) 795 (1978)
Kleeman and Engel p. 142
PDR p. 1736
OCDS Vo1.3 p. 128 (1984)
DOT 17 (6) 233 (1981); 18 (10) 554 (1982)
I.N. p. 180
REM p. 850
Ondetti, M.A. and Cushman, D.W.; US Patent 4,046,889; September 6, 1977; assigned to E.R. Squibb and Sons, Inc.
Ondetti, M.A. and Cushman, D.W.; US Patent 4,105,776; August 8, 1978; assigned to E.R. Squibb and Sons, Inc.
Ondetti, M.A. and Cushman, D.W.; US Patent 4,154,840; May 15,1979; assigned to E.R. Squibb and Sons, Inc.

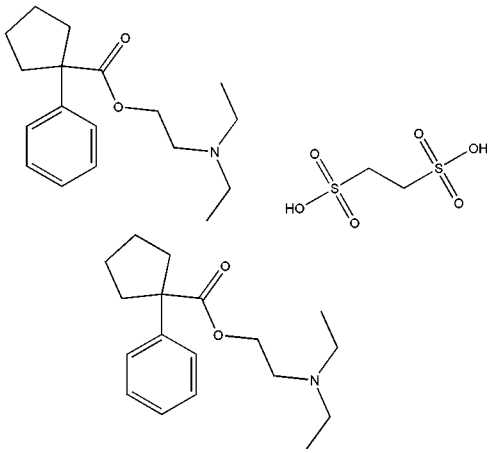
CARAMIPHEN EDISYLATE

Therapeutic Function: Antitussive

Chemical Name: 1-Phenylcyclopentanecarboxylic acid 2-(diethylamino)-ethyl ester 1,2-ethanedisulfonate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 125-86-0

Trade Name	Manufacturer	Country	Year Introduced
Panparnit	Geigy	US	1949
Toryn	Smith Kline	US	1953
Tuss-Ade	Schein	US	-
Tuss-Ornade	Smith Kline	US	-

Raw Materials

1-Phenylcyclopentyl-1-carboxylic acid chloride
Diethylaminoethanol
Ethanedisulfonic acid

Manufacturing Process

20.8 parts of 1-phenylcyclopentyl-1-carboxylic acid chloride, obtained from the acid (cf. Am. Soc. 1934, 56, 715) by means of thionyl chloride, are dissolved in 250 parts by volume of absolute ether, then, while stirring and cooling with a mixture of common salt and ice a solution of 12 parts of diethylaminoethanol in 50 parts by volume of absolute ether is allowed to drop there into, the temperature being maintained below 0°C, whereupon stirring is continued during 2 hours at room temperature. The whole is then twice shaken out with water and once with diluted hydrochloric acid, the combined aqueous solutions are made alkaline with a potassium carbonate solution and shaken out with ether. The ethereal solution is washed with water, dried over potassium carbonate and the solvent is distilled off. The base boils at a pressure of 0.07 mm at 112°C to 115°C.

The base may then be converted to the hydrochloride or to the ethanedisulfonic acid salt (edisylate).

References

Merck Index 1750
PDR pp. 1606,1730
OCDS Vol. 1 pg. 90 (1977)
I.N. p. 180
Martin, H. and Hafliger, F.; US Patent 2,404,588; July 23, 1946; assigned to J.R. Geigy A.G. (Switzerland)

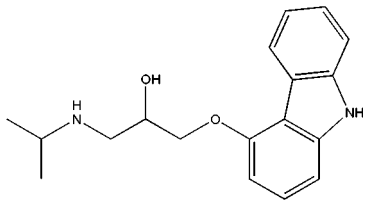
CARAZOLOL

Therapeutic Function: Beta-adrenergic blocker

Chemical Name: 4-(3-Isopropylamino-2-hydroxypropoxy)carbazole

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 57775-29-8

Trade Name	Manufacturer	Country	Year Introduced
Conducton	Klinge	W. Germany	1980

Raw Materials

Hydroxycarbazole
Epichlorohydrin
Isopropylamine

Manufacturing Process

The 4-(2,3-epoxypropoxy)carbazole used as starting material is prepared as follows. A solution of 16.3 g 4-hydroxycarbazole in a mixture of 190 ml dioxan and 98 ml 1 N sodium hydroxide is, after the addition of 66 ml epichlorohydrin, stirred for 2 hours at 40°C to 45°C. The reaction mixture is

then diluted with water and shaken out with methylene chloride. The methylene chloride phase is washed with water, dried over anhydrous sodium sulfate and evaporated. There are obtained 16.8 g 4-(2,3-epoxypropoxy)carbazole.

A solution of 3.5 g 4-(2,3-epoxypropoxy)carbazole in 50 ml absolute alcohol is mixed with 30 ml isopropylamine and heated for 3 hours under reflux. When the reaction is finished, the reaction mixture is evaporated to dryness. The residue obtained is taken up in methylene chloride and chromatographed over an aluminum oxide column (300 g basic aluminum oxide, activity stage IV; eluent methylene chloride). The eluted fractions are evaporated and the residue is dissolved in methanol and acidified with 2 N ethereal hydrochloric acid.

The precipitate obtained is filtered off and recrystallized from methanol. There are obtained 3.1 g (62% of theory) 4-(3-isopropylamino-2-hydroxypropoxy) carbazole hydrochloride; MP 234°C to 235°C.

References

Merck Index 1753
DFU 2 (11) 715 (1977)
Kleeman and Engel p. 143
DOT 17 (2) 53 (1981) and 18 (10) 551 (1982)
I.N. p. 180
Boehringer Mannheim GmbH; British Patent 1,369,580; October 9, 1974

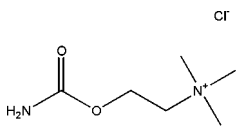
CARBACHOL

Therapeutic Function: Cholinergic

Chemical Name: 2-[(Aminocarbonyl)oxy]-N,N,N-trimethyl-ethanaminium chloride

Common Name: Carbocholine

Structural Formula:



Chemical Abstracts Registry No.: 51-83-2

Trade Name	Manufacturer	Country	Year Introduced
Miostat	Alcon	US	1979
Atonyl	Ferrosan	Denmark	-

Trade Name	Manufacturer	Country	Year Introduced
Cacholitin	Vaise	Denmark	-
Carbacel	Warner Lambert	US	-
Carbamiotin	Tilden Yates	US	-
Carbyl	Tubi Lux Pharma	Italy	-
Carcholin	Merck Sharp and Dohme	US	-
Doryl	Merck	W. Germany	-
Iricoline	Lematte/Boinot	France	-
Isopto-Carbachol	Alcon	US	-
Jestryl	Ankerwerk	E. Germany	-
Lentin	Merck	W. Germany	-
Lentivasan	Kwizda	Austria	-
Mistura	Lederle	US	-
Moryl	Savory and Moore	UK	-
Oftan-Karbakol	Star	Finland	-
P.V. Carbachol	Allergan	US	-
Rilentol	Richter	Austria	-
Secretin	Streuli	Switz.	-
Spersacarbachol	Dispersa	Switz.	-
Tonocholin	A.F.I.	Norway	-

Raw Materials

Choline chloride
Phosgene

Manufacturing Process

About 14 g of choline chloride are stirred with a solution of about 20 g of phosgene in 100 g of chloroform for about two hours at room temperature. The mixture becomes a two-phase liquid mixture. Hydrochloric acid and excess phosgene are removed by distillation in vacuo. Chloroform is added to the syrup, and the mixture is then added to a solution of excess ammonia in chloroform which was cooled with solid carbon dioxide-acetone. The mixture is filtered, and the solid is extracted with hot absolute alcohol. The solid in the alcoholic solution is precipitated with ether, and filtered. It is recrystallized from a methyl alcohol-ether mixture; the carbaminoyl-choline chloride obtained has a melting point of about 208°-210°C.

References

Merck Index 1754
Kleeman and Engel p. 144
I.N. p. 180
REM p. 896

Major, R.T. and Bonnett, H.T.; US Patent 2,374,367; April 24, 1945; assigned to Merck and Co., Inc.

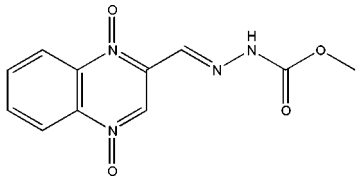
CARBADOX

Therapeutic Function: Antibacterial

Chemical Name: Hydrazinecarboxylic acid, (2-quinoxalinylmethylene)-, methyl ester, N,N'-dioxide

Common Name: Carbadox; Enterodox; Getroxel

Structural Formula:



Chemical Abstracts Registry No.: 6804-07-5

Trade Name	Manufacturer	Country	Year Introduced
Carbadox	Agrimex	-	-
Carbadox	Intraco LTD	-	-
Carbadox	Impextraco	-	-
Carbamix	Zineb	-	-
Enterodox	Orffa	-	-
Enterodox	Dox-Al Australia PTY Ltd.	-	-
Addi-dox	Addi-tech BVBA	-	-
Mecadox	Orffa	-	-
Mecadox	Pfizer Inc.	-	-

Raw Materials

Methylcarbazate
2-Formylquinoxaline-1,4-dioxide

Manufacturing Process

A solution of methylcarbazate (48.0 mg) in methanol (250 ml) is added all at once at room temperature to a well stirred solution of 2-formylquinoxaline-1,4-dioxide (100 g) in methanol (2.5 liters). Two drops of concentrated hydrochloric acid are added. The mixture is stirred for 3 hours then filtered to

remove the yellow crystalline product. The crystals of (2-quinoxalinylmethylene)hydrazinecarboxylic acid methyl ester are washed with methanol then air dried; M.P. 234.5-236°C (dec.). Yield=121.8 g. The product is purified by refluxing in chloroform for 2 hours, followed by filtration and air drying; M.P. 239.5-240°C (dec.).

The ultraviolet absorption spectrum (water) exhibits maxima at 236, 251, 303, 366 and 373 nm with extinction coefficients of 11,000, 10,900, 36,400, 16,100 and 16,200, respectively.

References

James David Johnston, Old Saybrook; US Patent No. 3,433,871; Mar. 18, 1962; Assigned to Chas. Pfizer and Co., Inc., New York, N.Y., a corporation of Delaware

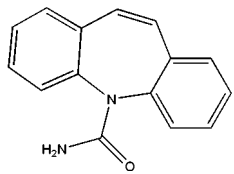
CARBAMAZEPINE

Therapeutic Function: Analgesic, Anticonvulsant

Chemical Name: 5H-Dibenz[b,f]azepine-5-carboxamide

Common Name: 5-Carbamyl iminostilbene

Structural Formula:



Chemical Abstracts Registry No.: 298-46-4

Trade Name	Manufacturer	Country	Year Introduced
Tegretol	Geigy	W. Germany	1964
Tegretol	Geigy	UK	1964
Tegretol	Geigy	France	1964
Tegretol	Geigy	US	1968
Tegretol	Geigy	Italy	1972
Biston	Spofa	Czechoslovakia	-
Convuline	Protea	Australia	-
Finlepsin	Arzneimittelwerk Dresden	E. Germany	-

Trade Name	Manufacturer	Country	Year Introduced
Hermolepsin	Laake	Finland	-
Lexin	Fujinaga	Japan	-
Mazepine	ICN	Canada	-
Neuritol	Eczacibasi	Turkey	-
Neurotol	Farmos	Finland	-
Nordotol	Farmos	Finland	-
Servimazepine	Servipharm	Switz.	-
Stazepine	Polfa	Poland	-
Telesmin	Yoshitomi	Japan	-
Temporol	Orion	Finland	-
Teril	Taro	Israel	-
Timonil	Desitin	W. Germany	-

Raw Materials

Iminostilbene
Phosgene
Ammonia

Manufacturing Process

19.3 parts of iminostilbene are dispersed in 100 parts by volume of toluene. Phosgene is then introduced whereupon the temperature of the reaction mixture rises to 70°C. While boiling under reflux, further phosgene is introduced until all the iminostilbene has dissolved and the hydrogen chloride development is complete. The reaction mixture is then cooled and the 5-chlorocarbonyl iminostilbene which has crystallized out is filtered off under suction. It melts at 168° to 169°C.

12.8 parts of 5-chlorocarbonyl iminostilbene are dispersed in 128 parts by volume of absolute ethanol and ammonia gas is introduced for three hours into this mixture while stirring at boiling temperature. The reaction is complete after this time; the reaction mixture is cooled and the crystals which precipitate are filtered off under suction. The ammonium chloride is washed from the crystals with water and the residue is recrystallized first from absolute ethanol and then from benzene. 5-carbamyl iminostilbene is obtained which melts at 204° to 206°C.

References

Merck Index 1758
Kleeman and Engel p. 144
PDR p. 900
OCDS Vol. 1 p. 403 (1977)
DOT 1 (3) 82 (1965)
I.N. p. 181
REM p. 1077
Schindler, W.; US Patent 2,948,718; August 9, 1960; assigned to Geigy Chemical Corporation

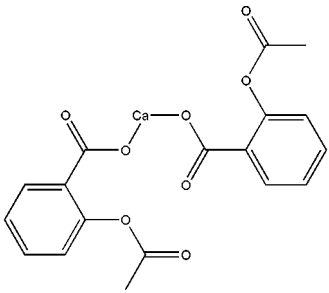
CARBASPIRIN CALCIUM

Therapeutic Function: Analgesic, Antipyretic, Antirheumatic

Chemical Name: 2-(Acetyloxy)benzoic acid calcium salt

Common Name: Calcium aspirin; Calcium acetylsalicylate

Structural Formula:



Chemical Abstracts Registry No.: 69-46-3

Trade Name	Manufacturer	Country	Year Introduced
Calurin	Dorsey	US	1959
Iromin	Iromedica	Switz.	-
Soluspan	UPSA	France	1983
Iromin	Omegin	W. Germany	-
Fiogesic	Sandoz	US	-
Ursinus	Dorsey	US	-

Raw Materials

Acetylsalicylic acid
Calcium carbonate

Manufacturing Process

500 g of finely powdered acetylsalicylic acid and 160 g of calcium carbonate (precipitated chalk), are intimately mixed and 3,000 cc of water are added. The mixture is stirred for 15 minutes or until the reaction is completed, which is indicated by the cessation of the liberation of carbon dioxide. The temperature is desirably maintained below 20°C by any suitable means. The mass is allowed to settle until the supernatant liquor is almost clear; this usually takes about 5 minutes, and the mixture is then filtered to remove unreacted material. This part of the process is carried out as quickly as possible so as to minimize any tendency of the calcium aspirin to hydrolyze in the solution. The filtrate is cooled to about 10°C and 1 to 1.5 volumes of 97%

methanol, or pure wood alcohol is added. This causes the calcium aspirin to precipitate and the mass is then filtered to remove as thoroughly as possible the mother liquor. The residue of calcium aspirin is then suspended in a quantity of methanol equivalent to the volume previously used as a precipitant, and it is allowed to stand there for one hour or more with occasional or continuous agitation. The mass is again filtered, the filtrate being employed for the precipitation of calcium aspirin in a later batch. After the filtering of the first wash liquor, the calcium aspirin is again suspended in another quantity of methanol of an equivalent volume. This constitutes the second wash and it is carried out in the same way as the first wash. The filtrate is employed as a first wash in a later batch and this filtrate in turn is used, as is the filtrate of the first wash, for the precipitation of more calcium aspirin. Fresh alcohol is used as a new wash in a later batch and the washes are carried out in series. After the second wash the calcium aspirin is dried in a suitable manner, as by passing dry warm air over it, the temperature not being allowed to rise to such an extent as to decompose the aspirin; preferably the temperature is not permitted to rise above 50°C, but should be high enough to avoid deposition of water vapor, and the drying is completed when there is no longer an odor of methanol.

References

Merck Index 1615
Kleeman and Engel p. 145
PDR p. 1583
Lawrence, W.H., Jr.; US Patent 2,003,374; June 4, 1935; assigned to Lee Laboratories, Inc.

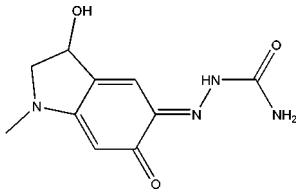
CARBAZOCHROME

Therapeutic Function: Hemostatic

Chemical Name: 3-Hydroxy-1-methyl-5,6-indolinedione semicarbazone

Common Name: Adrenochrome

Structural Formula:



Chemical Abstracts Registry No.: 69-81-8; 13051-01-9 (Salicylate)

Trade Name	Manufacturer	Country	Year Introduced
Adrenosem	Beecham	US	1953
Adrestat	Organon	US	1957
Adrenoxyl	Labaz	France	1957
Adrenoxyl	Nordmark	W. Germany	-
Anaroxyl	Organon	US	-
Cromosil	Zambeletti	Italy	-
Cromoxin	R. Rius	Spain	-
Meronyl	Santen	Japan	-

Raw Materials

Adrenalin
Silver oxide
Semicarbazide hydrochloride

Manufacturing Process

A suspension containing 1 part by weight of adrenalin and 2 to 6 parts by weight of silver oxide in 150 to 250 parts by weight of methanol or ethanol is stirred for about 10 minutes. The alcoholic adrenochrome solution obtained is separated by draining and the filtrate is quickly evaporated to dryness at low temperature and in vacuo. The red crystals of adrenochrome obtained are dissolved in 45 to 55 parts by weight of water. To this solution, 2 parts of sodium acetate dissolved in 2 to 3 parts of water and 2 parts of semicarbazide hydrochloride dissolved in 2 to 3 parts of water are added. The formed precipitate consisting of red-orange prismatic needles is separated by filtration and recrystallized from diluted ethanol. There is obtained 0.30 to 0.40 part by weight of adrenochrome monosemicarbazone dihydrate, melting at 203°C with decomposition.

References

Merck Index 1767, 1768
Kleeman and Engel p. 146
I.N. p. 182
REM p. 832
Dechamps, G., Le Bihan, H. and Baudet, C.; US Patent 2,506,794; May 2, 1950; assigned to Societe Belge de l'azote et des Produits Chimiques du Marly (Belgium)

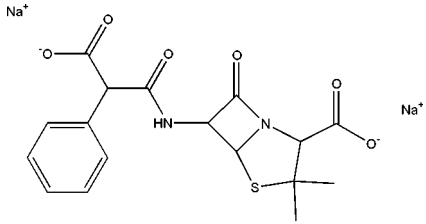
CARBENICILLIN DISODIUM

Therapeutic Function: Antibacterial

Chemical Name: N-(2-Carboxy-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0]hept-6-yl)-2-phenylmalonamic acid sodium salt

Common Name: Carboxybenzylpenicillin sodium salt

Structural Formula:



Chemical Abstracts Registry No.: 4800-94-6; 4697-36-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Pyopen	Beecham	Switz.	1968
Pyopen	Beecham	UK	1968
Carindapen	Pfizer	W. Germany	1968
Pyopen	Beecham	US	1970
Geopen	Roerig	US	1970
Gripenin	Fujisawa	Japan	1970
Geopen	Pfizer Taito	Japan	1971
Pyocianil	Farmitalia	Italy	1972
Anabactyl	Beecham	W. Germany	-
Carbapen	C.S.L.	Australia	-
Carbecin	Beecham	-	-
Fugacillin	Astra	Sweden	-
Microcillin	Bayer	W. Germany	-
Rexcilina	Wolner	Spain	-

Raw Materials

Phenylmalonic acid
Benzyl alcohol
Thionyl chloride
6-Amino penicillanic acid
Hydrogen
Sodium bicarbonate

Manufacturing Process

The required monobenzyl phenylmalonate, MP 68°C, was prepared by treating a mixture of phenylmalonic acid (18 g) and benzyl alcohol (13 g) in carbon tetrachloride (80 ml) with dry hydrogen chloride.

Monobenzyl phenylmalonate (13.3 g) in dry benzene (100 ml) was refluxed

with thionyl chloride (6.45 g) for 90 minutes, then concentrated in vacuo. The residual oil was dissolved in dry acetone (50 ml) and added to a stirred, ice-cooled solution of 6-aminopenicillanic acid (9.7 g) in N sodium bicarbonate solution (135 ml), water (150 ml), and acetone (300 ml). The mixture was stirred for 30 minutes at 0°C and then for 90 minutes at room temperature, then concentrated under reduced pressure to remove acetone. The aqueous solution was brought to pH 2 with dilute hydrochloric acid and extracted with ether (3 x 100 ml). The ether solution was washed with water and then itself extracted with sufficient N sodium bicarbonate solution to give an aqueous phase of pH 7.5. The aqueous layer was separated and evaporated at low temperature and pressure to leave the impure sodium salt of alpha-(benzyloxycarbonyl) benzylpenicillin.

This crude product (15.8 g) in water (360 ml) was added to a prehydrogenated suspension of 10% palladium on charcoal (4 g) in water (400 ml), and hydrogenation was continued for 30 minutes. The catalyst was removed and the filtrate was adjusted to pH 7.5 with sodium bicarbonate, then evaporated at low temperature and pressure. The residue was purified by chromatography on a column of cellulose powder, eluting first with butanol/ethanol/water mixture and then with acetone/isopropanol/water. The main fraction was evaporated at low temperature and pressure to give a 32% yield of the sodium salt of alpha-carboxybenzylpenicillin as a white powder. The product was estimated by monometric assay with penicillinase to be 58% pure.

References

Merck Index 1773
Kleeman and Engel p. 147
PDR p. 1404
OCDS Vol. 1 p. 414 (1977) and 2 p. 437 (1980)
DOT 4 (3) 96 (1968)
I.N. p. 183
REM p. 1194
Brain, E.G. and Nayler, J.H.C.; US Patents 3,282,926; November 1, 1966 and 3,492,291; January 27, 1970; both assigned to Beecham Group Limited, England

CARBENICILLIN INDANYL SODIUM

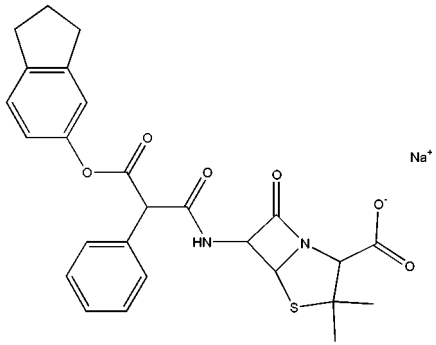
Therapeutic Function: Antibacterial

Chemical Name: N-(2-Carboxy-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0]hept-6-yl)-2-phenylmalonamic acid, 1-(5-indanyl ester), monosodium salt

Common Name: Carindacillin; Indanylcarbenicillin

Chemical Abstracts Registry No.: 26605-69-6; 35531-88-5 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Geocillin	Roerig	US	1972
Carindapen	Pfizer	W. Germany	1973
Geopen	Pfizer	Switz.	1973
Geopen-U	Pfizer Taito	Japan	1976
Unipen	Pfizer-Roerig	US	-
Urobac	Pfizer-Roerig	-	-

Raw Materials

Phenylmalonic acid
6-Aminopenicillanic acid
Triethylamine
5-Indanyl alcohol
Phosphorus pentachloride

Manufacturing Process

(A) Preparation of Phenylchlorocarbonyl Ketene: To phenylmalonic acid (20 g) in ethyl ether (100 ml) there is added phosphorus pentachloride (46 g). A vigorous reaction occurs. The reaction mixture is refluxed for 4 hours then the ether partially removed by heating on a steam bath. The reaction mixture becomes black when about half the ether is removed and the remaining ether is removed under reduced pressure (at 100 mm). The residue is distilled under vacuum and the fraction boiling at 75° to 90°C at 1.5 to 4 mm collected. The product, a yellow liquid, is redistilled at 74°C and 1.5 mm. It shows a strong peak in the infrared region of the spectrum at 4.69 mu. Repetition of this procedure but using 10 g of phenylmalonic acid instead of 20 g produces a less vigorous reaction on addition of the phosphorus pentachloride. The same product is obtained.

(B) Acylation of 6-Aminopenicillanic Acid: To a solution of the aryl halocarbonyl ketene (0.1 mol) in methylene chloride (sufficient to provide a clear solution and generally from about 5 to 10 ml per gram of ketene) there is added the proper alcohol R_2OH (0.1 mol), in this case 5-indanyl alcohol. The reaction mixture is maintained under an atmosphere of nitrogen and stirred for a period of from 20 minutes to 3 hours, care being taken to

exclude moisture. The temperature may range from about -70° to about -20°C. The infrared spectrum of the mixture is then taken to determine and confirm the presence of the ketene ester. A solution of 6-aminopenicillanic acid-triethylamine salt (0.1 mol) in methylene chloride (50 ml) is added and the mixture stirred at -70° to -20°C for 10 minutes. The cooling bath is then removed and the reaction mixture stirred continuously and allowed to warm to room temperature.

Various isolation methods are then spelled out in US Patent 3,679,801.

References

Merck Index 1823
Kleeman and Engel p. 155
PDR p. 1524
DOT 8 (8) 310 (1972 and 9 (4)128 (1973)
I.N. p. 189
REM p. 1195
Butler,K.; US Patents 3,557,090; January 19, 1971; 3,574,189; April 6, 1971; and 3,679,801; July 25, 1962; all assigned to Chas. Pfizer and Co., Inc.

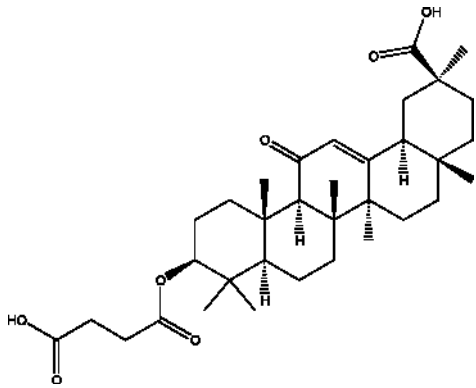
CARBENOXOLONE

Therapeutic Function: Antiinflammatory (gastric)

Chemical Name: 3β-Hydroxy-11-oxo-20β-olean-12-en-29-oic acid hydrogen butanedioate

Common Name: Glycyrrhetinic acid hydrogen succinate

Structural Formula:



Chemical Abstracts Registry No.: 5697-56-3; 7421-40-1 (Sodium salt)

Trade Name	Manufacturer	Country	Year Introduced
Biogastrone	Winthrop	UK	1963
Biogastrone	Homburg	W. Germany	1970
Gastrausil	Italseber	Italy	1971
Biogastrone	Richardson-Merrell	Switz.	1978
Biogastron	Shionogi	Japan	1979
Biogastrone	Abic	Israel	-
Bioral	Biorex, Berk	UK	-
Duogastrone	Merrell	France	-
Duogastrone	Abic	Israel	-
Karbenol	Yurtoglu	Turkey	-
Neogel	Homburg	W. Germany	-
Neutrogastrol Ulcus	Septa	Spain	-
Pyrogastone	Winthrop	UK	-
Sanodin	Leo	Spain	-
Sustac	Sintyal	Argentina	-
Terulcon	ISF	Italy	-
Ulcofer	Mulda	Turkey	-
Ulcus-Tablinen	Sanorania	W. Germany	-
Ulkon	Eczacibasi	Turkey	-
Ventroxol	Medica	Finland	-

Raw Materials

Glycyrrhetinic acid
Succinic anhydride

Manufacturing Process

23.5 g of glycyrrhetinic acid were dissolved in 50 cc of dry pyridine. A solution of 6.0 g of succinic anhydride in 30 cc of dry pyridine was added, followed by 30 cc of dry triethylamine and then, for washing purposes, 5 cc of dry pyridine. The solution was heated on a boiling water bath for ten hours and then poured into excess of dilute hydrochloric acid and ice. The fine gray precipitate formed was filtered off, washed with water, dissolved in chloroform, and the solution repeatedly extracted with dilute hydrochloric acid and later with water. It was dried over sodium sulfate and evaporated to dryness. Crystallization from methanol, using charcoal to effect decolorization, gave the hydrogen succinate as cream-colored crystals, MP 291° to 294°C, with previous softening.

One molecular proportion of glycyrrhetinic acid hydrogen succinate was ground with a dilute (5%) aqueous solution containing two molecular proportions of sodium hydroxide. The solution was filtered and evaporated in vacuum over concentrated sulfuric acid. The sodium salt is then obtained as a creamy white water-soluble solid. Glycyrrhetinic acid is obtainable from licorice root.

References

Merck Index 1774
Kleeman and Engel p. 147
I.N. p. 183
Gottfried,S. and Baxendale, L.; US Patent 3,070,623; December 25, 1962; assigned to Biorex Laboratories Limited, England

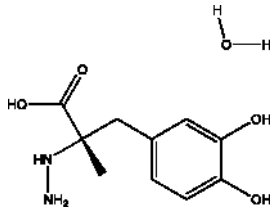
CARBIDOPA

Therapeutic Function: Muscle relaxant, Antiparkinsonian

Chemical Name: S-α-Hydrazino-3,4-dihydroxy-α-methylbenzenepropanoic acid monohydrate

Common Name: Methyldopahydrazine

Structural Formula:



Chemical Abstracts Registry No.: 38821-49-7; 28860-95-9 (Anhydrous)

Trade Name	Manufacturer	Country	Year Introduced
Sinemet	Merck Sharp and Dohme	Italy	1974
Sinemet	Merck Sharp and Dohme	UK	1974
Nacom	Sharp and Dohme	W. Germany	1975
Sinemet	Chibret	France	1975
Lodosyn	Merck Sharp and Dohme	US	1977
Menesit	Merck-Banyu	Japan	1980
Neo-Dopaston	Sankyo	Japan	1980

Raw Materials

Vanillin
Potassium cyanide
Nitroethane
Hydrazine hydrate

Butylamine	Acetic acid
Iron	Hydrogen chloride
Hydrobromic acid	Hydrochloric acid

Manufacturing Process

To a solution of vanillin in toluene is added nitroethane, butylamine and glacial acetic acid. The mixture is refluxed and the water of reaction is steadily azeotropically removed by distillation. After the theoretical amount of water is distilled out, distillation is continued to remove excess reactants. The last trace of excess reactants is then removed at room temperature under a vacuum. The product is then triturated with a hydrocarbon solvent such as Skellysolve B and is thus obtained in a crystalline state. In general, however, it is preferred to dissolve the residue directly in toluene for use in the next step, without isolating the 1-(2-nitropropen-1-yl)-4-hydroxy-3-methoxybenzene.

A mixture of iron, ferric chloride and water is added to the toluene solution. The mixture is heated to reflux and concentrated hydrochloric acid is added dropwise at a rate calculated to keep the mixture refluxing vigorously. After the hydrochloric acid is all added, the refluxing is continued by the application of heat for several hours. A siliceous filter aid is then added to the cooled reaction mixture and the material is removed by filtration. The filter cake is washed four times, each time with 90 ml of benzene. The organic layer is then separated from the filtrate. The water layer is acidified to a pH of 2 and extracted three times with 90 ml portions of benzene.

These extracts are then combined with the organic solvent layer and the combined organic phase is extracted four times with 100 ml portions of water. It is then stirred for an hour with 230 ml of 10% sodium bisulfite solution. The organic solvent phase is then separated, washed seven times with 100 ml portions of water and dried over magnesium sulfate. Evaporation of the solvent gives 1-(4-hydroxy-3-methoxyphenyl)-2-propanone in the form of an oil.

A mixture of 59.5 g of that oily product, 1.85 liters of benzene and 1 kg of potassium bisulfite in 200 liters of water is stirred at room temperature for two hours. The precipitated bisulfite addition product of the ketone is isolated by filtration and washed with isopropanol and then with ether. Five hundred grams of the adduct is mixed with 119.5 g of potassium cyanide, 292 ml of 85% hydrazine hydrate and 910 ml of water. The mixture is stirred overnight at room temperature after which the product is isolated by filtration. The product is washed 3 times with 250 ml portions of water and then 3 times with 230 ml portions of ether. It is then air dried and vacuum dried at room temperature.

Fifty cubic centimeters of concentrated hydrochloric acid is saturated with hydrogen chloride gas at -10°C. To the solution is then added 2.5 g of the intermediate product, of the formula shown above, slowly with vigorous stirring. The mixture is allowed to stir overnight while warming at room temperature gradually. It is then concentrated in vacuo to a syrup. To the residual syrup is added 100 ml of 48% hydrobromic acid. The reaction vessel is purged with nitrogen and the reaction mixture is then refluxed for 3 hours after which it is concentrated in vacuo to a mixture of a syrup and a solid. The

residue is taken up in sufficient water to form a clear solution. Activated charcoal is added and the mixture is heated to boiling and filtered.

The filtrate is concentrated to dryness in vacuo and the residue is taken up in 25 cc of ethanol. The residual ammonium bromide is removed by filtration and to the filtrate there is added sufficient diethylamine to change the pH to 6.4. The mixture is warmed to 60°C and then cooled to room temperature. It is then allowed to stand overnight to effect complete crystallization. It is then cooled to 0°C and the product is isolated by filtration, washed with methanol and air dried. The product (α-hydrazino-α-methyl-β-(3,4-dihydroxyphenyl)-propionic acid) is recrystallized once from water using a proportion of 15 cc water per gram of product.

References

Merck Index 1778
Kleeman and Engel p. 148
PDR p. 1210
OCDS Vol. 2p. 119 (1980)
DOT 10 (9) 322 (1974)
I.N. p. 184
REM p. 929
Chemerda, J.M., Sletzinger, M. and Bollinger, F.W.; US Patent 3,462,536; August 19, 1969; assigned to Merck and Co., Inc.

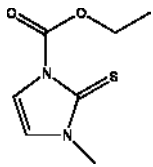
CARBIMAZOLE

Therapeutic Function: Thyroid inhibitor

Chemical Name: Ethyl 3-methyl-2-thioimidazoline-1-carboxylate

Common Name: Athyromazole; Carbimazole; Kabimazuo

Structural Formula:



Chemical Abstracts Registry No.: 22232-54-8

Trade Name	Manufacturer	Country	Year Introduced
Carbimazol	Cid Co.	-	-
Carbimazol	Henning Berlin	-	-
Carbimazol	Slovakofarma	-	-

Trade Name	Manufacturer	Country	Year Introduced
Carbimazol	Genfarma	-	-
Carbimazol	Pharbita	-	-
Carbimazol	Pharmachemie	-	-
Carbist AD	Stada	-	-
Neo-Carbimazole	Landerlan	-	-
Neo-mercazole	Roche	-	-
Neo-mercazole	Pharmacare Limited	-	-
Neo-mercazole	Nicholas Piramal	-	-
Neo-mercazole	Macleods	-	-
Neo-mercazole	Lagamed	-	-
Neo-mercazole	Nicholas	-	-
Neo-mercazole	Ferraz, Lynce	-	-
Neo-mercazole	Nicholas/Meda	-	-
Neo-Thyreostat	Herbrand	-	-
Neo-Tomizol	Robert	-	-
Thyrostat	NI-THE	-	-
Tyrazol	Orion Oy	-	-
Tyrazol	Algol Pharma Oy	-	-

Raw Materials

1-Methyl-2-mercaptoglyoxaline
Ethyl chloroformate
Pyridine

Manufacturing Process

0.1 mol of 1-methyl-2-mercaptoglyoxaline is dissolved in the minimum quantity of pyridine at 0°C 0.1 mol of ethyl chloroformate is added drop wise with stirring. More pyridine is added, if necessary, to keep the mixture semi-fluid. The sludge is then placed in an ice bath for 30 minutes. The crystals are filtered off and washed firstly with a little ethanol and secondly with ethanol and water. The non-basic desired ethyl 3-methyl-2-thioimidazoline-1-carboxylate is the colourless needles having a melting point of 122°-123°C.

References

Rimington C. et al.; US Patent No. 2,815,349; Dec. 3, 1957; Assigned to National Research Development Corporation, London, England, a British corporation
Rimington C. et al.; US Patent No. 2,671,088; Mar. 2, 1954; Assigned to National Research Development Corporation, London, England, a British corporation
Baker J.A., J. Chem. Soc. 1958, p. 2387

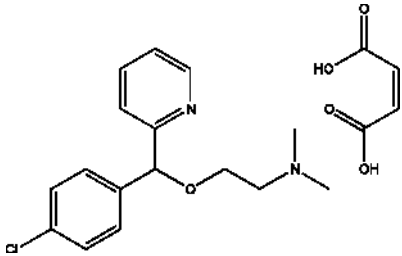
CARBINOXAMINE MALEATE

Therapeutic Function: Antihistaminic

Chemical Name: 2-[(4-Chlorophenyl)-2-pyridinyl-methoxy]-N,N-dimethylethanamine maleate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 3505-38-2; 486-16-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Clistin	McNeil	US	1953
Allergefon	Lafon	France	1962
Polistin	Trommsdorff	W. Germany	1963
Cardec	Schein	US	-
Cibelon	Taisho	Japan	-
Hislosine	Toho	Japan	-
Histex	Sigma	Australia	-
Histine	Pharbil	Belgium	-
Lergefin	Larma	Spain	-
Polistine	Pharbil	Netherlands	-
Rondec	Boss	US	-
Ziriton	Importex	Italy	-

Raw Materials

p-Bromochlorobenzene
2-Pyridine aldehyde
2-Dimethylaminoethyl chloride
Magnesium
Sodium metal

Manufacturing Process

As described in US Patent 2,800,485 a solution of p-chlorophenylmagnesium bromide is prepared by adding dropwise a solution of 230 g (1.2 mols) of p-bromochlorobenzene in 900 cc of anhydrous ether to 26.7 g (1.1 g-atoms) of

magnesium suspended in 100 cc of anhydrous ether containing a small crystal of iodine. To this solution, 107 g (1 mol) of 2-pyridinealdehyde are added slowly with stripping at a rate to maintain refluxing. The reaction mixture is then stirred for one hour at room temperature. The mixture is then poured onto an equal volume of crushed ice and water and acidified with concentrated hydrochloric acid. The ether layer is removed. The aqueous layer is made basic with ammonia and extracted with ether. The ether solution is evaporated and the residue dried by addition of benzene and removal by distillation to give 208 g (95%) of solid alpha-(p-chlorophenyl)-2-pyridinemethanol melting at 78° to 80°C. The p-chlorophenyl pyridinemethanol may alternatively be prepared from 4-chloroacetophenone, pyridine and granular aluminum as described in US Patent 2,606,195. In either case, the synthesis then proceeds as described in US Patent 2,800,485.

A solution of 219 g (1 mol) of α-(p-chlorophenyl)-2-pyridinemethanol in one liter of dry toluene is heated to 100°C with stirring. Twenty-three grams (1 g-atom) of sodium are then added in portions. After all the sodium has reacted, a dried solution of 2-dimethylaminoethyl chloride in benzene is added. This benzene solution is prepared by dissolving 173 g (1.2 mols) of 2-dimethylaminoethyl chloride hydrochloride in the minimum amount of water, adding 500 cc of benzene followed by 300 g of sodium carbonate decahydrate, stirring, separating the benzene layer and drying.

The mixture is refluxed with stirring for ten hours, cooled and filtered. The filtrate is extracted three times with 200 cc portions of 6 N acetic acid. The aqueous acetic acid solution is then made strongly basic with 10% sodium hydroxide solution, and extracted three times with 200 cc portions of ether. The ether extract is dried with anhydrous sodium sulfate, stirred with 5 g of activated carbon and filtered to provide 2-[p-chloro-α(2-dimethylaminoethoxy) benzyl]pyridine in solution. Addition of a solution of 116 g (1 mol) of maleic acid in 1,500 cc of ether gives 323 g (79%) of solid which, on recrystallization from ethyl acetate, gives white solid 2-[p-chloro-α(2-dimethylaminoethoxy) benzyl]pyridine maleate melting at 117° to 119°C.

References

Merck Index 1780
Kleeman and Engel p. 150
PDR pp.1561, 1606
OCDS Vol. 1 p.43 (1977) and 2 p. 32 (1980)
I.N.p. 184
REM p. 1126
Tilford. C.H. and Shelton, R.S.; US Patent 2,606,195; August 5, 1952; assigned to The Wm. S. Merrell Company
Swain, A.P.; US Patent 2,800,485; July 23, 1957; assigned to McNeil Laboratories, Inc.

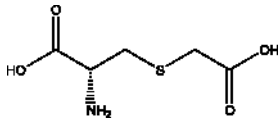
CARBOCYSTEINE

Therapeutic Function: Mucolytic, Expectorant, Nasal antiinfective

Chemical Name: S-(Carboxymethyl)-L-cysteine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 638-23-3

Trade Name	Manufacturer	Country	Year Introduced
Rhinathiol	Kramer	Switz.	-
Rhinathiol	Joullie	France	1961
Mucodyne	Berk	UK	1963
Transbronchin	Homburg	W. Germany	1975
Lisomucil	Lirca	Italy	1975
Mucodyne	Kyorin	Japan	1981
Actithiol	Funk	Spain	-
Bronchette	Continental Ethicals	S. Africa	-
Bronchipect	Mepros	Netherlands	-
Bronchokod	Genekod	France	-
Broncodeterge	Valderrama	Spain	-
Carbocit	C.T.	Italy	-
Flemex	Parke Davis	US	-
Fluifort	Lampugnani	Italy	-
Loviscol	Robins	US	-
Muciclar	Parke Davis	US	-
Mucocaps	Berk	UK	-
Mucocis	Crosara	Italy	-
Mucolex	Warner Lambert	US	-
Mucopront	Mack	W. Germany	-
Mucosirop	Berk	UK	-
Mucospect	Lennon	S. Africa	-
Mucoliz	Yurtoglu	Turkey	-
Pectox	Infar-Nattermann	Spain	-
Pulmoclase	UCB	Belgium	-
Reodyn	Remeda	Finland	-
Reomucil	Tosi	Italy	-
Siroxyl	Sopar	Belgium	-
Solvopact	Mepros	Netherlands	-

Raw Materials

L-Cysteine
Sodium metal
Chloroacetic acid

Manufacturing Process

There were placed 120g of L-cysteine (0.5 mol) in a 2 liter three-necked flask equipped with a stirrer thermometer and methanol/dry ice cooling and 1.5 liters of liquid ammonia were allowed to enter at -40°C. Then there were added under continuous cooling 50 g (2.17 mols) of sodium metal in portions of 1 to 2 g during the course of one hour. The end of the reaction was recognized by the continuation of the blue color. After the end of the reaction the excess sodium was destroyed by the addition of ammonium chloride and the ammonia vaporized at normal pressure. The residue was taken up in 500 ml of water and concentrated in a vacuum to 200 ml in order to remove residual ammonia, and again treated with 300 ml of water. The entire operations were carried out under a nitrogen atmosphere.

The aqueous solution of the disodium salt of L-cysteine obtained is then reacted at 20°C to 30°C under a nitrogen atmosphere in the course of 30 minutes with stirring with a solution of 104 g of chloroacetic acid (1.1 mols) and 4 g of sodium pyrosulfite in 200 ml of water. It is also allowed to post react for 15 minutes at 20°C, the solution clarified over activated carbon and the filtrate treated with 90 ml of concentrated hydrochloric acid to a pH of 2.5.

Thereby the S-carboxymethyl-L-cysteine precipitates out in crystalline form. The product is filtered off with suction, well stirred in 500 ml of water, again filtered with suction and dried in a vacuum at 70°C. The yield is 92% based on L-cysteine.

References

Merck Index 1785
Kleeman and Engel p. 151
I.N. p. 185
Maierhofer, A. and Wagner. H.; US Patent 4,129,593; December 12, 1978: assigned to Deutsche Gold und Silber-Scheideanstalt vormals Roessler (Germany)

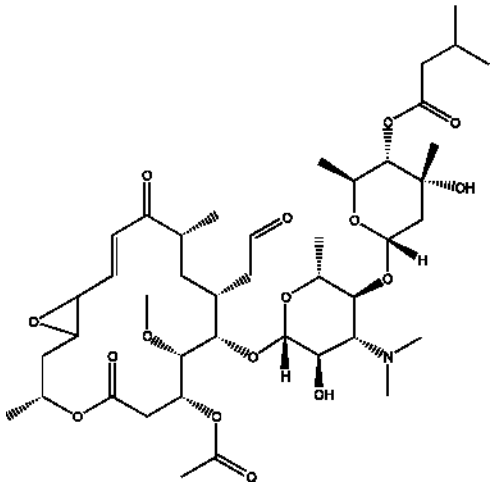
CARBOMYCIN

Therapeutic Function: Antibiotic

Chemical Name: 9-Deoxy-12,13-epoxy-9-oxo-leucomycin V-3-acetate-4^B-(3-methylbutanoate)

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 4564-87-8

Trade Name	Manufacturer	Country	Year Introduced
Magnamycin	Pfizer	US	1953

Raw Materials

Nutrient broth
Streptomyces halsredii bacterium

Manufacturing Process

A selected strain of Streptomyces halstedii was cultivated in an aqueous nutrient medium under aerobic conditions and the resulting broth containing carbomycin antibiotics was filtered. The solutions was extracted twice at pH 6.5 with one-quarter volume of methyl isobutyl ketone. The combined extracts were concentrated to one-tenth volume under vacuum, and the antibiotics were extracted into water adjusted to a pH of about 2 with sulfuric acid. After adjusting the separated aqueous solution to pH 6.5, the antibiotic was extracted into benzene and the solution was concentrated to a small volume. Addition of hexane resulted in the separation of a solid product containing the benzene complexes of carbomycin A and carbomycin B, present in the fermentation broth.

References

Merck Index 1790
I.N.p. 186
Tanner, F.W. Jr., Lees, T.M. and Routien, J.B.; US Patent 2,771,392; November 20, 1956; assigned to Chas. Pfizer and Co., Inc.

Friedman, I.J., Martin, E.G., Taylor, R.J. and Wagner, R.L. Jr.; US Patent 2,960,438; November 15, 1960; assigned to Chas. Pfizer and Co., Inc.

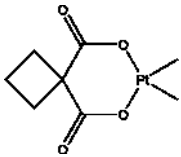
CARBOPLATIN

Therapeutic Function: Antitumor

Chemical Name: Platinum, diammine(1,1-cyclobutanedicarboxylato(2-)-O,O')-, (SP-4-2)-

Common Name: Carboplatin

Structural Formula:



Chemical Abstracts Registry No.: 41575-94-4

Trade Name	Manufacturer	Country	Year Introduced
Blastocarb	Lemery	Mexico	-
Carboplatin	Teva	Israel	-
Carboplatin	Yunnan Gejiu Biochemical Pharmaceutical Factory	China	-
Carboplatin	Pharmacia and Upjohn	Australia	-
Carboplatin-Ebewe	Ebewe	Australia	-
Carboplatin-Teva	Pharmachemie	Netherlands	-
Cycloplatin	Pliva-Lachema	Czech Republic	-
Paraplatin	Bristol-Myers Squibb	Italy	-

Raw Materials

cis-Diammine platinum diiodide
Silver sulfate
Barium salt of 1,1-cyclobutanedicarboxylic acid

Manufacturing Process

cis-Diammine platinum diiodide was reacted with silver sulfate to give cis-

diaquodiammine platinum sulfate. This was reacted with the barium salt of 1,1-cyclobutanedicarboxylic acid to yield Carboplatin.

References

Harrison R.C. et al.; Inorg. Chem. Acta, 46, L15 (1980)

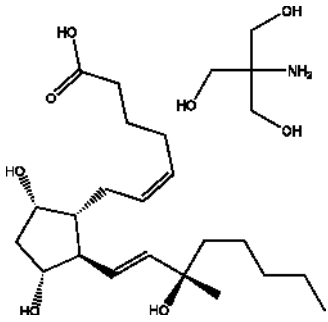
CARBOPROST TROMETHAMINE

Therapeutic Function: Oxytocic

Chemical Name: Prosta-5,13-dien-1-oic acid, 9,11,15-trihydroxy-15-methyl-, (5Z,9α,11α,13E,15S)-, compd. with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)

Common Name: Carboprost Trometamol; Carboprost Tromethamine; Prostodin

Structural Formula:



Chemical Abstracts Registry No.: 58551-69-2

Trade Name	Manufacturer	Country	Year Introduced
Hemabate	Pharmacia and Upjohn Company	-	-
Prostinfenem	Pfizer	-	-
Prostin 15M	Pharmacia and Upjohn Company	-	-
Prostodin	AstraZeneca	-	-
Deviprost	Dr. Reddy`s Laboratories Ltd.	-	-

Raw Materials

(+)-2β,4β-Dihydroxy-3α-iodo-5α-(methoxymetyl)cyclopentane-1β-acetic acid γ-lactone
Lithium aluminum hydride
(2-Oxoheptyl)phosphonate
Methyl magnesium bromide
Diisobutylaluminum hydride
Carboxybutyltriphenylphosphonium bromide
Benzoyl chloride
Tributyltin chloride
Boron trifluoride
Sodium hydride
Sodium hydroxide
Sodium bisulfate
Diazomethane
2-Amino-2-(hydroxymethyl)-1,3-propanediol

Manufacturing Process

(+)-2β4β-Dihydroxy-3α-iodo-5α-(methoxymetyl)cyclopentane-1β-acetic acid γ-lactone 4-benzoate:

To a stirred solution at 20°C of 75 g of (+)-2β,4β-dihydroxy-3α-iodo-5α -(methoxymetyl)cyclopentane-1β-acetic acid γ-lactone (M.P. 101-102°C, $[\alpha]_D$ = -50° (c 0.98, $CHCl_3$) in 135 ml of dry pyridine was added 30.4 ml of benzoyl chloride. After 30 min, 250 ml of toluene was added and the resulting solution evaporated to dryness under reduced pressure. The residue was dissolved in 1000 ml of ethyl acetate. The organic solution was washed with 200 ml 20% of aqueous sulfuric acid and 200 ml of brine. The aqueous solution was washed with 200 ml of ethyl acetate. The ethyl acetate solution was dried and evaporated under reduced pressure to give 95 g of oil which crystallized. The crude product was recrystallized to give 90 g of the white solid, M.P. 84-86°C, $[\alpha]_D$ = +5° (c 1.03, $CHCl_3$).

(-)-3α,5α-Dihydroxy-2β-(methoxymethyl)cyclopentane-1-α-acetic acid γ-lactone 3-benzoate:

To a solution of 4.2 g of lithium aluminum hydride in 420 ml of ether under a nitrogen atmosphere and cooled in a ice bath was added dropwise a solution of 99 g of tributyltin chloride in 210 ml of ether. The cooling bath was removed and stirring continued at ambient temperature for 1.5 hours. To the cooled solution was added 260 ml of water. The organic layer was washed with water and dried. This solution was added slowly at 15°C to a solution of (+)-2β,4β-dihydroxy-3α-iodo-5α-(methoxymethyl)cyclopentane-1β-acetic acid γ-lactone 4-benzoate in 240 ml of benzene. Then the solution was evaporated and the product was stirred with water. Yield of (-)-3α,5α-dihydroxy-2β-(hydroxymethyl)cyclopentane-1α-acetic acid γ-lactone 3-benzoate 93%.

(-)-3α,5α-Dihydroxy-2β-(methoxymethyl)cyclopentane-1α-acetic acid γ-lactone 3-benzoate:

To a solution of 20 g of (-)-3α,5α-dihydroxy-2β-(hydroxymethyl)cyclopentane-1α-acetic acid γ-lactone 3-benzoate in 320 ml of methylene chloride under nitrogen atmosphere and cooled in an ice bath was added dropwise 24.8 ml of boron trifluoride in 320 ml of methylene chloride. After 1 hour to the solution was added 78 g of sodium carbonate in 200 ml of water and then 66 g of solid sodium chloride. The aqueous phase was extracted with ethyl acetate. Yield of (-)-3α,5α-dihydroxy-2β-(methoxymethyl)cyclopentane-1α-acetic acid

γ-lactone 3-benzoate 95%, M.P. 116-118°C.

(-)-3α,5α-Dihydroxy-2β-(3-oxo-trans-1-octenyl)cyclopentane-1α-acetic acid γ-lactone 3-benzoate:

To a mixture of 1.75 g of sodium hydride and 2509 ml of tetrahydrofuran at 5°C was added 8.0 g of (2-oxoheptyl)phosphonate. After 2.5 hours a thick white precipitate formed (ilide mixture). To a stirred mixture of 11 g of anhydrous cromium trioxide and 150 ml of methylene chloride under nitrogene atmosphere and cooled in an ice bath was added 17 g of anhydrous pyridine. The mixture was stirred for 15 min at 0°C for 2 hours at room temperature, then at 0°C again. A solution of 5.0 g of (-)-3α,5α-dihydroxy-2β-(methoxymethyl)cyclopentane-1α-acetic acid γ-lactone 3-benzoate in 150 ml methylene chloride was added to at 0°C to a to the cold Collins oxidant solution. The resulting black mixture was stirred 5 min. After addition of 100 ml of benzene, the mixture was filtered through Celite, washing with benzene. The filtrate was concentrated to 50 ml under reduced pressure and then diluted with 100 ml of benzene. This solution was added to the cold ilide mixture. The resulting dark mixture was stirred for 1.5 hours at room temperature. After dropwise addition of 3 ml of acetic acid the mixture was concentrated to dryness. The residue was dissolved in 400 ml of ethyl acetate. The solution was washed with water and then with brine. Organic phase was dried and evaporated to give dark oil. This oil was purified on silica gel, yield of (-)-3α,5α-dihydroxy-2β-(3-oxo-trans-1-octenyl)cyclopentane-1α-acetic acid γ-lactone 3-benzoate 48%, M.P. 63-63.8°C, $[\alpha]_D$ = -113° (c 1.18, $CHCl_3$).

(-)-3α,5α-Dihydroxy-2β-[(3RS)-3-hydroxy-3-methyl-trans-octenyl] cyclopentane-1α-acetic acid γ-lactone 3-benzoate:

To a solution of 0.20 g of (-)-3α,5α-dihydroxy-2β-(3-oxo-trans-1-octenyl) cyclopentane-1α-acetic acid γ-lactone 3-benzoate in 15 ml of tetrahydrofuran at -78°C under nitrogen was added dropwise 3 ml etheral solution 3 M methylmagnesium bromide. The solution became heterogeneous after 2 hours, to the mixture was added 10 ml of saturated aqueous ammonium chloride and then ether and water. Organic extract was washed with brine, dried over sodium sulfate, and evaporated to give 0.21 g of (-)-3α,5α-dihydroxy-2β-[(3RS)-3-hydroxy-3-methyl-trans-octenyl]cyclopentane-1α-acetic acid γ-lactone 3-benzoate as a colorless oil; $[\alpha]_D$ = -80° (c 1.0, $CHCl_3$).

(-)-3α,5α-Dihydroxy-2β-[3-(RS)-3-hydroxy-3-methyl-trans-octenyl] cyclopentane-1α-acetaldehyde γ-lactol 3-benzoate:

To a solution of 0.50 g of (-)-3α,5α-dihydroxy-2β-[(3RS)-3-hydroxy-3-methyl-trans-octenyl]cyclopentane-1α-acetic acid γ-lactone 3-benzoate in 15 ml of tetrahydrofuran at -78°C under nitrogen was added 10 ml of 10% diisobutylaluminum hydride in toluene. After a gas evolution was ceased, the reaction was quenched by addition of 10 ml of saturated aqueous ammonium chloride. The resulting mixture was stirred at room temperature, filtered through Celite, and extracted with ethyl acetate. Extract was evaporated to give 0.48 g of (-)-3α,5α-dihydroxy-2β-[3-(RS)-3-hydroxy-3-methyl-trans-octenyl]cyclopentane-1-α-acetaldehyde γ-lactol 3-benzoate as an oil.

(15R)- and (15S)-15-methyl-$PGF_{2\alpha}$ methyl esthers:

A mixture of 0.23 g sodium hydride (50% dispersion in mineral oil) and 10 ml of dimethyl sulfoxide stirred under nitrogene at 70-75°C. After 1 hours, gas evolution had ceased. After 0.5 hour, the mixture was cooled to room temperature. To the mixture was added 1.06 g 4-carboxybutyltriphenylphosphonium bromide and the resulting dark red solution stirred 0.5 hour. To this solution was added a solution of 0.48 g of (-)-3α,5α-dihydroxy-2β-[3-(RS)-3-hydroxy-3-methyl-trans-octenyl] cyclopentane-1α-acetaldehyde γ-lactol 3-benzoate in 15 ml of dimethyl sulfoxide. The resulting dark orange mixture was stirred at room temperature for 12 hours. Another 1.2 mmol of freshly prepared ilide in 3.6 ml of solution (prepared as above) was added. After 24 hours, the reaction was quenched by addition to 15 ml of 2 M sodium bisulfate (diluted with ice water) and 25 ml of ether. The organic extract was washed with 5 ml of 1 N sodium hydroxide, and twice with water. The aqueous washings were combined (pH £ 11) and acidified with sodium bisulfate to pH about 1 in the presence of ether. The aqueous phase was extracted with ether. The extract was evaporated to give 0.45 g of dark oily solid. The crude product was dissolved in a mixture of methylene chloride, ether and methanol and treated with excess etheral diazomethane. Evaporation gave 0.40 g of dark oil. The crude product was chromatographed on 10 g of silica gel. Fraction 9-12 contained a mixture of epimers (15R)- and (15S)-15-methyl-$PGF_{2\alpha}$-methyl esthers, yield 160 mg (35%) as an oil. The structure of product was confirmed by ^{1}H-NMR spectrum.

(15S)-15-methyl-$PGF_{2\alpha}$ methyl esthers:

1 g of the mixture of epimers was chromatographed on 100 g (eluent acetone-methylene chloride). It was obtained 150 mg of pure (15S)-15-methyl-$PGF_{2\alpha}$ methyl esthers; M.P. 55-56°C, $[\alpha]_D$ = +24° (c 0.81, ethanol).

Carboprost tromethamine:

The drug was prepared by mixing of (15S)-15-methyl-$PGF_{2\alpha}$ methyl esthers with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1).

References

Yankee E.W. et al.; J. Amer. Chem. Soc.; 1974, 96, 5865
US Patent No. 6,211,233; Apr. 3, 2001; Assigned to Nixon S.A., Paris (FR)

CARBOQUONE

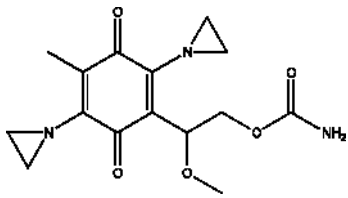
Therapeutic Function: Antineoplastic

Chemical Name: 2,5-Bis(1-aziridinyl)-3-(1-methoxy-2-carbamoyloxyethyl)-6-methyl-1,4-benzoquinone

Common Name: Carbazilquinone

Chemical Abstracts Registry No.: 24279-91-2

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Esquinon	Sankyo	Japan	1974

Raw Materials

2-Methyl-5-(1-methoxy-2-carbamoyloxyethyl)-1,4-benzoquinone
Aziridine

Manufacturing Process

In 10 ml of ethanol was dissolved with heating 200 mg of 2-methyl-5-(1-methoxy-2-carbamoyloxyethyl)-1,4-benzoquinone and the resulting solution was cooled. To the cooled solution was added 0.5 ml of aziridine and then the resulting mixture was allowed to stand in a refrigerator at 5°C to 8°C for 4 days. Thereafter, the crystalline substance which precipitated in situ was recovered by filtration and washed with ethanol to give 50 mg of the desired product as red crystals melting at 200°C (with decomposition).

References

Merck Index 1806
Kleeman and Engel p. 151
DOT 11 (9) 344 (1975)
I.N. p. 186
Nakao, H., Arakawa, M. and Nakamura, T.; US Patent 3,631,026; December 28, 1971; assigned to Sankyo Co., Ltd.

CARBROMAL

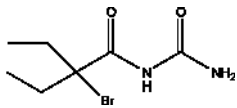
Therapeutic Function: Hypnotic, Sedative

Chemical Name: Urea, (2-bromo-2-ethylbutyryl)-

Common Name: Bromacetocarbamidum; Bromdiaethylacetylcarbamidum; Bromadal; Carbromal

Chemical Abstracts Registry No.: 77-65-6

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Antineuralgiae	Jelfa	-	-
Seduan	Pharmed	-	-
Adalin	Bayer	-	-
Diacid	Daro	-	-
Addisomnol	Synochem	-	-
CARBRITAL	WARNER-LAMBERT CO.	-	-
CARBROMAL	Shanghai Lancheng Corporation	-	-
Adabrom	Hosco	-	-
Carbalin	Arochem Industries	-	-
Dulcipan	Cl Ocana	-	-
P.R.	Boots	-	-
Sedadorm	Pharma Funcke	-	-
Sedamon	Sapic	-	-

Raw Materials

Urea
2-Bromo-2-ethyl-butyrylbromide

Manufacturing Process

120 parts urea and 258 parts 2-bromo-2-ethylbutyrylbromide was mixed and stood at room temperature for 12 hours; then the mixture was heated about 3 hours on water bath and adjusted to alkaline pH with sodium bicarbonate after cooling. The unreacted products was dissolved in brine, the insoluble part was filtered off. The recrystallization from ethanol gave the title product - (2-bromo-2-ethyl-butyryl)urea as the colorless, odorless crystals. MP 114°-118°C.

References

Bayer F.; D.R. Patent No. 225,710; 10 July 1909; Assigned to Farbenfabriken F. Bayer and Co. in Elberfeld

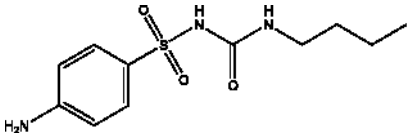
CARBUTAMIDE

Therapeutic Function: Oral hypoglycemic

Chemical Name: Benzenesulfonamide, 4-amino-N-((butylamino)carbonyl)-

Common Name: Aminophenurobutane; Butylcarbamide; Carbutamide; Glybutamide; Sulfabutylharnstoff

Structural Formula:



Chemical Abstracts Registry No.: 339-43-5

Trade Name	Manufacturer	Country	Year Introduced
Carbutamide	Servier	-	-
Carbutamide	Shanghai Lancheng Corporation	-	-
Bucarban	Chinoin	-	-
Glucidoral	Servier	-	-
Oranil	Berlin-Chemie	-	-
Glucofren	Cophar	-	-
Invenol	Hoechst	-	-
Nadisan	Boehringer, Mann	-	-
Bucarban	Chinoin	-	-
Bucarban	Sanofi	-	-
Diabetin	Diasan	-	-
Diabeton	Servier	-	-
Diabex	Dambergis	-	-
Diabex	Alphapharm	-	-
Diaboral	PHARMEX	-	-
Diabutan	G. Streuli and Co. AG	-	-
Dibefanil	Mepha Pharma AG	-	-
Glucidoral	Servier	-	-
Insoral	Valeas	-	-
Insoral	Elvetium S.A.	-	-
Norboral	Silanes	-	-
Orabetic	Lilly	-	-
Orabetic	Biotech	-	-
Orabetic	Cathay	-	-
Orabetic	Mibe GmbH Arzneimittel	-	-
Oranil	AGRINDUSTRIAL, S.A.	-	-
Oranil	A.Menarini Pharmaceutical Industre's Group Ltd.	-	-

Raw Materials

Sodium salt of acetylsulfaniamide
N-Butyl isothiocyanate
Sodium nitrite

Manufacturing Process

223 g of the sodium salt of acetylsulfaniamide are stirred with 223 ml of triethylene glycol. 118 g of n-butyl isothiocyanate are added to the resulting homogeneous mixture. The resulting syrup is heated to 85°C for 4 hours. The mixture is then stirred with 1000 ml of chloroform and 1000 ml of water. The chloroform layer is twice shaken with water, each time with 250 ml. The aqueous extracts are combined and rendered weakly alkaline to phenolphthalein by addition of hydrochloric acid. Unreacted acetyl sulfanilamide precipitates and filtered off. The filtrate is acidified to a pH of 6.5 by the addition of HCl. An oily precipitate settles from the reaction solution and is separated therefrom. N-Butyl acetyl sulfanilylthiourea is precipitated from mother liquors obtained thereby by addition of HCl until Congo paper changes its color to blue. 210 g N-butyl acetyl sulfanilylthiourea are dissolved in 1400 ml of acetone while heating. The solution is mixed with 500 ml of water. A solution of 63 g of sodium nitrite in 120 ml of water is added thereto within about 45 minutes while stirring and cooling to 15°-20°C.

A suspension of crystals is obtained. 240 ml of 25% glacial acid are added thereto within 30 minutes. Stirring of the mixture is continued for 6 hours. N-Butyl acetyl sulfanilylurea mixed with sulfur is precipitated and filtered off. The crude reaction product is suspended in 1000 ml of water and is rendered weakly alkaline to phenolphthalein. Undissolved sulfur is filtered off. The filtrate is acidified by the addition of HCl. 250 g of N-butyl acetyl sulfanilylthiourea having a melting point of 186°-189°C are obtained. It is heated with 500 ml of 5 N potassium hydroxide solution to a temperature of 92°C for 2 hours while stirring. The solid reaction product is dissolved by heating with 750 ml of water and is purified by means of activated charcoal. The resulting solution is heated to 60°C and acidified by addition of HCl. 187 g of N-butyl acetyl sulfanilylthiourea melting at 139°-141°C obtained thereby.

References

Haak E. et al.; US Patent No. 2,907,692; Oct.6, 1959; Assigned to C.F. Boehringer and Soehne G.m.b.H., Mannheim-Waldhof, Germany, a corporation of Germany

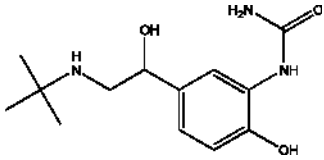
CARBUTEROL

Therapeutic Function: Bronchodilator

Chemical Name: [5-[2-[(1,1-Dimethylethyl)amino]-1-hydroxyethyl]-2-hydroxyphenyl]urea

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 34866-47-2

Trade Name	Manufacturer	Country	Year Introduced
Bronsecur	SK and F	W. Germany	1980
Bronsecur	SK and F	Italy	1980
Pirem	Sasse	W. Germany	1982
Dilabron	Warner Lambert	-	-
Rispan	SK and F	-	-

Raw Materials

3-Amino-4-benzyloxyacetophenone
Ammonia
N-Benzyl-N-t-butylamine
Phosgene
Bromine
Hydrogen

Manufacturing Process

A stirred solution of 40 g (0.41 m) of phosgene in 150 ml of toluene is held at 25°C with a cooling bath while a mixture of 252 g (0.105 m) of 3-amino-4-benzyloxyacetophenone and 220 ml of toluene are added slowly. The mixture is heated to reflux and continued for 30 minutes. Nitrogen is passed through the mixture and then concentrated in vacuo to give a crystalline isocyanate, MP 105°-106°C.

A stirred solution of the isocyanate (28.0 g) in 500 ml of dry benzene is saturated with ammonia. After one hour, the mixture is cooled to give the crystalline 4-benzyloxy-3-ureidoacetophenone, MP 184°-186°C.

To a stirred solution of 5.7 g (0.02 m) of 4-benzyloxy-2-ureidoacetophenone in 100 ml of chloroform is added 32 g (0.02 m) of bromine. The mixture is stirred at room temperature for about 45 minutes and the solution is concentrated in vacuo at 25°-30°C. The amorphous residue (hydrobromide salt of 4-benzyloxy-α-bromo-3-ureidoacetophenone) is dissolved in 80 ml of acetonitrile and 98 g (0.06 m) of N-benzyl-N-t-butylamine is added. The mixture is stirred and refluxed for 1.5 hours, then it is cooled to 0°C in an ice bath. Crystalline N-benzyl-N-t-butylamine hydrobromide is filtered. The filtrate is acidified with ethereal hydrogen chloride. The semicrystalline product is filtered after diluting the mixture with a large excess of ether. Trituration of the product with 60 ml of cold ethanol gives 4-benzyloxy-α-(N-benzyl-N-t-butylamino)-3-ureidoacetophenone hydrochloride, MP 200°-221°C (decomposition).

A solution of 10.5 g (0.0218 m) of 4-benzyloxy-α-(N-benzyl-N-t-butylamino)-

3-ureidoacetophenone hydrochloride in 65 ml of methanol and 25 ml of water is added to a suspension of 1.5 g of 10% palladium-on-carbon in 10 ml of water. The mixture is hydrogenated on the Parr apparatus at room temperature, using an initial pressure of 60 psi of hydrogen. After 4 hours about 80% of the theoretical volume of hydrogen has been absorbed. The mixture is filtered, an additional 1.5 g of 10% palladium-on-carbon is added and the mixture is again hydrogenated on the Parr apparatus under the same conditions. After hydrogenating for an additional 3 hours, the mixture is filtered and the filtrate is concentrated in vacuo. The residue is stripped twice with toluene and crystallized with ether-ethanol to give α-(t-butylaminomethyl)-4-hydroxy-3-ureidobenzyl alcohol hydrochloride, MP 214°-215°C.

References

Merck Index 1817
DFU 1 (9) 412 (1976)
Kleeman and Engel p. 153
OCDS Vol. 2 p. 41 (1980)
DOT 12 (2) 483 (1976)
I.N. p. 187
Kaiser, C. and Ross, S.T.; US Patent 3,763,232; October 2, 1973; assigned to Smith Kline and French Laboratories
Kaiser, C. and Ross, S.T.; US Patent 3,917,847; November 4, 1975; assigned to Smith Kline Corp.

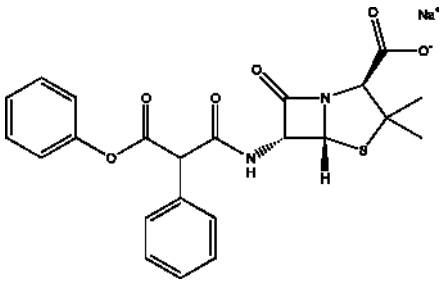
CARFECILLIN SODIUM

Therapeutic Function: Antibiotic

Chemical Name: Malonamic acid, N-(2-carboxy-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo(3.2.0)hept-6-yl)-2-phenyl-, 1-phenyl ester monosodium salt

Common Name: Carbenicillin phenyl sodium; Carfecillin sodium

Structural Formula:



Chemical Abstracts Registry No.: 21649-57-0

Trade Name	Manufacturer	Country	Year Introduced
Carfecillin sodium	Beecham (GSK)	-	-

Raw Materials

Phenylmalonic acid
Thionyl chloride
Phenol
6-Aminopenicillanic acid

Manufacturing Process

Phenylmalonic acid (27 g) was mixed with dry ether (80 ml) and treated with thionyl chloride (17.85 g, 10.9 ml) and dimethylformamide (4 drops). The mixture was refluxed for 3 hours on a hot water bath. The solvent was evaporated under reduced pressure and the residue dissolved in fresh dry ether (80 ml). Phenol (14.1 g) was added all at once and the mixture refluxed for 2 hours. The reaction was cooled to room temperature, washed with water (25 ml) and extracted with saturated sodium bicarbonate solution until the extracts were alkaline. The combined aqueous extracts were washed with ether (100 ml) and acidified with 5 N HCl. The precipitated oil was extracted with methylene chloride. The combined organic extracts were washed thoroughly with water (6x120 ml) dried over anhydrous magnesium sulphate and evaporated. The solid residue was crystallised from benzene to give monophenyl phenylmalonate, a colourless crystalline solid 30.2 g (78.7 %) MP 115-117°C. This product (5.12 g, 0.02 m) was mixed with thionyl chloride (20 ml) and heated in a water bath at 75°C for 1 hour. The excess thionyl chloride was evaporated under reduced pressure. The residue was mixed with dry benzene (10 ml) and again evaporated to dryness to remove residual thionyl chloride. The final residue was dissolved in dry acetone (100 ml) and added, with stirring, to a solution of 6-aminophenicillanic acid (4.32) in water (100 ml), 1 N sodium hydroxide (20 ml), 1 N sodium bicarbonate solution (30 ml) and acetone (50 ml) cooled to 12°C. The reaction mixture was stirred for 2 hours. The resulting mixture was stirred at room temperature for 2 hours. The resulting solution was extracted with ether (3x60 ml) and the extracts discarded. The aqueous layer was covered with ether (60 ml) and acidified with 1 N HCl to pH 2. The ether layer was separated and the aqueous layer extracted with ether (2x60 ml). The combine ether extracts were washed with water (20 ml) and extracted with 1 N sodium bicarbonate solution to pH 7. The neutral aqueous extract was evaporated under reduced temperature and pressure. The residue was dried over phosphorous pentoxide in vacuo to give 6.7 (70.4%) of penicillin salt as an amorphous solid. The solid, when dissolved in ethanol (50 ml) at room temperature gave on standing 30 min the penicillin salt as a colorless crystalline solid 5.23 g (78.1 %).

References

Hardy K. et al.; US Patent No. 3,853,849; Dec. 10, 1974; Assigned to Beecham Group Limited, Brentford Middlesex, England

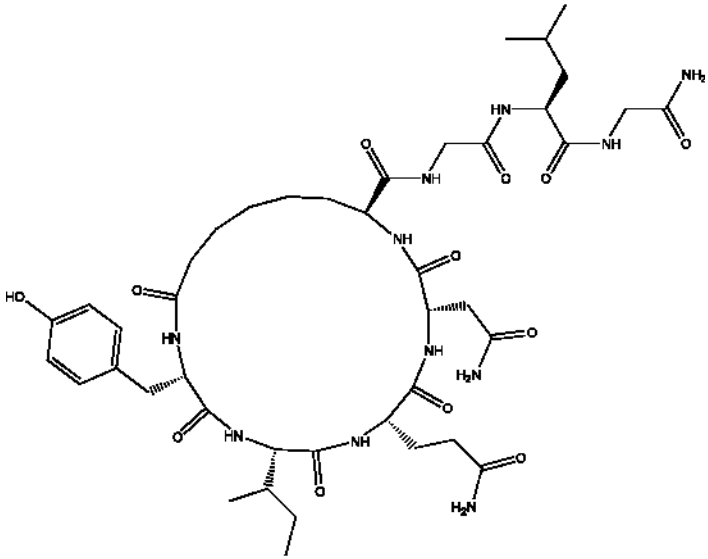
CARGUTOCIN

Therapeutic Function: Oxytocic

Chemical Name: 1-Butanoic acid-7-glycine-1,6-dicarbaoxytocin

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 33065-67-3

Trade Name	Manufacturer	Country	Year Introduced
Statocin	Yoshitomi	Japan	1982

Raw Materials

Cyclic polypeptide
Hydrogen

Manufacturing Process

To a suspension of Z-Tyr(Bz)-Ile-Gln-Asn-Asu(OTCP)-Gly-Leu-Gly-NH_2 (1,310 mg) in DMF (350 ml) is added a suitable amount of palladium black. Hydrogen gas is introduced with stirring at room temperature (25°C) for about 40 hours. After stirring the mixture at 30°-35°C for several hours, the catalyst is filtered off and the filtrate is concentrated under reduced pressure. A large amount of ether is added to the residue, and the white coagulum is collected

by filtration, washed with ether and dried. This is dissolved in water (30 ml), and the solution is filtered. The filtrate is passed through a column (3 x 11.5 cm) of Amerlite IR-45 (OH-form). The fractions which show a UV-absorption maximum at 280 nm are combined and passed through a column (3 x 125 cm) of CM-Sephadex C-25 to remove the noncyclic compound and obtain neutral parts. The detection of the objective compound is made by UV-absorption at 280 nm. The aqueous solution of the neutral parts is concentrated below 35°C, under reduced pressure, and the concentrate is lyophilized to give 504 mg of the crude title compound in the form of 5 hydrate.

References

Merck Index 1822
DFU 8 (3) 188 (1983)
DOT 19 (3) 130 (1983)
Sakakibara, S. and Yamanaka, T.; US Patent 3,749,705; July 31, 1973; as signed to Yoshitomi Pharmaceutical Industries Ltd. (Japan)

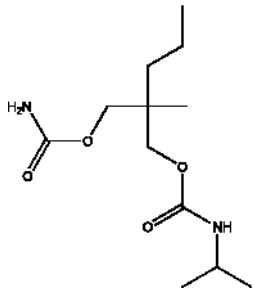
CARISOPRODOL

Therapeutic Function: Muscle relaxant

Chemical Name: (1-Methylethyl)carbamic acid 2-([(aminocarbonyl)oxy] methyl)-2-methylpentyl ester

Common Name: Isopropyl meprobamate

Structural Formula:



Chemical Abstracts Registry No.: 78-44-4

Trade Name	Manufacturer	Country	Year Introduced
Soma	Wallace	US	1959
Rela	Schering	US	1959
Sanoma	Heilit	W. Germany	-
Flexartal	Clin Midy	France	1961

Trade Name	Manufacturer	Country	Year Introduced
Caprodat	Ferrosan	Denmark	-
Carisol	AFI	Norway	-
Carisoma	Wallace	US	-
Diolene	Pharma. Farm. Spec.	Italy	-
Erbasoma	Erba	Italy	-
Meprodat	Star	Finland	-
Mioril	Rossini	Italy	-
Mioxom	Dessy	Italy	-
Myobutazolidin	Fujisawa	Japan	-
Relasom	Rafa	Israel	-
Relaxo-Powel	Erba	Italy	-
Soma	Horner	Canada	-
Soma	Guidotti	Italy	-
Somadril	Dumex	Denmark	-
Somalgit	Wallace	US	-
Somalgit Simple	Inibsa	Spain	-
Somanil	Banyu	Japan	-
Soprodol	Schein	US	-

Raw Materials

Isopropylamine
Phosgene
2-Methyl-2-propyl-1,3-propanediol
Sodium cyanate

Manufacturing Process

A cooled 10% solution of 1 mol of phosgene in toluene was added with stirring to a cooled solution of 1 mol of 2-methyl-2-propyl-1,3-propanediol and 2 mols of dimethylaniline also dissolved in toluene, at such a rate that the temperature of the mixture was maintained at about 25°C. The mixture was allowed to remain at this temperature for several hours, then cooled and extracted with cold 5% hydrochloric acid solution to remove the dimethylaniline. The toluene layer was dried using a suitable drying agent and the 2-methyl-2-propyl-3-hydroxypropyl chlorocarbonate used in subsequent reactions in the form of its solution in anhydrous toluene.

A quantity of solution obtained as described containing 0.1 mol of the chlorocarbonate was treated with 0.2 mol of anhydrous isopropylamine and allowed to react at ordinary room temperature. The solution was cooled, extracted with dilute hydrochloric acid and the organic layer concentrated by evaporation of the solvent. The crude monocarbamate was purified by distilling at 86° to 88°C at about 0.01 mm. It was a clear, viscous liquid.

21.7 g (0.1 mol) of N-isopropyl-2-methyl-2-propyl-3-hydroxypropylcarbamate and 7.5 g (0.11 mol) of anhydrous sodium cyanate are stirred in 200 ml anhydrous chloroform in a suitable vessel equipped with a gas inlet tube,

stirrer and thermometer. While cooling the vessel, anhydrous hydrogen chloride is passed into the stirred mixture slowly for 5 hours maintaining the temperature between 0° and 5°C. Alternatively ethyl urethane in the presence of aluminum isopropylate as a catalyst may be used in place of the sodium cyanates and HCl. The mixture is then allowed to stand at room temperature overnight.

The solid material is separated by filtration and the chloroform solution concentrated to an oil under reduced pressure. The oil is dissolved in 50 ml of trichloroethylene, the solution treated with charcoal, filtered and the filtrate added to 125 ml of hexane. The crystalline material which forms on standing at refrigerator temperature is removed by filtration, washed with light petroleum ether and dried at about 50°C. Approximately 20 g of product are obtained. On recrystallizing from trichloroethylene-hexane, 17.8 g of purified compound are obtained, MP 89° to 91°C.

References

Merck Index 1824
Kleeman and Engel p. 155
PDR pp. 830, 1606,1883
OCDS Vol. 1 p. 219 (1977)
I.N.p. 189
REM p. 926
Berger, F.M. and Ludwig, B.J.; US Patent 2,937,119; May 17, 1960; assigned to Carter Products, Inc.

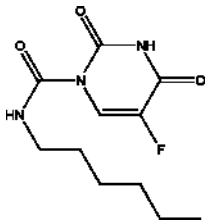
CARMOFUR

Therapeutic Function: Antineoplastic

Chemical Name: 5-Fluoro-N-hexyl-3,4-d-dihydro-2,4-dioxo-1(2H)-pyrimidinecarboxamide

Common Name: HCFU

Structural Formula:



Chemical Abstracts Registry No.: 61422-45-5

Trade Name	Manufacturer	Country	Year Introduced
Mifurol	Mitsui	Japan	1981
Yamafur	Yamanouchi	Japan	1981

Raw Materials

5-Fluorouracil
n-Hexyl isocyanate

Manufacturing Process

13.0 g (0.10 mol) of 5-fluorouracil was suspended in 60 ml of dimethyl acetamide, then 14.0 g (0.11 mol) of n-hexyl isocyanate was added thereto at room temperature and stirred at 50°C for 8 hours. After the reaction mixture was concentrated under reduced pressure, the residue was poured into 400 ml of water and resultant precipitate was filtered off. The precipitate was washed and dried and 19.3 g (75.0% yield) of 5-fluoro-1-(n-hexylcarbamoyl)uracil was obtained.

The product was recrystallized from ether and there were obtained white crystals melting at 283°C (decomposition).

References

Merck Index 1828
DFU 1 (4) 235 (1982)
DOT 18 (9) 424 (1982)
I.N. p. 190
Ozaki, S. and Mori, H.; US Patent 4,071,519; January 31, 1978; assigned to Mitsu Toatsu Chemicals, Inc.

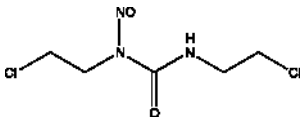
CARMUSTINE

Therapeutic Function: Antitumor

Chemical Name: Urea, 1,3-bis(2-chloroethyl)-1-nitroso-

Common Name: Carmustine

Structural Formula:



Chemical Abstracts Registry No.: 154-93-8

Trade Name	Manufacturer	Country	Year Introduced
BCNU	Gencorp Aerojet	US	-
BCNU	Bristol-Myers Squibb	-	-
BiCNU	Bristol-Myers Squibb	-	-
Gliadel Wafer	Rhone-Poulenc Rorer	-	-

Raw Materials

N,N'-Bis-(2-chloroether)-urea
Sodium nitrite
Formic acid

Manufacturing Process

A solution of sodium nitrite (6.9 g, 0.10 mole) in water (60 ml) was added dropwise to a cold (0-5°C), stirred solution of 1,3-bis(2-chloroethyl)urea (8.0 g, 0.044 mole) in formic acid (50 ml). The reaction mixture was stirred further at 0°C until the pale yellow oil that had formed solidified. The nitrosourea was collected and washed quickly with cold water (2 x 10 ml), and dried in vacuum; yield 6.7 g. (71%).

References

Johnston T.P. et.al.; J. Med. Chem. 6, 669, (1963)
Bastian H., Justus Liebigs, Ann. Chem., 566, 210 (1950)

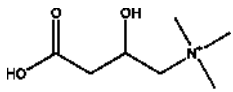
CARNITINE

Therapeutic Function: Gastric stimulator, Pancreatic stimulator

Chemical Name: 3-Carboxy-2-hydroxy-N,N,N-trimethyl-1-propanaminium hydroxide, inner salt

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 461-06-3; 5842-94-8 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Flatistine	Sauba	France	1978
Carnetina	Sigma Tau	Italy	1981
Nefrocarnit	Nefro Pharma	W. Germany	1983
Carnitene	Refarmed SA	Switz.	1983
Abedine	Nippon Zoki	Japan	-
Bicarnesine	Labaz	France	-
Carn	Benvegna	Italy	-
Carnitan	Kakenyaku Kako	Japan	-
Carnitine	Tyson	US	-
Carnitolo	Sirt-B.B.P.	Italy	-
Entomin	Maruko	Japan	-
Metina	Francia	Italy	-
Monocamin	Tanabe	Japan	-
Polycartin	Daigo Eiyo	Japan	-

Raw Materials

Trimethylamine
Epichlorohydrin
Sodium cyanide
Hydrogen chloride

Manufacturing Process

9.3 g of epichlorohydrin was added at a temperature of 40°-50°C under stirring to 9.6 g of trimethylamine hydrochloride dissolved in 10 cc of water. Continuing the reaction for an hour at the above temperature, the reaction product was concentrated under reduced pressure to obtain the crystals of 3-chloro-2-oxypropyl trimethyl ammonium chloride which were recrystallized with 25 cc of ethanol. The crystals obtained by concentrating the mother liquor were also recrystallized. The yield was 17.4 g (MP 190°C, yield 91.5%). This substance occurs as white, somewhat hygroscopic crystals and is readily soluble in water or alcohol, but insoluble in benzene, toluene, ether, acetone or chloroform.

The result of analysis assuming $(C_6H_{15}C_{10}N)^+Cl^-$-calculated value: N, 7.45%; total Cl, 37.7%; Cl^-, 18.88%. Observed value: N, 7.36%; total Cl, 37.54%; Cl^-, 18.98%.

18.8 g of 3-chloro-2-oxypropyl trimethyl ammonium chloride was dissolved in a mixed solvent composed of 19 cc of methanol and 1 cc of water. 5.1 g of sodium cyanide dissolved in 8 cc of water was dropped into the solution at 50°C under stirring. After dropping, the mixture was held at this temperature for 30 minutes under stirring. The reaction product was then neutralized with 6 N hydrochloric acid toward pH 5, and, after cooling, sodium chloride separated out and was filtered. The filtrate was concentrated to dryness under reduced pressure, and the residue was washed with small quantity of ethanol. Drying the residue, dissolving in hot methanol, filtering off insoluble matters, and cooling mother liquor, the crystals of 3-cyano-2-axypropyl trimethyl ammonium chloride which deposited out were filtered and dried. Yield 16.7 g [MP (decomposition) 220°-223°C, yield 93.4%].

12.5 cc of concentrated hydrochloric acid was added to 17.9 g of 3-cyano-2-oxypropyl trimethyl ammonium chloride. Gradually heating the mixture on a water bath under stirring, so bringing the temperature up to 98°C at the end of about 3 hours, 9 cc of water was added. After cooling, free hydrochloric acid was neutralized with 3 cc of 6 N sodium hydroxide, and then by adding 1 g of active charcoal, the reaction product was decolorized and filtered. The filtrate was concentrated to almost dryness under reduced pressure. Then, this concentrate was, after washing with 10 cc of ethanol, dried. Yield 24.7 g.

The dried product was dissolved in 46.5 cc of glacial acetic acid by heating on a boiling water bath. The insoluble matter is removed by filtering hot, and on cooling the mother liquor, crystals of carnitine hydrochloride separated out. The crystals were filtered, washed with 10 cc of ethanol, and dried. Recrystallizing 19.7 g of the crude carnitine with methanol, 17 g of the refined carnitine was obtained [MP 195°-198°C (decomposing point), yield 86%], The overall yield of the refined carnitine through whole steps was about 74%. Carnitine thus prepared was an odorless, white, crystalline powder, having a strong acid taste.

References

Merck Index 1833
Kleeman and Engel p. 156
PDR p. 1807
DOT 19 (4) 185 (1983)
I.N. p. 190
Noguchi, J. and Sakota, N.; US Patent 3,135,788; June 2, 1964; assigned to Nihon Zoki Seiyaku Kabushikikaisha (Japan)

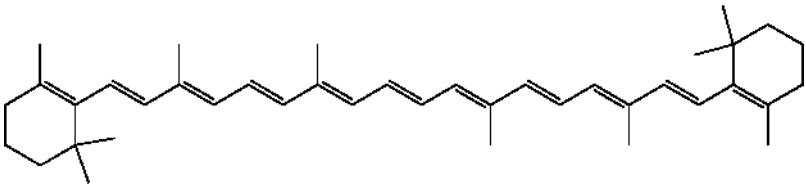
β-CAROTENE

Therapeutic Function: Vitamin A precursor, Sunscreen agent

Chemical Name: β-Carotene

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 7235-40-7

Trade Name	Manufacturer	Country	Year Introduced
Carotaben	Hermal	W. Germany	1975
Solatene	Roche	US	1975
Vitacarotene	Pellestier	Spain	-
Beta-carotene	Solgar	US	-

Raw Materials

3,8-Dimethyl-3,5,7-decatrien-1,9-diyne
Phenyl lithium
4-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-2-methyl-2-buten-1-al
Hydrogen

Manufacturing Process

3.6 g (0.023 mol) of 3,8-dimethyl-3,5,7-decatrien-1,9-diyne were dissolved in 50 ml of absolute ether, and to the solution was added 0.05 mol of ethereal phenyl-lithium solution. The mixture was refluxed for 30 minutes. Then a solution of 11 g (0.05 mol) of 4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-methyl-2-buten-1-al in 100 ml of ether was added dropwise, and the reaction mixture was boiled for 2 hours. The reaction mixture was then hydrolyzed with aqueous ammonium acetate solution, and the ethereal layer was separated, dried and concentrated. The residue, i.e., 1,18-di(2,6,6-trimethyl-1-cyclohexen-1-yl)-3,7,12,16-tetramethyl-4,15-dihydroxy-2,7,9,11,16-octadecapentaen-5,13-diyne, was a resinous product (having 1.9 active hydrogen atoms and absorption maxima in the ultraviolet spectrum at 326 and 341 nm) which was used for the next step without any further purification. The resin was dissolved in 200 ml of methylene chloride, 10 ml of glacial acetic acid were added to the solution, and the mixture was cooled to -40°C in a carbon dioxide atmosphere, while stirring. Then, 9 ml of aqueous hydrobromic acid (60%) were added in one portion, the mixture was stirred at -35°C for 1.5 minutes, and subsequently 200 ml of ice water were run into the mixture. After further stirring the mixture for 2 hours at 0°C, the methylene chloride layer was separated, washed with water and sodium bicarbonate solution, dried with Na_2SO_4 andconcentrated in vacuo. The residue, i.e., 11,12-11',12'-bisdehydro-betta-carotene, was a tough resin or a foamy solid (having no active hydrogen atoms and possessing absorption maxima in the ultraviolet spectrum at 334 and 408 nm). This product can be purified by chromatography. The crude product can also be used for the next step without any preliminary purification.

11.4 g of 11,12-11',12'-bisdehydro-β-carotene were dissolved in 100 ml of petroleum ether (boiling range 80° to100°C), and the solution was hydrogenated under normal conditions after the addition of 0.5 ml of quinoline and 5 g of a lead-poisoned palladium catalyst. After the calculated amount of hydrogen had been absorbed, the catalyst was removed by filtration and the filtrate was extracted with dilute sulfuric acid to remove the quinoline. By concentrating the solution in the usual manner there was obtained 11,12-11',12'-di-cis-carotene. The product was purified by recrystallization from benzene-alcohol. The purified product melts at 154°C; absorption maxima in the ultraviolet spectrum at 276, 334, 338, 401 and 405 nm. The isomerization was effected by heating the product for 10 hours at 90 to 100°C in high-boiling petroleum ether in a carbon dioxide atmosphere. The resulting and

carotene melted at 180°C; ultraviolet absorption maxima at 452 and 480 nm.

Preparation of the intermediates for the above chemical synthesis are also described in US. Patent 2,917,539. The other patents cited below describe a fermentation route. US Patent 2,848,508 describes preparation from carrots.

References

Merck Index 1837
PDR pp. 1501, 1734
I.N.P. 136
REM p. 1005
Barnett, H.M., Hartmann, M.L., Mosher, R.C. and Espoy, H.M.; US Patent 2,848,508; August 19, 1958; assigned to Barnett
Isler, O., Montavon, M., Ruegg, R. and Zeller, P.; US Patent 2,917,539; December 15, 1959; assigned to Hoffmann - La Roche Inc.
Zajic, J.E.; US Patents 2,959,521 and 2,959,522; November 8, 1960; both assigned to Grain Processing Corp.
Miescher, G.M., US Patent 3,001,912; September 26, 1961; assigned to Commercial Solvents Cow.
Zajic, J.E.; US Patent 3,128,236; April 7, 1964; assigned to Grain Processing Corp.

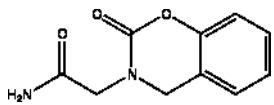
CAROXAZONE

Therapeutic Function: Antidepressant

Chemical Name: 2-Oxo-2H-1,3-benzoxazine-3(4H)-acetamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 18464-39-6

Trade Name	Manufacturer	Country	Year Introduced
Timostenil	Farmitalia	Italy	1975

Raw Materials

Ethyl glycinate HCl
Salicylic aldehyde
Ammonia
Hydrogen
Phosgene

Manufacturing Process

37.9 g of ethyl glycinate hydrochloride were dissolved in 400 cc of ethanol and 33.5 g of salicylic aldehyde were added. It is refluxed for half an hour and cooled. 38 cc of triethylamine and 25 g of Raney nickel are then added where after hydrogenation is carried out at room temperature and under atmospheric pressure. After hydrogen adsorption was complete, the mixture was filtered and the alcohol evaporated off. The residue was taken up with acidified water, extracted with ether to eliminate part of the by-products, consisting mainly of o-cresol, then made alkaline with ammonia and extracted with ethyl acetate. The solvent was removed in vacuo and the residue crystallized from ether/petroleum ether. 36.7 g of o-hydroxybenzylaminoacetic acid ethyl ester melting at 47°C are obtained.

20 g of this compound were dissolved in 100 cc of tetrahydrofuran and 100 cc of a 30% solution of phosgene in tetrahydrofuran solution were added. After one night at room temperature, the reaction mixture was dried, taken up with 150 cc of anhydrous pyridine and allowed to stand overnight. The pyridine was then removed in vacuo and the residue dissolved in benzol was washed several times with water and chromatographed over 250 g of alumina. Elution with benzene/petroleum ether yielded 16 g of 4H-3-carboethoxymethyl-1,3-benzoxazine-2-one, melting at 90°-91°C.

5 g of this last compound were dissolved in 120 cc of absolute ethanol and saturated with NH_3 at 0°C. It was allowed to stand overnight where after 1.5 g of 4H-3-carboxamidomethyl-1,3-andenzoxazine-2-one, melting at 205°C, were obtained. By evaporation from the mother liquors further quantities of the same product were obtained.

References

Merck Index 1842
Kleeman and Engel p. 157
OCDS Vol. 3 p. 191 (1984)
DOT 12 (6) 236 (1976)
I.N. p. 190
Bernardi, L., Coda, S., Pegrassi, L. and Suchowsky, G.K.; US Patent 3,427,313; February 11, 1969; assigned to Societa Farmaceutici Italia (Italy)

CARPHENAZINE MALEATE

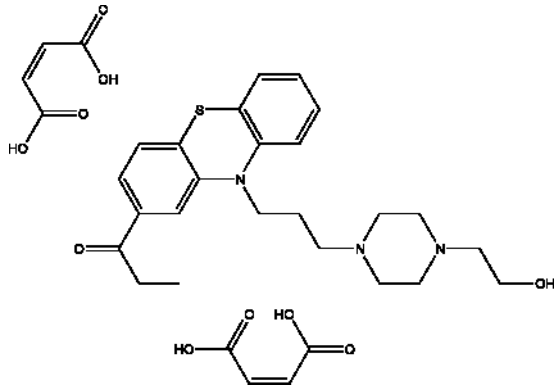
Therapeutic Function: Tranquilizer

Chemical Name: 1-[10-[3-[4-(2-Hydroxyethyl)-1-piperazinyl]propyl]-10H-phenothiazin-2-yl]-1-propanone dimaleate

Common Name: Carfenazine maleate

Chemical Abstracts Registry No.: 2975-34-0; 2622-30-2 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Proketazine	Wyeth	US	1962

Raw Materials

2-Propionylphenothiazine
N-(2-Hydroxyethyl)piperazine
Sodium hydride
Trimethylene chlorobromide

Manufacturing Process

As described in US Patent 3,023,146, in a round-bottomed flask were placed 35 g of 2-propionyl phenothiazine (0.14 mol) 7 g of 50% sodium hydride in mineral oil (0.14 mol), and 240 cc of dimethyl formamide dried over sodium hydride. The resultant solution was stirred at room temperature for 2 hours, and then 88 g (0.56 mol) of trimethylene chlorobromide was added at once.

The mixture was stirred for 2 hours, heated at 60 to 70°C for 1 hour and poured into 2 liters of H_2O. The resulting suspension was extracted with ether, the ether layer separated and the ether removed under vacuum. A gummy mass remained which was dissolved in decalin and the solution was partly distilled to remove excess chlorobromide. After removal of most of the decalin under vacuum, the residue was treated with a large excess of N-(β-hydroxyethyl)-piperazine and heated on a steam bath for 2 hours. This material was extracted with dilute aqueous HCl, this acid layer neutralized with aqueous base and the resulting oil extracted into ether. The ether layer was washed with water until the washings were neutral and dried over anhydrous potassium carbonate. On treatment with maleic acid in ether a yellow solid separated which was recrystallized from isopropanol. This yellow solid had MP 175° to 177°C.

References

Merck Index 1844
Kleeman and Engel p. 154

OCDS Vol. 1 p.383 (1977)
I.N. p. 188
REM p. 1086
Tislow, R.F., Bruce, W.F. and Page, J.A.; US Patent 3,023,146; February 27, 1962; assigned to American Home Products Corporation
Sherlock, M.H. and Sperber, N.; US Patent 2,985,654; May 23, 1961; assigned to Schering Corporation

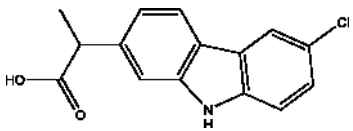
CARPROFEN

Therapeutic Function: Antiinflammatory

Chemical Name: 6-Chloro-α-methylcarbazole-2-acetic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 53716-49-7

Trade Name	Manufacturer	Country	Year Introduced
Imadyl	Roche	Switz.	1981
Imadyl	Roche	W. Germany	1982
Imafen	Roche	-	-
Rimadyt	Roche	-	-

Raw Materials

6-Chloro-α-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester
p-Chloranil
Sodium hydroxide
Hydrogen chloride

Manufacturing Process

A mixture of 34.9 g of 6-chloro-α-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester (mixture of diastereomers), 350 ml CP xylene and 56.0 g of p-chloranil was stirred and heated under an atmosphere of dry nitrogen. The reaction flask was wrapped in aluminum foil in order to keep out any extraneous light. After the reaction mixture had stirred at reflux temperature for 6 hours, heating and stirring were stopped and the reaction mixture was left overnight at room temperature. The supernatant liquid was decanted

through a filter. The residue was triturated with 100 ml of warm benzene and the supernatant liquid was decanted through a filter. This process was repeated three more times. Ether (300 ml) was added to the combined filtrates. The solution was extracted with cold 2 N sodium hydroxide (3 x 100 ml), washed by extraction with water until neutral and dried over anhydrous magnesium sulfate. Following filtration of the desiccant and evaporation of the solvent, a residue of 35.5 g remained. Crystallization from 50 ml of methanol gave 14.8 g of 6-chloro-α-methylcarbazole-2-acetic acid ethyl ester, MP 106°-107.5°C (43.2%).

A stirred mixture of 11 g of 6-chloro-α-methylcarbazole-2-acetic acid ethyl ester, 100 ml ethanol and 100 ml of 3 N sodium hydroxide was heated (N_2 atmosphere). After 2 hours at reflux, the reaction mixture was concentrated to dryness under reduced pressure. Water (300 ml) and ice (200 g) were added to the residue and concentrated hydrochloric acid was added until the mixture was strongly acid. The acidic mixture was extracted with ether (3 x 200 ml). The ether extracts were combined, washed by extraction with water (3 x 100 ml) and dried over anhydrous magnesium sulfate. Following filtration of the desiccant and evaporation of the solvent, a yield of 9.89 (98.2%) was obtained. Crystallization from $CHCl_3$ yielded 6.2 g (62.0%) of 6-chloro-α-methylcarbazole-2-acetic acid, MP 197°-198°C. A second crop of 1.6 g, MP 195°-199°C was obtained from the mother liquors.

References

Merck Index 1846
DFU 2 (1) 15 (1977)
OCDS Vol. 3 p. 169 (1984)
DOT 18 (4) 172 (1982)
I.N. p. 191
Berger, L. and Corraz, A.J.; US Patent 3,896,145; July 22, 1975; assigned to Hoffmann-LaRoche, Inc.

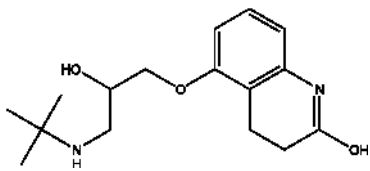
CARTEOLOL

Therapeutic Function: Beta-adrenergic blocker

Chemical Name: 5-(3-tert-Butylamino-2-hydroxypropoxy)-3,4-dihydrocarbostyril

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 51781-06-7

Trade Name	Manufacturer	Country	Year Introduced
Mikelan	Otsuka	Japan	1981
Endak	Madaus	W. Germany	1982

Raw Materials

5-Hydroxy-3,4-dihydrocarbostyril
Epibromohydrin
t-Butylamine

Manufacturing Process

A mixture of 1.63 g of 5-hydroxy-3,4-dihydrocarbostyril, 2.5 g of epibromohydrin and 2 drops of piperidine was heated at a temperature of 95°C to 100°C for a period of 4 hours with stirring. The reaction mixture was then concentrated to dryness under reduced pressure and the residue was recrystallized from acetone to obtain 1.2 g of 5-(2,3-epoxy)propoxy-3,4-dihydrocarbostyril as a colorless powder having a melting point of 172°C to 173°C.

A mixture of 0.75 g of 5-(2,3-epoxy)propoxy-3,4-dihydrocarbostyril, 1.0 g of tert-butylamine and 25 ml of ethanol was stirred at a temperature of from 50°C to 55°C for a period of 4 hours. Ethanol and unreacted tert-butylamine were distilled off under reduced pressure and the resulting residue was dissolved in acetone.

References

Merck Index 1850
DFU 2 (5) 288 (1977)
Kleeman and Engel p. 158
OCDS Vol. 3 p. 183 (1984)
DOT 18 (10) 551 (1982) and 19 (7) 413 (1983)
I.N. p. 191
Tamura, Y., Nakagawa, K., Yoshizaki, S. and Murakami, N.; US Patent 3,910,924; October 7, 1975; assigned to Otsuka Pharmaceutical Co., Ltd.

CARTICAINE

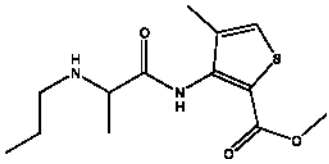
Therapeutic Function: Local anesthetic

Chemical Name: 4-Methyl-3-[[1-oxo-2-(propylamino)propyl]amino]-2-thiophene carboxylic acid methyl ester

Common Name: -

Chemical Abstracts Registry No.: 23964-58-1; 23964-57-0 (Hydrochloride salt)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Ultracain	Hoechst	W. Germany	1976
Ultracain	Hoechst	France	1981

Raw Materials

3-Amino-2-carbomethoxy-4-methyl thiophene
Chloropropionyl chloride
n-Propylamine

Manufacturing Process

3-α-Chloropropionylamino-2-carbomethoxy-4-methylthiophene (prepared from 3-amino-2-carbomethoxy-4-methylthiophene and chloropropionyl chloride) was dissolved in toluene and n-propylamine added. The whole mixture was heated to boiling for 6 to 7 hours. After cooling, the propylamine hydrochloride that had formed was removed by washing with water, The toluene phase was dried with sodium sulfate, and then the solvent and excess propylamine were removed by distillation. The oily residue was taken up in ether. The hydrochloride of 3-n-propylamino-α-propionylamino-2-carbomethoxy-4-methylthiophene was obtained by introducing hydrogen chloride gas or by means of methanolic hydrogen chloride. The base boils at 162°C to 167°C under 0.3 mm of mercury pressure and the hydrochloride melts at 177°C to 178°C.

References

Merck Index 1853
Kleeman and Engel p. 158
DOT 12 (4) 132 (1976)
Ruschig, H., Schorr, M., Muschaweck, R. and Rippel, R .; U.S. Patent 3,855,243; December 17, 1974; assigned to Farbwerke Hoechst AG (Germany)

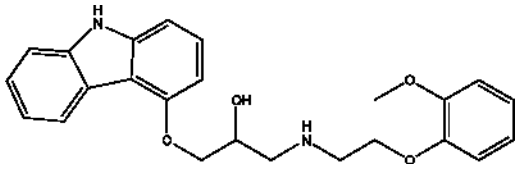
CARVEDILOL

Therapeutic Function: Beta-adrenergic blocker

Chemical Name: 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-((2-(2-methoxyphenoxy)ethyl)amino)-

Common Name: Carvedilol; Karvedilol

Structural Formula:



Chemical Abstracts Registry No.: 72956-09-3

Trade Name	Manufacturer	Country	Year Introduced
Coreg	Roche	-	-
Coreg	GlaxoSmithKline	UK	-
Coropres	Roche	-	-
Dimitone	Roche	-	-
Eucardic	Roche	-	-

Raw Materials

Epichlorohydrin
4-Hydroxycarbazole
o-Methoxyphenoxyethylamine

Manufacturing Process

1-(9H-Carbazol-4-yloxy)-3-((2-(2-methoxyphenoxy)ethyl)amino)-2-propanol may be synthesized by the method of preparation of S-(-)-(1-carbazol-4-yloxy)-3-[2-(2-methoxyphenoxy)]ethylaminopropan-2-ol (Patent US 4,697,022 and 4,824,963).

27.5 g 4-hydroxycarbazole are dissolved in a mixture of 150 ml 1 N aqueous sodium hydroxide solution and 70 ml dimethylsulfoxide. To this is added at ambient temperature 13.9 g epichlorohydrin, followed by stirring for 18 hours at ambient temperature. 280 ml water are then added thereto, followed by stirring for 15 min and filtering off with suction. The filter residue is washed with 0.1 N aqueous sodium hydroxide solution and water and subsequently dissolved in methylene chloride. The methylene chloride solution is dried over anhydrous sodium sulfate, treated with active charcoal and floridin and evaporated. 4-(2,3-Epoxypropoxy)-carbazole is purified by recrystallising twice from ethyl acetate. From the mother liquors there are isolated a further 4-(2,3-epoxypropoxy)-carbazole.

10 g 4-(2,3-epoxypropoxy)-carbazole are, together with 13.97 g o-methoxyphenoxyethylamine, heated under reflux in 70 ml isopropanol for 2 hours. The solvent is evaporated off and the residue is stirred for 2 hours with a mixture of 115 ml toluene, 35 ml cyclohexane and 40 ml ethyl acetate. After filtering off with suction, the (1-carbazol-4-yloxy)-3-[2-(2-

methoxyphenoxy)]-ethylaminopropan-2-ol is recrystallised from 150 ml ethyl acetate.

References

Leinert H., US Patent No. 4,697,022; Sep. 29, 1987; Assigned to Boehringer Mannheim GmbH
Leinert H., US Patent No. 4,824,963; Apr. 25, 1989; Assigned to Boehringer Mannheim GmbH

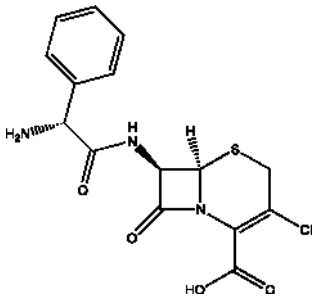
CEFACLOR

Therapeutic Function: Antibiotic

Chemical Name: 7-(D-α-Phenylglycylamido)-3-chloro-3-cephem-4-carboxlic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 53994-73-3

Trade Name	Manufacturer	Country	Year Introduced
Ceclor	Lilly	US	1979
Panoral	Lilly	W. Germany	1979
Distaclor	Dista	UK	1979
Ceclor	Lilly	Switz.	1980
Alfatil	Lilly	France	1980
Panacef	Lilly	Italy	1981
Kefral	Shionogi	Japan	1982
Kefolor	Lilly	-	-

Raw Materials

p-Nitrobenzyl-7-amino-3-chloro-3-cephem-4-carboxylate HCl
Methyl chloroformate
Hydrogen
N,O-Bis-(trimethylsilyl)acetamide
Methyl-3α-carboxybenzylamino-crotonate sodium salt

Manufacturing Process

Preparation of 7-amino-3-chloro-3-cephem-4-carboxylic acid: To a solution of 750 mg (185 mmol) of p-nitrobenzyl 7amino-3-chloro-3cephem-4-carboxylate hydrochloride in 20 ml of tetrahydrofuran and 40 ml of methanol was added a suspension of 750 mg of prereduced 5% palladium on carbon catalyst in 20 ml of ethanol and the suspension was hydrogenated under 50 psi of hydrogen at room temperature for 45 minutes. The catalyst was filtered and washed with THF and water. The filtrate and catalyst washes were combined and evaporated to dryness, The residue was dissolved in a water-ethyl acetate mixture and the pH adjusted to pH 3. The insoluble product was filtered and triturated with acetone. The product was then dried to yield 115 mg of 7-amino-3-chloro-3-cephem-4-carboxylic acid.

Preparation of 7-(D-α-phenylglycylamido)-3-chloro-3-cephem-4-carboxylic acid: To a suspension of 280 mg (1.2 mmol) of 7-amino-3-chloro-3-cephem-4-carboxylic acid in 14 ml of acetonitrile was added with stirring at room temperature 0.5 ml of N,O-bis-(trimethylsilyl)acetamide to form the soluble disilylmethyl derivative thereof. The solution was cooled to 0 C and was slowly added to a solution of the mixed anhydride formed by reacting 408 mg (1.5 mmol) of methyl-3-α-carboxybenzylaminocrotonate sodium salt with 161 mg (1.7 mmol) of methyl chloroformate in the presence to 2 drops of N,N-dimethylbenzyl amine in 7 ml of acetonitrile.

The mixture was stirred at ice bath temperature for 2 hours, 1 ml of methanol was added and the mixture was filtered to remove insoluble impurities. Two milliliters of water were added to the filtrate and the pH was adjusted momentarily to pH 1.5, to effect removal of the enamine block, and then to pH 4.5 with triethylamine. After stirring for an additional hour at ice bath temperature the reaction product, 7-(D-α-phenylglycylamido)-3-chloro-3-cephem-4-carboxylic acid (zwitterion) precipitated from the reaction mixture as a crystalline solid. The product was filtered, washed with acetonitrile and dried in vacuo to yield 200 mg.

References

Merck Index 1896
DFU 2 (6) 368 (1977)
Kleeman and Engel p. 160
OCDS Vol. 3 p. 209 (1984)
DOT 15 (7) 311 (1979)
I.N. p. 193
REM p. 1184
Chauvette, R R.; British Patent 1,461,323; January 13, 1977; assigned to Eli Lilly and Co.
Chauvette, R.R.; US Patent 3,925,372; December 9, 1975; assigned to Eli Lilly and Co.

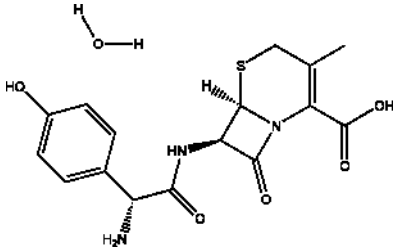
CEFADROXIL

Therapeutic Function: Antibacterial

Chemical Name: 7-[[Amino-(4-hydroxyphenyl)acetyl]amino]-3-methyl-8-oxo-5-thia-1-aza-bicyclo[4.2.0]- act-2-ene-2-carboxylic acid monohydrate

Common Name: p-Hydroxycephalexine monohydrate

Structural Formula:



Chemical Abstracts Registry No.: 50370-12-2

Trade Name	Manufacturer	Country	Year Introduced
Oracefal	Bristol	France	1977
Duricef	Mead Johnson	US	1978
Ultracef	Bristol	US	1980
Duracef	Ciba Geigy	Switz.	1980
Cephamox	Bristol	W. Germany	1980
Duracef	Bristol	Italy	1980
Sedral	Banyu	Japan	1982
Baxan	Bristol	UK	1982
Bidocef	Bristol-Myers	-	-
Cefos	C.T.	Italy	-
Droxicef	Alfa Farm.	Italy	-

Raw Materials

Sodium N-(1-methoxycarbonyl-1-propen-2-yl)-D(-)-α-amino-(4-hydroxyphenyl)acetate
Ethyl chlorocarbonate
7-Amino-3-methyl-3-cephem-4-carboxylic acid

Manufacturing Process

1.8 g of sodium N-(1-methoxycarbonyl-1-propen-2-yl)-D(-)-α-amino-(4-hydroxyphenyl)acetate was suspended in 10 ml of acetone, and one droplet of N-methylmorpholine was added thereto, and the mixture was cooled to -15°C.

There was added 0.85 g of ethyl chlorocarbonate thereto, and the mixture was reacted at -13°C to -10°C for 30 minutes, and then the reaction solution was cooled to -20°C.

On the other hand, 1 g of 7-amino-3-methyl-3-cephem-4-carboxylic acid was suspended in 20 ml of methanol, and 1.4 g of triethylamine was added thereto to be dissolved, and 0.4 ml of acetic acid was further added thereto. This solution was cooled to -20°C and the mixed acid anhydride prepared previously was added thereto. After the mixture was reacted at -20°C for 1 hour, the temperature of the reaction mixture was raised to 0°C over a period of 1 hour, and the mixture was reacted for 3 hours at the same temperature.

After the reaction, 1 ml of water was added to the reaction mixture, and the mixture was adjusted to a pH of 1.0 with concentrated hydrochloric acid while being cooled, and then stirred for 30 minutes, The insoluble matters were filtered off, and the filtrate was adjusted to a pH of 5.5 with triethylamine. This solution was concentrated under reduced pressure, and the residue was diluted with 20 ml of acetone to precipitate white crystals. The crystals were collected by filtration and washed with ethanol to obtain 1.46 g of white crystals of 7-[D(-)-α-amino-(4-hydroxyphenyl)acetamido]-3-methyl-3-cephem-4-carboxylic acid having a decomposition point of 197°C.

References

Merck Index 1897
Kleeman and Engel p. 161
PDR pp.716, 1124
OCDS Vo1. 2 p. 440 (1980)
DOT 13 (3) 126 (1977) and 13 (11) 471 (1977)
I.N. p. 194
REM p. 1185
Ishimaru, T. and Kodama. Y.: US Patent 3,864,340; February 4, 1975; assigned to Toyama Chemical Co. Ltd. (Japan)
Crast, L.B. Jr. and Gottstein, W.J.; US Patent 3,985,741; October 12, 1976; assigned to Bristol-Myers Co.

CEFAMANDOLE NAFATE SODIUM SALT

Therapeutic Function: Antibiotic

Chemical Name: Sodium 7-(D-2-formyloxy-2-phenylacetamido)-3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylate

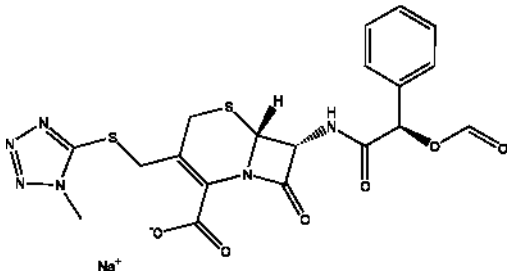
Common Name: -

Chemical Abstracts Registry No.: 42540-40-9; 34444-01-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Mandokef	Lilly	W. Germany	1977
Kefadol	Lilly	UK	1978

Trade Name	Manufacturer	Country	Year Introduced
Mandol	Lilly	US	1978
Kefandol	Lilly	France	1978
Mandokef	Lilly	Italy	1981
Cedol	Tiber	Italy	-
Cefam	Magis	Italy	-
Cefman	I.B.P.	Italy	-
Cemado	Farmochimica	Italy	-
Cemandil	S.I.T.	Italy	-
Fado	Errekappa	Italy	-
Lampomandol	A.G.I.P.S.	Italy	-
Mandolsan	San Carlo	Italy	-
Neocefal	Gibipharma	Italy	-

Structural Formula:



Raw Materials

Mandelic acid, D-
Formic acid
Thionyl chloride
Monotrimethyl silyl acetamide
Sodium 2-ethylhexanoate
7-Amino-3-(1-methyl-1H-tetrazol-5-yl-thiomethyl)-3-cephem-4-carboxylic acid

Manufacturing Process

To 21.6 kg (17.8 l) of 98% formic acid was added 1.14 kg (7.5 mols) of D-(-)-mandelic acid and the reaction mixture was heated for 4 hours at 70°C with stirring. The excess formic acid was evaporated off in vacuo and the residual syrup was dissolved in 6 l of benzene. The solution was washed twice with 6 l portions of water and was dried over magnesium sulfate. The drying agent was filtered and washed with 1.5 l of benzene, the washes being added to the filtrate. The dried filtrate was evaporated in vacuo to obtain the D-(-)-mandelic acid formate ether as a syrup. The product can be crystallized from cyclohexane to yield material melting at about 55°C to 58°C.

The mandelic acid formate ester obtained as a syrup as described above is stirred for 2 hours with 2.9 kg (~1.75 l) of thionyl chloride at a temperature of about 70°C. The excess thionyl chloride is removed by evaporation and the residual green solution is vacuum distilled. The product, O-formyl mandeloyl chloride, distills over at 127°C to 130°C (15 mm) or at 108°C to 112°C (7 mm).

To 13 l of ethyl acetate were added 85.1 g (2.59 mols) of 7-amino-3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid and 1,361 g (10.37 mols) of monotrimethylsilyl acetamide, and the mixture was stirred at 50°C until a clear solution was obtained. The solution was cooled to 20°C and 514 g (2.59 mold of O-formyl mandeloyl chloride was added at a rate such that the temperature of the reaction solution was maintained between about 20°C to 25% with ice-cooling.

The reaction mixture was stirred for 1.5 hours at about room temperature after the addition of the mandeloyl chloride was completed. Five liters of water were then added to the reaction mixture and the diluted mixture was stirred for about 10 minutes. The organic layer was separated and was washed twice with water. The combined washes are extracted with 1.5 l of ethyl acetate and the extract is combined with the washed organic layer. The whole was dried over magnesium sulfate, filtered and evaporated in vacuo on a 25°C water bath to yield 1,460 g of product, 7-(D-2-formyloxy-2-phenylacetamido)-3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid, as a yellow foam.

The product was dissolved in 5 l of acetone and the solution was mixed with a solution of 430 g (2.59 mols) of sodium 2-ethylhexanoate in 5.4 l of acetone. The combined solutions were seeded and stirred in an ice bath for 1.5 hours. The crystalline precipitate of sodium 7-(D-2-formyloxy-2-phenylacetamido)-3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylate was filtered and washed with 5 l of acetone. The crystalline salt was dried overnight in a vacuum oven at 40°C to yield 1,060 g (80%)of product, melting at 182°C to 184°C.

References

Merck Index 1898
DFU 2 (10) 646 (1977)
Kleeman and Engel p. 166
PDR p. 1059
OCDS Vol. 2 p. 441 (1980) and 14 (4) 151 (1978)
DOT 12 (5) 177 (1976)
I.N.p. 196
REM p. 1185
Greene, J.M. and Indelicato, J.M.; US Patent 3,928,592; December 23, 1975; assigned to Eli Lilly and Co.

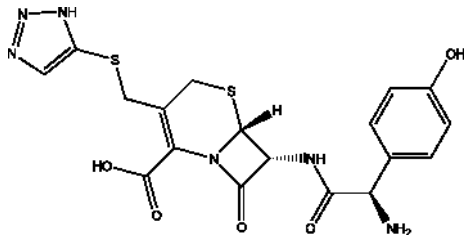
CEFATRIZINE

Therapeutic Function: Antibiotic

Chemical Name: 7-[D-α-Amino-α-(p-hydroxyphenyl)acetamido]-3-(1,2,3-triazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 51627-14-6

Trade Name	Manufacturer	Country	Year Introduced
Bricef	Bristol Banyu	Japan	1980
Cepticol	Banyu	Japan	1980
Cefatrix	Ausonia	Italy	1982
Latocef	Dukron	Italy	1982

Raw Materials

7-[D-α-t-Butoxycarbonylamino-α-(p-hydroxyphenyl)acetamido]-3-(1,2,3-triazol-5-ylthiomethyl)-3-cephem-4-carboxylicacid
Formic acid

Manufacturing Process

A total 6.5 g (1 1.55 mmol) of 7-[D-α-t-butoxycarbonylamino-α-(p-hydroxyphenyl)acetamido]-3-(1,2,3-triazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid was dissolved in 175 ml (98 to 100% formic acid under anhydrous conditions. The mixture was stirred at room temperature for 2.5 hours. Part of the solution, 125 ml, was evaporated under reduced pressure to an amber oil. The oil was then azeotroped 3 times with 70 ml of toluene under reduced pressure. The residue was suspended in an 80:20 H_2O-CH_3OH solution (700 ml) and stirred for 0.5 hour until most of the solid dissolved, then filtered. The filtration was treated with 1.59 of (Darko) charcoal for about 20 minutes. The charcoal was filtered off through a Celite pad. The solution was then freeze-dried in 9 separate 100 ml round bottom flasks. The freeze-dried material weighed 2.415 g. It was recrystallized in batches of 0.200 g as described above to yield a total of 0.923 g 7-[D-α-amino-α-(p-hydroxyphenyl) acetamidol-3-(1,2,3-triazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid. NMR was consistent, indicating the presence of 0.33 mol of CH_3OH.

References

Merck Index 1899
DFU 2 (10) 653 (1977)
OCDS Vol. 3 p. 211 (1984)
DOT 12 (5)183 (1976)
I.N. p. 197
Kaplan, M.A. and Granatek, A.P.; US Patent 3,970,651; July 20, 1976; assigned to Bristol-Myers Co.

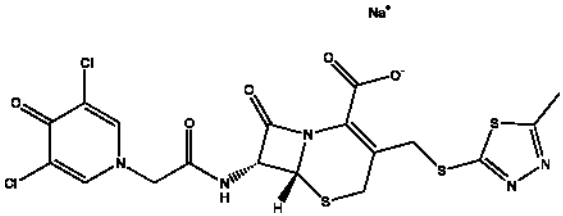
CEFAZEDONE SODIUM

Therapeutic Function: Antibiotic

Chemical Name: 5-Thia-1-azabicyclo(4.2.0)oct-2-ene-2-carboxylic acid, 7-(((3,5-dichloro-4-oxo-1(4H)-pyridinyl)acetyl)amino)-3-(((5-methyl-1,3,4-thiadiazol-2-yl)thio)methyl)-8-oxo-, (6R-trans)-, sodium salt

Common Name: Cefazedone sodium

Structural Formula:



Chemical Abstracts Registry No.: 63521-15-3; 56187-47-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Cefazedone Sodium	Arocor Holdings Inc.	-	-
Cefazedone Sodium	Yick-Vic Chemicals and Pharmaceuticals (HK) Ltd.	-	-
Cefazedone Sodium	CKD Pharm	-	-
Refosporen	Teva Pharmaceuticals	-	-

Raw Materials

tert-Butyl ester of 7-aminocephalosporanic acid
Dicyclohexylcarbodiimide
3,5-Dichloro-4-pyridone-1-acetic acid
Trifluoroacetic acid
5-Methyl-1,3,4-thiadiazole-2-thiol

Manufacturing Process

A solution of 1 eq. of the tert-butyl ester of 7-aminocephalosporanic acid and 1 eq. of dicyclohexylcarbodiimide in 100 ml of methylene chloride/DMF (1:1) is cooled to 0°C. The mixture is combined with 1 eq. of 3,5-dichloro-4-pyridone-1-acetic acid; after 5 min the ice bath is removed and the mixture agitated for another 30 min at 25°C. The thus-formed urea is filtered off and the filtrate filtered over silica gel (eluent: ethyl acetate/1% methanol). The solvent is concentrated by evaporation, and the thus-obtained tert-butyl ester of 7-(3,5-dichloro-1,4-dihydro-4-oxo-1-pyridylacetamido)cephalosporanic acid is crystallized from ether.

1 eq. of the tert-butyl ester is dissolved in 30 ml of trifluoroacetic acid. After 30 minutes, the solution is evaporated and the thus-produced 7-(3,5-dichloro-1,4-dihydro-4-oxo-1-pyridylacetamido)cephalosporanic acid crystallized from ether.

1 eq. of the obtained 7-(3,5-dichloro-1,4-dihydro-4-oxo-1-pyridylacetamido) cephalosporanic acid is dissolved in 60 ml of saturated aqueous sodium bicarbonate solution at a pH of below 7 and combined with 1 eq. of 5-methyl-1,3,4-thiadiazole-2-thiol in 20 ml of acetone. The reaction solution is agitated for 2 hours at 80°C and at a pH of 6.3 under a nitrogen atmosphere. The acetone is thereupon removed, the solution is washed with ether and acidified to pH 2. The thus-obtained 3-(1-methyltetrazolyl-5-mercaptomethyl)-7-(3,5-dichloro-1,4-dihydro-4-oxo-1-pyridylacetamido)-3-cephem-4-carboxylic acid is filtered off and dried. IR spectrum confirmed the structure of cefazedone.

In practice it is usually used as sodium salt.

References

Gericke R.; US Patent No. 4,153,693; May 8, 1979; Assigned to Merck Patent Gesellschaft mit beschrankter Haftung, Darmstadt, Fed. Rep. of Germany

CEFAZOLIN SODIUM

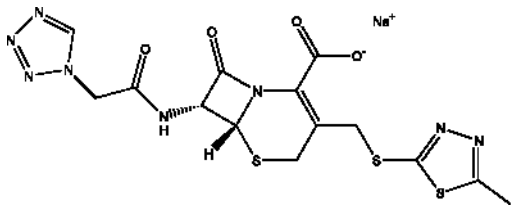
Therapeutic Function: Antibacterial

Chemical Name: (6R-trans)-3-([(5-Methyl-1,3,4-thiadiazol-2-yl)thio]methyl)-8-oxo-7-([(1-H-tetrazol-1-yl)acetyl]amino)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt

Common Name: -

Chemical Abstracts Registry No.: 27164-46-1; 25953-19-9 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Cefamedin	Fujisawa	Japan	1971
Kefzol	Lilly	US	1973
Ancef	SKF	US	1973
Totacef	Bristol	Italy	1973
Grammaxin	Boehringer Mannheim	W. Germany	1974
Kefzol	Lilly	UK	1974
Kefzol	Serum Impfinst.	Switz.	1974
Cefacidal	Allard	France	1976
Kefzol	Lilly	France	1976
Acef	Tiber	Italy	-
Areuzolin	Areu	Spain	-
Atirin	Intersint	Italy	-
Biazolina	Panthox and Burck	Italy	-
Bor-Cefazol	Proter	Italy	-
Brizolina	Bristol-Myers	-	-
Caricef	Antibioticos	Spain	-
Cefacene	Centrum	Spain	-
Cefalomicina	Marxer	Argentina	-
Cefamezin	Fujisawa	Japan	-
Cefazina	Chemil	Italy	-
Celmetin	A.L.	Norway	-
Cromezin	Crosara	Italy	-
Elzogram	Lilly	W. Germany	-
Fidesporin	Fides	Spain	-
Firmacel	Firma	Italy	-
Kurgan	Normon	Spain	-
Legemzolina	Legem	Spain	-
Lifezolina	Lifepharma	Spain	-
Liviclina	Sierochimica	Italy	-
Maksipor	Fako	Turkey	-
Neofazol	Rubio	Spain	-
Vifazolin	Vianex	Greece	-
Zolicef	Bristol-Myers	W. Germany	-

Raw Materials

7-Aminocephalosporanic acid
5-Methyl-1,3,4-thiadiazole-2-thiol
Sodium bicarbonate
1H-Tetrazole-1-acetyl chloride
Sodium hydroxide

Manufacturing Process

7-Aminocephalosporanic acid is converted to its sodium salt and acylated with 1H-tetrazole-1-acetyl chloride. The acetoxy group is then displaced by reaction with 5-methyl-1,3,4-thiadiazole-2-thiol in buffer solution. The product acid is converted to the sodium salt by $NaHCO_3$.

References

Merck Index 1901
Kleeman and Engel p. 168
PDR pp. 1058, 1701
OCDS Vol. 3 p. 442 (1984)
DOT 7 (5) 146, 167, 181 (1971)
I.N. p. 197
REM p. 1185
Takano, T., Kurita, M., Nikaido, H., Mera, M., Konishi, N. and Nakagawa, R.; US Patent 3,516,997; June 23, 1970; assigned to Fujisawa Pharmaceutical Co., Ltd., Japan

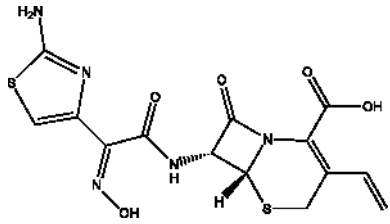
CEFDINIR

Therapeutic Function: Antibiotic

Chemical Name: 5-Thia-1-azabicyclo(4.2.0)oct-2-ene-2-carboxylic acid, 7-(((2Z)-(2-amino-4-thiazolyl)(hydroxyimino)acetyl)amino)-3-ethenyl-8-oxo-, (6R,7R)-

Common Name: Cefdinir; Cefdinyl

Structural Formula:



Chemical Abstracts Registry No.: 91832-40-5

Trade Name	Manufacturer	Country	Year Introduced
Adcef	Torrent Pharmaceuticals Ltd.	India	-
Cednir	Sarabhai Piramal Pharmaceuticals Ltd.	India	-
Cefdiel	Ranbaxy Laboratories Limited	India	-
Cefzon	Fujisawa Pharmaceutical Co., Ltd.	-	-
Oceph Cap	Emcure Pharmaceuticals Ltd.	India	-
Omnicef	Hikma	-	-
Omnicef	Abbott Laboratories	-	-
Sefdin	Unichem Laboratories Ltd.	India	-
Zefdinir	German Remedies Limited	Germany	-

Raw Materials

7-Amino-8-oxo-3-vinyl-5-thia-1-azabicyclo(4.2.0)oct-2-ene-2-carboxylic acid 4-methoxyphenyl ester
4-Bromoacetyl bromide
Sodium nitrite
Trifluoroacetic acid

Manufacturing Process

By interaction of 7-amino-8-oxo-3-vinyl-5-thia-1-azabicyclo(4.2.0)oct-2-ene-2-carboxylic acid 4-methoxyphenyl ester with 4-bromoacetyl bromide was prepared 7-(4-bromo-3-oxo-butyrylamino)-8-oxo-3-vinyl-5-thia-1-azabicyclo (4.2.0)oct-2-ene-2-carboxylic acid 4-methoxyphenyl ester. The active methylene group in that product was then nitrosated with sodium nitrite. The initial product spontaneously tautomerizes to afford 7-(4-bromo-2-hydroxyimino-3-oxo-butyrylamino)-8-oxo-3-vinyl-5-thia-1-azabicyclo(4.2.0) oct-2-ene-2-carboxylic acid 4-methoxyphenyl ester. By the reaction of that compound with thiourea and then with trifluoroacetic acid was obtained (6R,7R)-7-(2-(2-amino-4-thiazolyl)glyoxylamido)-8-oxo-3-vinyl-5-thia-1-azabicyclo(4.2.0)oct-2-ene-2-carboxylic acid sodium nitrite, (Z)-oxime (Cefdinir sodium nitrile).

In practice it is usually used as free acid.

Synthesis of 7β-[2-(2-aminothiazol-4-yl)-2-(Z)-(trytiloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid x p-toluenesulfonic acid x 2 N,N-dimethylacetamide (the precursor of Cefdinir) was described in Patent US 6,093,814.

References

Inamoto Y. et al., J. Antibiotics, 1988, V. 41, P. 828
Org. Chem. Drug. Synth., V.6, P.170

Gwan S.L. et al.; US Patent No. 6,093,814; Jul 25, 2000; Assigned to Hanmi Pharmaceutical Co, Ltd., Rep. Korea

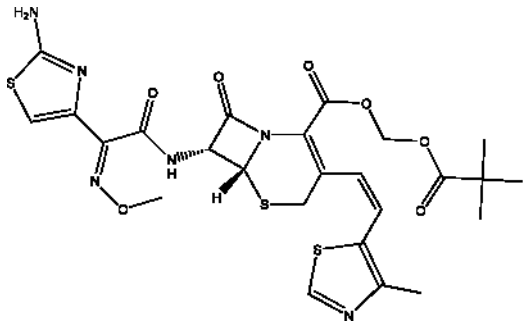
CEFDITOREN PIVOXIL

Therapeutic Function: Antibiotic

Chemical Name: 5-Thia-1-azabicyclo(4.2.0)oct-2-ene-2-carboxylic acid, 7-(((2Z)-(2-amino-4-thiazolyl)(methoxyimino)acetyl)amino)-3-((1Z)-2-(4-methyl-5-thiazolyl)ethenyl)-8-oxo-, (2,2-dimethyl-1-oxopropoxy)methyl ester, (6R,7R)-

Common Name: Cefditoren pivoxil; Cefoviten pivoxil

Structural Formula:



Chemical Abstracts Registry No.: 117467-28-4

Trade Name	Manufacturer	Country	Year Introduced
Meiact	Meiji Seika	Japan	-
Spectracef	TAP Pharmaceuticals	-	-
Spectracef	Abbott Laboratories	-	-

Raw Materials

(Z)-(2-Aminothiazol-4-yl)methoxyimino acetic acid
Bis-(2-oxo-oxazolidinyl)phosphinic chloride
2-Mercapto-5-phenyl-1,3,4-oxadiazole
7-Amino-3-[(Z)-2-(methyl-5-thiazolyl)vinyl]-3-cephem-4-carboxylic acid
Triethylamine

Manufacturing Process

A mixture of THF (250 ml) and water (150 ml) was stirred under inert atmosphere. At 0°-1°C, 7-amino-3-[(Z)-2-(methyl-5-thiazolyl)vinyl]-3-

cephem-4-carboxylic acid (25.0 g) and 2-mercapto-5-phenyl-1,3,4-oxadiazolyl-(Z)-2-(2-aminothiazol-4-yl)-2-methoxyimino acetate (33.3 g) were added. Triethylamine (10.5 g) was slowly added to reaction by maintaining the pH between 7.5 to 8.5. The reaction was monitored by HPLC. After 4-5 hrs., the reaction mixture was extracted by methylene chloride. The aqueous layer is subjected for charcoal (0.125 g) treatment. Ethylacetate was added to the filtrate and the solution was acidified with diluted HCl at 10°C to pH 3.0. The solid separated was filtered, washed with water and ethylacetate and then dried under vacuum at 40-45°C to get 3-[(Z)-2-(4-methyl-5-thiazolyl)vinyl]-7-[(Z)-(2-aminothiazolyl-4-yl)-2-(methoxyimino)acetamido]-3-cephem-4-carboxylic acid (Cefditoren acid), 35.0 g (yield 90%), HPLC (purity)=96-98%.

In practice it is often used as Cefditoren pivoxil.

References

Deshpande P. B., Luthra P. K.; US Patent No. 6,713,625; August 27, 2002; Assigned to Orchid Chemicals and Pharmaceuticals Ltd.

Yasui K. et al.; US Patent No. 6,441,162; August 27, 2002; Assigned to Meiji Seika Kaisha, Ltd. (Tokyo, JP)

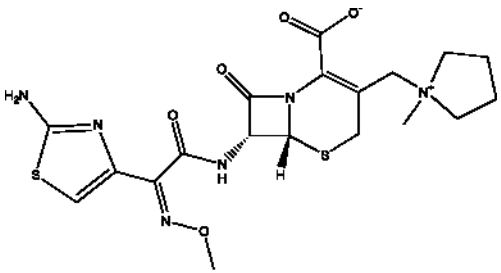
CEFEPIME

Therapeutic Function: Antibiotic

Chemical Name: Pyrrolidinium, 1-(((6R,7R)-7-(((2Z)-(2-amino-4-thiazolyl)(methoxyimino)acetyl)amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo(4.2.0)oct-2-en-3-yl)methyl)-1-methyl-, inner salt

Common Name: Cefepime

Structural Formula:



Chemical Abstracts Registry No.: 88040-23-7

Trade Name	Manufacturer	Country	Year Introduced
Ceficad	Cadila Pharmaceuticals Ltd.	India	-
Forpar	Cipla Limited	India	-

Trade Name	Manufacturer	Country	Year Introduced
Ivipime	VHB Life Sciences	India	-
Maxicef	Aristo Pharmaceutical Ltd.	India	-
Maxipime	Bristol-Myers Squibb	USA	-
Maxipime	EPI	USA	-
Ultipime	Recon Healthcare Ltd.	India	-
Zwiter	Lyka Hetro Labs. Ltd.	India	-

Raw Materials

Ethyl (Z)-2-hydroxyimino-2-(2-tritylaminothiazol-4-yl) acetate
Methyliodide
7-Phenylacetimidocephalosporanic acid sodium salt
Diphenyldiazomethane
Bis(trimethylsilyl)acetamide
Potassium carbonate
Phosphorus pentachloride

Manufacturing Process

A mixture of ethyl (Z)-2-hydroxyimino-2-(2-tritylaminothiazol-4-yl) acetate (5 g, 10.9 mmoles), methyliodide (2.04 ml, 32.8 mmoles) and K_2CO_3 (4.54 g, 32.8 mmoles) in dry DMSO (100 ml) was stirred at room temperature overnight and then poured into water (250 ml). The precipitate was collected, washed with water and dried to give 2-methoxyimino-2-(2-tritylaminothiazol-4-yl) acetate (1.15 g, melting point 115°C (dec.))

Ethyl (Z)-2-hydroxyimino-2-(2-tritylaminothiazol-4-yl) acetate (6 g, 12.7 mmol) in ethanol was treated with 2 N NaOH (12.7 ml) at room temperature overnight. The mixture was adjusted to pH 8 by the addition of powdered dry ice and the solvent evaporated. The residue was dissolved in water (100 ml) and was added to the solution which was acidified with 1 N HCl to pH 2 and then extracted with ethyl acetate. Extract was evaporated, the residue was crystallized from ethyl acetate-hexane to afford ethyl (Z)-2-hydroxyimino-2-(2-tritylaminothiazol-4-yl)acetic acid (5.56 g, melting point 138-143°C (dec.)).

To a suspension of phosphate buffer (pH 7, 162.5 ml) and wheat bran (20 g, dry) at room temperature was added 7-phenylacetimidocephalosporanic acid sodium salt (5 g). After 5 hours the suspension was filtered to remove wheat bran and the filtrate was cooled to 5-10°C, then was added methylene chloride (32 ml) and 0.5 M solution of diphenyldiazomethane in methylene chloride (24 ml). The pH was then adjusted to 3.0 with 28% phosphoric acid. After 1 hour the mixture was allowed to rise to 20°C. Heptane was slowly added (56 ml) and was recovered benzhydryl 3-hydroxymethyl-7-phenylacetamido-3-cephem-4-carboxylate (3.0 g, 50%).

The mixture of PCl5(8.3 g) and pyridine (3.2 g) in CH_2Cl_2 was added to benzhydryl 3-hydroxymethyl-7-phenylacetamido-3-cephem-4-carboxylate (5.1 g) at -40°C. The mixture was stirred at -10°C for 15 minutes and allowed to stand at -15-10°C for 7 hours. To the solution at -20°C was added propane-1,3-diol (10 ml) and the mixture was allowed to stand at -20°C for 16 hours

and then at room temperature for 20 minutes. The resulting solution was washed with ice-water and saturated aqueous NaCl (10 ml), dried and concentrated. The gummy residue (12 g) was dissolved in $CHCl_3$-hexane (2:1), and subjected to chromatography using silica gel column and the same solvent as eluant. After evaporation of the solvents was obtained benzhydryl-7-amino-3-chloromethyl-3-cephem-4-carboxylate (2.1 g, 51%, melting point >110°C(dec.)).

Benzhydryl 7-amino-3-chloromethyl-3-cephem-4-carboxylate (2.29 g) was treated with bis(trimethylsilyl)acetamide (4.06 ml) at room temperature for 50 min to give a clear solution. Top the solution was added an acid chloride solution, which was prepared from (Z)-2-hydroxyimino-2-(2-tritylaminothiazol-4-yl)acetic acid (2.04 g) and PCl_5 (1.15 g) in methylene chloride (20 ml). The mixture was stirred at room temperature for 30 min, poured in cold water (200 ml) and extracted with ethyl acetate (100 ml x 3). After evaporation of the solution was obtained the syrup (4 g) which was chromatographed on a silica gel column by eluting with 10:1 and 3:1 mixture of toluene and ethyl acetate successively. After evaporation of the solvents was obtained benzhydryl 3-chloromethyl-7-[(Z)-2-methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-cephem-4-carboxylate (2.62 g, 68%).

A mixture of the benzhydryl 3-chloromethyl-7-[(Z)-2-methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-cephem-4-carboxylate (1.50 g, 1.79 mmoles) and NaI (1.34 g, 8.93 mmoles) in methyl ethyl ketone (30 ml) was stirred at room temperature for 1 hour. After evaporation of the solvent the residue was dissolved in ethyl acetate (100 ml) and washed with water, aqueous $Na_2S_2O_3$ and aqueous NaCl, dried and evaporated to give 7-[(Z)-2-ethoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-iodomethyl-3-cephem-4-carboxilate (1.47 g, 89%) as an amorphous powder.

A mixture of 7-[(Z)-2-ethoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-iodomethyl-3-cephem-4-carboxilate (4.5 g, 4.83 mmoles) and N-methylpyrrolidine (0.65 ml, 6.28 mmoles) in CH_2Cl_2 (45 ml) was stirred at room temperature for 20 min. Ether (300 ml) was added to the mixture to separate the quaternary salt of the blocked cephalosporin, which was collected by filtration and treated with 90% trifluoroacetic acid (TFA) (40 ml) at room temperature for 1 hour. The mixture was then evaporated under reduced pressure below 20°C. The residue was triturated with ether to give the TFA salt of 7-[(Z)-2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[(1-methyl-1-pyrrolidinium)methyl]-3-cephem-4-carboxylate (2.40 g), which was dissolved in methanol (5 ml) and treated with 1 M solution of sodium-2-ethylhexoate in ethyl acetate (8 ml) at room temperature for 30 min. After the addition of ethyl acetate (100 ml), the precipitate (1.94 g) formed was collected by filtration. HPLC analysis showed that the crude product was 7% pure with a 1:8 ratio of the δ^3 isomer to the δ^2 isomer. Purification of the product by HPLC was repeated three times (Lichrosorb RP-18, eluted with 5% aqueous methanol or 0.01 M ammonium phosphate buffer (pH 7.2 containing 5% of methanol) to give 35 mg (1.5%) of the title product as a colorless powder of 7-[(Z)-2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[(1-methyl-1-pyrrolidinium)methyl]-3-cephem-4-carboxylate. Estimated purity (by HPLC) 90%. M.p. 150°C (dec.).

References

Aburaki Sh. et al.; US Patent No. 4,406,899; 09.27.1983; Assigned to Bristol-Myers Company

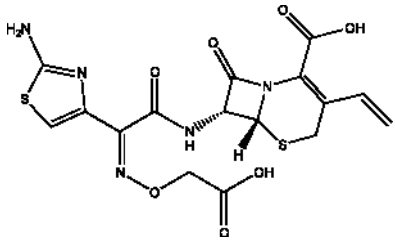
CEFIXIME

Therapeutic Function: Antibiotic

Chemical Name: 5-Thia-1-azabicyclo(4.2.0)oct-2-ene-2-carboxylic acid, 7-(((2Z)-(2-amino-4-thiazolyl)(carboxymethoxy)imino)acetylamino)-3-ethenyl-8-oxo-, (6R,7R)-

Common Name: Cefixime; Cefvixime

Structural Formula:



Chemical Abstracts Registry No.: 79350-37-1

Trade Name	Manufacturer	Country	Year Introduced
Acrotex	Acron Pharmaceuticals	India	-
Biotax-O	Biochem Pharma Industries	-	-
Cebay D. Syp.	Leben Laboratories Pvt. Ltd.	India	-
Cefaden-O	Eden Healthcare	India	-
Cefex	Talent Laboratories	India	-
Cefixime	Rhone-Poulenc Rorer	-	-
Cefnax	Andromaco	-	-
Cefspan	Hikma Pharmaceuticals	Iordania	-
Cefspan	Glaxo Smithkline	-	-
Ceftiwin	Parenteral Drugs (India) Ltd.	India	-
Defender	Skymax Laboratories Pvt. Ltd.	India	-
Evacef O	Neon Laboratories Ltd.	India	-
Excef-DT	Ind-Swift Ltd.	India	-

Trade Name	Manufacturer	Country	Year Introduced
Exime	J.K. Drugs and Pharmaceuticals Ltd.	India	-
Fixx	Unichem Laboratories Ltd.	India	-
Lyceft-O	Lyka Hetro Labs. Ltd.	India	-
Ocef	Osper Pharmanautics Pvt. Ltd.	India	-
Omnatax-O	Nicholas Piramal India Ltd. (Npil)	India	-
O-Powercef	Wockhardt Ltd.	India	-
Pancef-O	Aglowmed Limited	India	-
Pedixim	Biological E. Limited	India	-
Suprax	Hikma Pharmaceuticals	Iordania	-
Suprax	Aventis Pharma	-	-

Raw Materials

7-Amino-3-vinyl-3-cephem-4-carboxylic acid
2-(Aminothiazol-4-yl)-2-(tert-butoxycarbonylmethoxyimino)acetic acid S-mercaptobenzothiazole ester
Triethylamine

Manufacturing Process

To a suspension of 7-amino-3-vinyl-3-cephem-4-carboxylic acid (11.25 g), 2-(aminothiazol-4-yl)-2-(tert-butoxycarbonylmethoxyimino)acetic acid S-mercaptobenzothiazole ester (23.88 g) in ethylacetate (266 ml) and water (9 ml) at 2°C is added triethylamine. After completion of the reaction, water is added and pH is adjusted to 2.1 with diluted sulfuric acid. The phases are separated and the aqueous phase is extracted with ethylacetate. The organic extracts are combined and concentrated to a volume of 120 ml, then acetonitrile (100 ml) and formic acid (22 ml) are added. The mixture is stirred at 30-35°C for 1 hour. The mixture is cooled to 2°C, the precipitate is filtered, washed with acetonitrile and dried to obtain 20.86 g of 5-thia-1-azabicyclo(4.2.0)oct-2-ene-2-carboxylic acid, 7-(((2Z)-(2-amino-4-thiazolyl)(carboxymethoxy)imino)acetylamino)-3-ethenyl-8-oxo-, (6R,7R)-(Cefixime).

References

Carbi W. et al.; WO03040148, Nov. 9, 2001

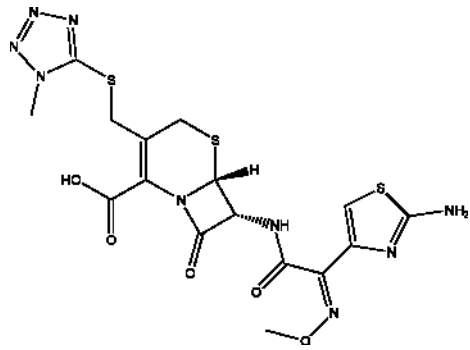
CEFMENOXIME

Therapeutic Function: Antibacterial

Chemical Name: 7β-[α-Methoxyimino-α-(2-aminothiazol-4-yl)acetamido]-3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 65085-01-0

Trade Name	Manufacturer	Country	Year Introduced
Tacef	Takeda	W. Germany	1983
Bestcall	Takeda	Japan	1983

Raw Materials

7β-[α-Methoxyimino-α-(2-aminothiazol-4-yl)acetamido] cephalosporanicacid trifluoroacetic acid salt
1-Methyl-5-mercapto-1H-tetrazole

Manufacturing Process

7β-[α-Methoxyimino-α-(2-aminothiazol-4-yl)acetamido]cephalosporanicacid trifluoroacetic acid salt is dissolved in a solution of 272 mg of 1-methyl-5-mercapto-1H-tetrazole, 555 mg of sodium bicarbonate and 68 mg of triethylbenzylammonium bromide in 10 ml of water. The solution is heated at 60°C in nitrogen atmosphere for 6 hours. After cooling, the reaction solution is passed through a column of Amberlite XAD-2 and eluted with water and then with 2.5% ethanol. The procedure yields sodium 7β-[α-methoxyimino-α-(2-aminothiazol-4-yl)acetamido]-3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylate, MP 174°C to 175°C (decomposition).

References

Merck Index 1902
DFU 5 (3) 146 and (12) 635 (1980) (as SCE-1365)
DOT 19 (6) 335 and (8) 429 (1983)
I.N. p. 198
REM p. 1189
Ochiai, M., Okada, T., Aki, O., Morimoto, A., Kawakita, K. and Matsushita, Y.; US Patent 4,098,888; July 4, 1978; assigned to Takeda Chemical Industries, Ltd.

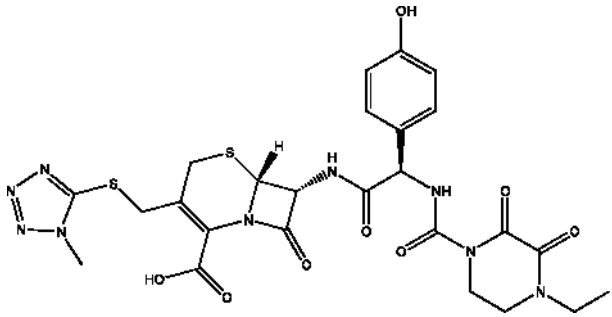
CEFOPERAZONE

Therapeutic Function: Antibiotic

Chemical Name: 7-[D-(-)-α-(4-Ethyl-2,3-dioxo-1-piperazinecarboxamido)-α-(4-hydroxyphenyl)acetamido]-3-[(1-methyl-1H-tetrazol-5-yl)thiomethyl]-3-cephem-4-carboxylic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 62893-19-0; 62893-20-3 (Sodium Salt)

Trade Name	Manufacturer	Country	Year Introduced
Cefobid	Pfizer	W. Germany	1981
Cefobine	Pfizer	France	1981
Cefobis	Pfizer	Switz.	1981
Cefoperazin	Pfizer Taito	Japan	1982
Cefobid	Roerig	US	1982

Raw Materials

7-[D-(-)-α-Amino-p-hydroxyphenylacetamido]-3-[5-(1-methyl-1,2,3,4-tetrazolyl)-thiomethyl]-δ(3)-cephem-4-carboxylic acid
4-Ethyl-2,3-dioxo-1-piperazinocarbonyl chloride

Manufacturing Process

To a suspension of 3.0 g of 7-[D-(-)-α-amino-p-hydroxyphenylacetamido]-3-[5-(1-methyl-1,2,3,4-tetrazolyl)thiomethyl]-Δ^3-cephem-4-carboxylic acid in 29 ml of water was added 0.95 g of anhydrous potassium carbonate. After the solution was formed, 15 ml of ethyl acetate was added to the solution, and 1.35 g of 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride was added to the resulting solution at 0°C to 5°C over a period of 15 minutes, and then the mixture was reacted at 0°C to 5°C for 30 minutes. After the reaction, an aqueous layer was separated off, 40 ml of ethyl acetate and 10 ml of acetone

were added to the aqueous layer, and then the resulting solution was adjusted to a pH of 2.0 by addition of dilute hydrochloric acid. Thereafter, an organic layer was separated off, the organic layer was washed two times with 10 ml of water, dried over anhydrous magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was dissolved in 10 ml of acetone, and 60 ml of 2-propanol was added to the solution to deposit crystals. The deposited crystals were collected by filtration, washed with 2-propanol, and then dried to obtain 3.27 g of 7-[D-(-)-α-(4-ethyl-2,3-dioxo)-1-piperazinocarbonylamino)-p-hydroxyphenylacetamido]-3-[5-(1-methyl-1,2,3,4-tetrazolyl)thiomethyl]-Δ^3-cephem-4-carboxylicacid, yield 80.7%. The product forms crystals, MP 188°C to 190°C (with decomposition).

References

Merck Index 1905
DFU 4 (9) (675) and (12) 911 (1979) (as T-1551)
Kleeman and Engel p. 169
PDR p. 1521
DOT 17 (12) 535 (1981)
I.N. p. 198
REM p. 1185
Saikawa, I., Takano, S., Yoshida, C., Takashima, O., Momonoi, K., Kuroda, S., Komatsu, M., Yasuda, T. and Kodama, Y.; British Patent 1,508,071; April 19, 1978;assigned to Toyama Chemical Co., Ltd. and US Patent 4,110,327; August 29, 1978; also assigned to

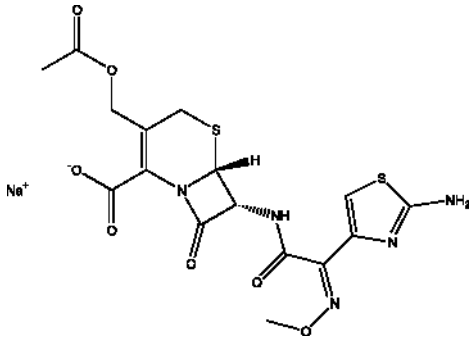
CEFOTAXIME SODIUM

Therapeutic Function: Antibiotic

Chemical Name: Sodium 3-acetoxymethyl-7-[2-(2-amino-4-thiazolyl)-2-methoxyimino]-acetamido-3-cephem-4-carboxylate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 64485-93-4; 63527-52-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Claforan	Hoechst-Roussel	W. Germany	1980
Claforan	Roussel Maestretti	Italy	1980
Claforan	Roussel	France	1980
Zariviz	Hoechst	Italy	1980
Claforan	Roussel-Hoechst	Switz.	1981
Claforan	Roussel	UK	1981
Cefotax	Roussel	Japan	1981
Claforan	Hoechst	US	1981
Pretor	Hoechst	-	-
Primafen	Hoechst	-	-
Ralopar	Hoechst	-	-
Tolvcar	Hoechst	-	-

Raw Materials

Sodium bicarbonate
3-Acetoxymethyl-7-[2-(2-amino-4-thiazolyl)-2-methoxyiminoacetamido]-ceph-3-em-4-carboxylic acid (Cefotaxime)

Manufacturing Process

A solution of 8 g of sodium bicarbonate in about 20 ml of ethanol was progressively added to 45.55 g of pure 3-acetoxymethyl-7-[2-(2-amino-4-thiazolyl)-2-methoxyiminoacetamido]-ceph-3-eme-4-carboxylic acid in 100 ml of distilled water and another 80 ml of ethanol and 4.5 g of activated carbon were added thereto. The mixture was stirred for 5 minutes and was filtered. The filter was rinsed with ethanol and the filtrate was evaporated to dryness under reduced pressure. The residue was taken up in 100 ml of ethanol and evaporated to dryness again. The residue was dissolved in 100 ml of methanol and the solution was poured into 2 l of acetone. The mixture was vigorously stirred and was vacuum filtered. The recovered product was rinsed with acetone and then ether and dried under reduced pressure to obtain 43.7 g of a white product which rehydrated in air to obtain a final weight of 45.2 g of sodium 3-acetoxymethyl-7-[2-(2-amino-4-thiazolyl)-2-methoxyiminoacetamido]-ceph-3-eme-4-carboxylate.

References

Merck Index 1907
DFU 3 (12) 905 (1978)
Kleeman and Engel p. 171
PDR p. 935
OCDS Vol. 3 p. 216 (1984)
DOT 17 (1) 16 (1981)
I.N.p. 198
REM p. 1186
Heymes, R. and Lutz, A.; US Patent 4,152,432; May 1, 1979; assigned to Roussel Uclaf

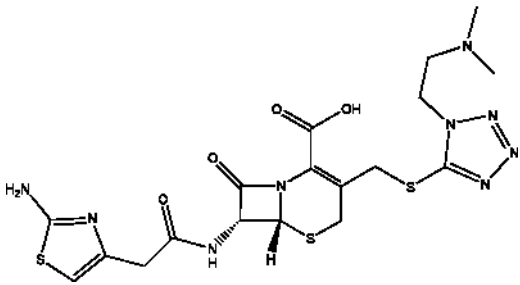
CEFOTIAM

Therapeutic Function: Antibiotic

Chemical Name: 5-Thia-1-azabicyclo(4.2.0)oct-2-ene-2-carboxylic acid, 7-(((2-amino-4-thiazolyl)acetyl)amino)-3-(((1-(2-(dimethylamino)ethyl)-1H-tetrazol-5-yl)thio)methyl)-8-oxo-, (6R-trans)-

Common Name: Cefotiam; Ceftiazole

Structural Formula:



Chemical Abstracts Registry No.: 61622-34-2

Trade Name	Manufacturer	Country	Year Introduced
Cefotiam	Qingdao Ftz United International Inc.	-	-
Cefotiam	Terio Corporation	-	-
Cefotiam	Arocor Holdings Inc.	-	-
Ceradolan	Takeda	-	-
Halospor	Novartis	-	-
Halospor	Ciba-Geigy	-	-
Sporidyn	Zoja	-	-
Spizef	Grunenthal	-	-
Pansporin	Takeda	-	-
Taketiam	Takeda	-	-
Texodil	Cassenne	-	-

Raw Materials

7-Acetamindocephalosporinic acid
1-(2-Dimethylaminoethyl-1H-tetrazol-5-thiol
2-(2-Aminothiazol-4-yl)acetic acid
Hydroxylamine hydrochloride
N-Hydroxysuccinimide
Triethylamine
Amberlite

Manufacturing Process

2 mmol of 7-acetamindocephalosporinic acid in phosphate buffer (pH 7), 2 mmol of 1-(2-dimethylaminoethyl-1H-tetrazol-5-thiol and 2.2 mmol of sodium hydrogen carbonate are mixed and resulting solution was stirred at 60°-65°C for 16 hours. After cooling the mixture was adjusted pH 3.6 and hydrochloride of NH_2OH was added to give 7-amino-3-[2-(2-dimethylaminoethyl)-2H-tetrazol-5-ylsulfanylmethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

0.4 g (2 mmol) of 2-(2-aminothiazol-4-yl)acetic acid hydrochloride in 10 ml of dimethylformamide are dissolved, 0.25 g (2.2 mmol) of N-hydroxysuccinimide and 0.412 g (2 mmol) of dicyclohexylcarbodiimide and the solution is allowed to stand at room temperature for 3 hours. The reaction mixture is subjected to filtration under suction to remove the precipitate of N,N'-dicyclohexylurea. The filtrate is added at a stroke to a solution of 2 mmol of above prepared 7-amino-3-[2-(2-dimethylaminoethyl)-2H-tetrazol-5-ylsulfanylmethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 0.404 g (4 mmol) of triethylamine in 20 ml of dichloromethane and the mixed solution is stirred for 24 hours at room temperature. The solvent is distilled off under reduced pressure and the residue is adjusted pH from to 6 to 7 by adding a 10% aqueous solution of sodium hydrogen carbonate. The resultant solution is chromatographed on column of polystyrene resin (Amberlite XAD-2) and developed with water. The fractions containing the desired product are pooled and freeze-dried to obtain the title product.

References

Numata M. et al.; US Patent No. 4,517,361; May 14, 1985; Assigned to Takeda Chemical Industries, Ltd., Osaka, Japan
Tsushima S. et al.; US Patent No. 4,245,088; Jan. 13, 1981; Assigned to Takeda Chemical Industries, Ltd., Osaka, Japan

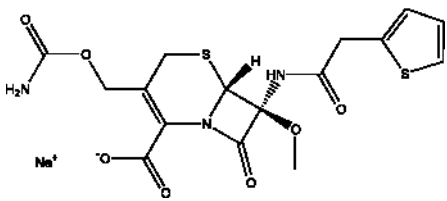
CEFOXITIN SODIUM

Therapeutic Function: Antibiotic

Chemical Name: 3-Carbamoyloxymethyl-7-α-methoxy-7β-(2-thienylacetamido)decephalosporanic acid sodium salt

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 33654-30-6; 35607-66-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Mefoxin	Merck Sharp and Dohme	US	1978
Mefoxitin	Sharp and Dohme	W. Germany	1978
Mefoxin	MSD	UK	1978
Mefoxitin	MSD	Switz.	1979
Mefoxin	MSD	Italy	1979
Cenomicin	Daiichi Seiyaku	Japan	1980
Mefoxin	MSD	France	1980
Merkicin	Merck-Banyu	Japan	1980
Betacel	Firma	Italy	-
Boncefin	MSD	-	-
Cefaxicina	Cefa	Spain	-
Cefoctin	Teva	Israel	-
Farmoxin	Farm. Carlo Erba	Italy	-

Raw Materials

Benzhydryl 3-carbamyloxymethyl-7α-hydroxy-7β-(2-thienylacetamino)-decephalosporanate
Sodium hydride
Dimethyl sulfate
Trifluoroacetic acid

Manufacturing Process

Benzhydryl 3-carbamoyloxymethyl-7α-hydroxy-7β-(2-thienylacetamido) decephalosporanate, 543 mg, is stirred in 15 ml dry DMSO. Sodium hydride, 24 mg (48 mg of a 50% suspension of NaH in mineral oi1, which has been washed with hexane to remove the oil), is added. When hydrogen evolution has ceased, 126 mg dimethyl sulfate is added. The solution is stirred for one hour at room temperature, diluted with 100 ml benzene and washed six times with water; the last wash is made to pH 8, if necessary, by adding sodium bicarbonate. The solution is dried over $MgSO_4$, filtered and evaporated, leaving benzhydryl 3-carbamoyloxymethyl-7β-(2-thienylacetamido)-7α-methoxydecephalosporanate, which may be purified if desired by chromatography on silica gel, eluting with 25:1 chloroformethyl acetate.

Other methylating agents may be used in place of methyl sulfate, e.g., an equimolar amount of methyl iodide, bromide or chloride, using the same conditions, or methyl trifluoromethylsulfonate or trimethyloxonium trinitrobenzenesulfonate. The solvent in the latter two reagents is dimethyl ether-HMPA 1:1, using a reaction temperature of -20°C warming later to 25°C. In each instance, the benzhydryl 3-carbamoyloxymethyl-7β-(2-thienylacetamido)-7α-methoxydecephalosporanate is obtained.

Benzhydryl 3-carbamoyloxymethyl-7β-(2-thienylacetamido)-7α-methoxydecephalosporanate (300 mg) in 0.5 ml in anisole and 2.5 ml of trifluoroacetic acid is reacted for 15 minutes at 10°C. The resulting mixture is

evaporated at reduced pressure and flushed twice with anisole. The residue is dissolved in methylene chloride and extracted with 5% sodium bicarbonate solution. The aqueous solution is adjusted to pH 1.8 with 5% phosphoric acid and extracted with ethyl acetate. The organic solution is dried and evaporated to yield the pure 3-carbamoyloxymethyl-7α-methoxy-7β-(2-thienylacetamido)decephalosporanic acid, MP 165°C to 167°C. This may then be converted to the sodium salt.

References

Merck Index 1910
DFU 3 (6) 434 (1978)
Kleeman and Engel p. 173
PDR p. 1194
OCDS Vol. 2 pp. 435, 443 (1980)
DOT 14 (2) 545 (1978)
I.N. p. 199
REM p. 1186
Christiansen, B.G. and Firestone, R.A.; US Patent 3,775,410; November 27, 1973; assigned to Merck and Company, Inc.
Hazen, G.C.; US Patent 3,780,033; December 18, 1973; assigned to Merck and Company, Inc.

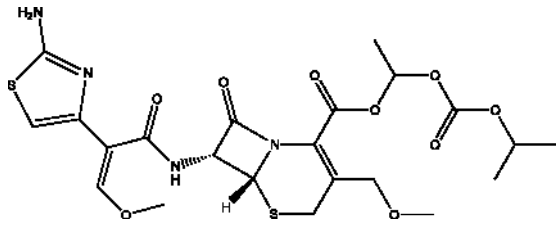
CEFPODOXIME PROXETIL

Therapeutic Function: Antibiotic

Chemical Name: 5-Thia-1-azabicyclo(4.2.0)oct-2-ene-2-carboxylic acid, 7-(((2Z)-(2-amino-4-thiazolyl)(methoxyimino)acetyl)amino)-3-(methoxymethyl)-8-oxo-, 1-(((1-methylethoxy)carbonyl)oxy)ethyl ester, (6R,7R)-

Common Name: Cefpodoxime proxetil

Structural Formula:



Chemical Abstracts Registry No.: 87239-81-4

Trade Name	Manufacturer	Country	Year Introduced
Cefpodoxime proxetil	Ranbaxy Laboratories Limited	India	-
Orelox	Hoechst Marion Roussel	-	-
Vantin	Pharmacia and Upjohn	-	-

Raw Materials

7-Amino-3-methoxymethyl-3-cephem-4-carboxylic acid
1,8-Diazabicyclo[5.4.0]undec-7-ene
Z-(2-Formamidothiazol-4-yl)-methoxy-acetyl chloride hydrochloride

Manufacturing Process

A suspension of 30 g of 7-amino-3-methoxymethyl-3-cephem-4-carboxylic acid in 300 ml acetone is mixed with 18.6 g 1,8-diazabicyclo[5.4.0]undec-7-ene. The solution obtained mixed at ca. 0°C with 261 g of a 14% toluene solution of 1-iodoethylisopropyl carbonate. After 4 hours the solution is poured onto a mixture of 600 ml of water and 21 ml conc. HCl. The pH of mixture is adjusted to ca. 1.0. The aqueous phase is extracted with 200 ml of hexane, mixed with 700 ml ethyl acetate and pH is adjusted to ca. 8.2. A solution of 7-amino-3-methoxymethyl-3-cephem-4-carboxylic acid 1-(isopropoxycarbonyloxy)ethyl ester is obtained. Diastereoisomeric ratio B/(A+B)=0.49 (B is more apolar of the two diastereoisomers).

To a solution of 37.4 g of 7-amino-3-methoxymethyl-3-cephem-4-carboxylic acid 1-(isopropoxycarbonyloxy)ethyl ester in 689 ml ethyl acetate at 2-3°C is added for 25 min 0.105 moles Z-(2-formamidothiazol-4-yl)-methoxy-acetyl chloride hydrochloride. After 25 min pH is adjusted to ca. 6.5-7.3. After 1 hour the organic layer is washed with water and concentrated. It was obtained a crude 5-thia-1-azabicyclo(4.2.0)oct-2-ene-2-carboxylic acid, 7-(((2Z)-(2-amino-4-thiazolyl)(methoxyimino)acetyl)amino)-3-(methoxymethyl)-8-oxo-, 1-(((1-methylethoxy)carbonyl)oxy)ethyl ester, (6R,7R)- (Cefpodoxime proxetil). Diastereoisomeric ratio 0.49.

For purification 5 g of cefpodoxime proxetil are added to a mixture of 35 ml of methanol and 0.6 ml conc. H_2SO_4. The mixture is stirred for 90 min and slowly added during 25 min to a mixture of 2.1 g sodium bicarbonate and 400 ml water. The suspension obtained is stirred for 1 hour and the precipitate is isolated through a suction filter, washed with water and dried over phosphorus pentoxide at 35°C in a vacuum. 5-Thia-1-azabicyclo(4.2.0)oct-2-ene-2-carboxylic acid, 7-(((2Z)-(2-amino-4-thiazolyl)(methoxyimino)acetyl)amino)-3-(methoxymethyl)-8-oxo-, 1-(((1-methylethoxy)carbonyl)oxy)ethyl ester, (6R,7R)-; (Cefpodoxime proxetil) is obtained in a diastereoisomeric ratio 0.528.

References

Takaya T. et al.; US Patent No. 4,409,215; 10.11.1983; Assignee to Fujisawa Pharmaceutical Co., Ltd, Japan.

Nakao H. et al.; US Patent No. 4,486,425; Dec. 4, 1984; Assigned to Sankyo Co., Ltd. (Tokyo)
Grell Ju. et al.; US Patent No. 6,489,470; 12.03.2002; Assigned to Biochemie Gesellschaft
Lee G.-S. et al.; US Patent No. 6,620,930; Assigned to Hanml Pharm. Co., Ltd.

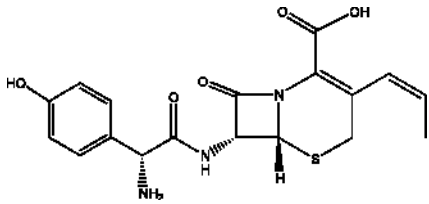
CEFPROZIL

Therapeutic Function: Antibiotic

Chemical Name: 5-Thia-1-azabicyclo(4.2.0)oct-2-ene-2-carboxylic acid, 7-(((2R)-amino(4-hydroxyphenyl)acetyl)amino)-8-oxo-3-(1-propenyl)-, (6R,7R)-

Common Name: Cefprozil; Cephprozyl

Structural Formula:



Chemical Abstracts Registry No.: 92665-29-7

Trade Name	Manufacturer	Country	Year Introduced
Cefprozil	Bristol-Myers Squibb	USA	-
Cefzil	Bristol-Myers Squibb	USA	-

Raw Materials

Ammonium hydroxide
Sulfuric acid
Ethylene glycol
Recombinant penicillin G amidase
4-Hydroxy-D-phenylglycine
Immobilized recombinant penicillin G amidase

Manufacturing Process

A mixture of 4-hydroxy-D-phenylglycine (10 g), ethylene glycol (15 ml) and concentrated sulfuric acid (5 ml) was stirred for 18 hours at 55°C under anhydrous conditions. The solution was cooled, and then ice (10 g) was added to it, and the pH was adjusted to 1.0 with 10 N NH_4OH (4.5 ml) giving 40 ml of solution of hydroxyethyl ester of 4-hydroxy-D-phenylglycine.

The enzyme mixture of 20 ml containing immobilized recombinant penicillin G amidase as the enzyme, 10% hydroxyethyl ester of 4-hydroxy-D-phenylglycine, 4% cefprozil (amine source), and 8% enzyme (immobilized recombinant penicillin G amidase, equivalent to 32 IU/ml of enzyme) was made up without buffer. The above prepared ester solution (6.9 ml) was mixed with water (2 ml) and adjusted to pH 7.5 with 10 N NH_4OH. Then the amine source (0.8 g) was added to it and the pH adjusted to 7.5 with 1 N NH_4OH and the volume to 18.4 ml. Then the mixture was cooled to 5-15°C and solid enzyme (1.6 g; 640 IU) was added to it. The pH was not maintained at 7.5 and fell about 0.6 units during the reaction. The reaction mixture was analyzed by HPLC on a C18 Reverse Phase column. The mobile phase was 10% acetonitrile/0.3% H_3PO_4. The isomers of cefprozil appeared at 2.9 minutes (cis) and at 5.1 minutes (trans). The final product was obtained with a maximum yield of 92-96%. The whole experiment was completed in 25-50 min.

Synthesis of cefprozil may be carried out at 15°C using Boehringer penicillin G amidase as the enzyme and hydroxyethyl ester of 4-hydroxy-D-phenylglycine. A maximum yield of about 95%. The experiment was completed in 35 minutes.

References

Usher J.J., Romancik G.; US Patent No. 6,156,534; 12.05.2000; Assigned to Bristol-Myers Squib Company

Van Dooren Th.J.G.M., Smeets J.Ch.M., Moody H.M.; US Patent No. 6,287,799; 09.11.2001; Assigned to DSM N.V.

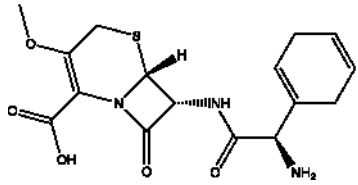
CEFROXADINE

Therapeutic Function: Antibacterial

Chemical Name: 7-[(Amino-1,4-cyclohexadien-1-yl-acetyl)amino]-3-methoxy-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 51762-05-1

Trade Name	Manufacturer	Country	Year Introduced
Oraspor	Ciba Geigy	Switz.	1981
Oraspor	Ciba Geigy	Japan	1982
Oraspor	Ciba Geigy	W. Germany	1983
Oraspor	Ciba Geigy	Italy	1983

Raw Materials

D-α-Amino-α-(1,4-cyclohexadienyl)acetic acid
Phosphorus pentachloride
7β-Amino-3-methoxy-3-cephem-4-carboxylic acid hydrochloride dioxanate
Bis(trimethylsilyl)acetamide
Propylene oxide
Sodium hydroxide

Manufacturing Process

A suspension of 30.64 g (0.2 mol) of D-α-amino-α-(1,4-cyclohexadienyl)-acetic acid in 600 ml of methylene chloride is cooled under a stream of argon to 6°C, whereupon hydrogen chloride is passed in for about 30 minutes until the mixture is saturated. Phosphorpentachloride (62.4 g, 0.3 mol) is added in two portions. The mixture is stirred for 2 hours at 6°C to 8°C. The colorless precipitate is filtered off under nitrogen and exclusion of moisture, washed with methylene chloride and dried for 18 hours at 0.05 mm Hg at room temperature to give D-α-amino-α-(1,4-cyclohexadienyl)-acetylchloride hydrochloride in form of colorless crystals.

A suspension of 37.3 g (0.1 mol) of 7β-amino-3-methoxy-3-cephem-4-carboxylic acid hydrochloride dioxanate in 500 ml methylene chloride is stirred for 15 minutes at room temparature under an argon atmosphere and treated with 57.2 ml (0.23 mol) of bis-(trimethylsilyl)acetamide. After 45 minutes the faintly yellow slightly turbid solution is cooled to 0°C and treated within 10 minutes with 31.29 (0.15 mol) of D-α-amino-α-(1,4-cyclohexadienyl)-acetyl chloride hydrochloride. Thirty minutes thereafter 15 ml (about 0.21 mol) of propylene oxide is added and the mixture is further stirred for 1 hour at 0°C: A cooled mixture of 20 ml of absolute methanol in 200 ml of methylene chloride is added within 30 minutes, after another 30 minutes the precipitate is filtered off under exclusion of moisture, washed with methylene chloride and dried under reduced pressure at room temperature. The obtained hygroscopic crystals of the hydrochloride of 7β-[D-α-(1,4-cyclohexadienyl)-acetylamino]-3-methoxy-3-cephem-4-carboxylic acid are stirred into 200 ml of ice water and the milky solution treated with about 66 ml of cold 2 N sodium hydroxide solution until pH 3.5 is reached. The solution is clarified by filtration through diatomaceous earth, washed with ice water, cooled to 0°C and treated with 20 ml of 2 N sodium hydroxide solution until pH 5.7 is reached. A second filtration through a glass filter frit results in a clear solution which is treated with acetone (800 ml) at 0°C. The crystals are filtered washed with acetone:water (2:1), acetone and diethyl ether and dried for 20 hours at room temperature and 0.05 mm Hg to give the 7β-[D-α-amino-α-(1,4-cyclohexadienyl)-acetylamino]-3-methoxy-3-cephem-4-carboxylic acid dihydrate.

References

Merck Index 1911
DFU 4 (12) 911 (1979)
OCDS Vol. 3 p. 210 (1984)
DOT 19 (4) 190 (1983)
I.N. p. 200
Scartazzini, R. and Bickel, H.; US Patent 4,073,902; February 14, 1978; assigned to Ciba-Geigy Corp.

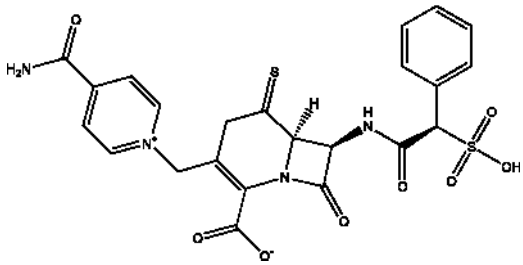
CEFSULODIN

Therapeutic Function: Antibiotic

Chemical Name: 7-(α-Sulfophenylacetamido)-3-(4'-carbamoylpyridinium) methyl-3-cephem-4-carboxylate

Common Name: Sulcephalosporin

Structural Formula:



Chemical Abstracts Registry No.: 52152-93-9 (Sodium salt)

Trade Name	Manufacturer	Country	Year Introduced
Pseudomonil	Ciba Geigy	W. Germany	1980
Monaspor	Ciba Geigy	Switz.	1980
Pyocefalin	Cassenne	France	1981
Takesulin	Takeda	Japan	1981
Tilmapor	Ciba Geigy	Japan	1981
Monaspor	Ciba Geigy	UK	1982
Pseudocef	Gruenenthal	W. Germany	-

Raw Materials

7-(α-Sulfophenylacetamido)cephalosporanic acid
Isonicotinamide
Potassium thiocyanate

Manufacturing Process

0.514 g (4 x 10^{-3} mol) of 7-(α-sulfophenylacetamido)cephalosporanic acid, 0.466 g (3 x 10^{-3} mol) of isonicotinamide and 2.0 g (2.06 x 10^{-3} mol) of potassium thiocyanate were dissolved in 2.5 ml of water. The resulting solution was allowed to stand and heated for 20 hours in a thermostat kept at 50°C and then directly purified by chromatography on an Amberlite XAD-2 column (16 x 880 mm). Subsequently, the fractions containing the cephalosporins were collected and subjected to freeze-drying to obtain 270 g of the title product in the form of a pale yellowish white powder. The product is usually used as the sodium salt.

References

Merck Index 1912
DFU 5 (2) 67 (1980)
OCDS Vol. 3 p. 214 (1984)
DOT 17 (12) 542 (1981)
I.N. p. 200
REM p. 1188
British Patent 1,387,656; March 19, 1975; assigned to Takeda Chemicals Industries, Ltd.

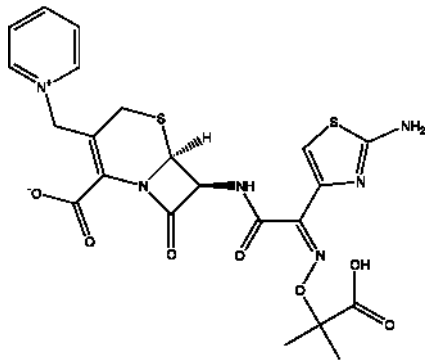
CEFTAZIDIME

Therapeutic Function: Antibiotic

Chemical Name: (6R,7R)-1-[(Z)-2-(2-Aminothiazol-4-yl)-2-(2-carboxyprop-2-oxyimino)-acetamido]-3-(1-pyridiniummethyl)-ceph-3-em-4-carboxylic acid inner salt

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 72558-82-8

Trade Name	Manufacturer	Country	Year Introduced
Fortum	Glaxo	UK	1983

Raw Materials

(Z)-2-(2-t-Butoxycarbonylprop-2-oxyimino)-2-(2-tritylaminothiazol-4-yl)acetic acid
t-Butyl-(6R,7R)-3-acetoxymethyl-7-aminoceph-3-em-4-carboxylate
Pyridine

Manufacturing Process

(a) t-Butyl(6R,7R)-3-acetoxymethyl-7-[(Z)-2-(2-t-butoxycarbonylprop-2-oxyimino)-2-(2-tritylaminothiazol-4-yl)acetamido]ceph-3-em-4-carboxylate: A stirred solution of (Z)-2-(2-t-butoxycarbonylprop-2-oxyimino)-2-(2-tritylaminothiazol-4-yl)acetic acid (572 mg) and t-butyl(6R,7R)-3-acetoxymethyl-7-aminoceph-3-em-4-carboxylate (328 mg) in dimethylformamide (10 ml) was cooled to 0°C, and 1-hydroxybenzotriazole (150 mg) was added, followed by dicyclohexylcarbodiimide (225 mg). The mixture was warmed to room temperature, stirred for 5 hours and allowed to stand overnight. The mixture was filtered, and the white solid washed with a little ether. The filtrate and washings were diluted with water (50 ml) and extracted with ethyl acetate. The organic extracts were combined, washed successively with water, 2 N hydrochloric acid, water, sodium bicarbonate solution, and saturated brine, dried and evaporated. The residue was eluted through a silica column with ether. The product-containing eluate was collected and concentrated to give the title compound (533 mg). A portion was recrystallized from diisopropyl ether, MP 103°C to 113°C (decomp.); $[\alpha]_D^{20}$ +8.5 (conc. 1.0, DMSO).

(b) (6R,7R)-3-Acetoxymethyl-7-[(Z)-2-(2-aminothiazol-4-yl)-2-(2-carboxyprop-2-oxyimino)acetamido]ceph-3-em-4-carboxylic acid: Trifluoroacetic acid (18 ml) was added to a solution of the product of (a) (2.4 g) in anisole (18 ml) at 0°C. The mixture was stirred at room temperature for 2 hours and concentrated. The residue was dissolved in ethyl acetate and extracted with saturated sodium bicarbonate solution. The pH of the aqueous extracts was adjusted to 6, and the solution washed with ethyl acetate. The aqueous phase was acidified to pH 1.5 under ethyl acetate, saturated with sodium chloride, and extracted with ethyl acetate. The combined organic extracts were washed with saturated brine, dried and evaporated. The residue was dissolved in warm 50% aqueous formic acid (20 ml) and allowed to stand for 2 hours. The mixture was diluted with water (50 ml) and filtered. The filtrate was concentrated. The residue was taken up in water (50 ml), refiltered, and lyophilized to give the title compound (920 mg).

(c) (6R,7R)-7-[(Z)-(2-Aminothiazol-4-yl)-2-(2-carboxyprop-2-oxyimino)acetamido]-3-(1-pyridiniummethyl)-ceph-3-em-4-carboxylate, monosodium salt: Pyridine (2 ml) and the product of (b) (1.8 g) were added to a stirred solution of sodium iodide (7.12 g) in water (2.2 ml) at 80°C. The solution was stirred at 80 C for 1 hour, cooled, and diluted to 100 ml with water. The pH of the solution was adjusted to 6.0 with 2N sodium hydroxide solution, and this solution was concentrated to remove pyridine. The aqueous residue was diluted to 100 ml with water, methyl isobutyl ketone (2 drops)

was added, and the solution was acidified to pH 1 with 2 N hydrochloric acid. The mixture was filtered, and the solid was washed with a little water. The filtrate and washings were collected and washed with ethyl acetate, and the pH adjusted to 6.0 with 2 N sodium hydroxide solution. The solution was concentrated to 50 ml and applied to a column of 500 g Amberlite XAD-2 resin, using first water and then 20% aqueous ethanol as eluting solvent. The product-containing fractions were concentrated and lyophilized to give the title compound (0.56 g).

References

Merck Index 1913
DFU 6 (10) 612 (1981)
PDR p. 909
OCDS Vol. 3 p. 216 (1984)
DOT 19 (6) 336 (1983)
REM p. 1188
O'Callaghan, C.H., Livermore, D.G.H. and Newall, C.E.; British Patent 2,025,398; January 23, 1980; assigned to Glaxo Group Ltd.

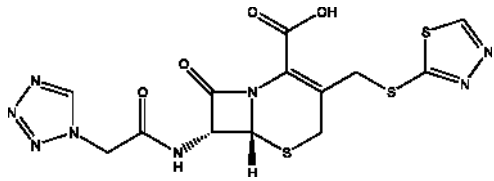
CEFTEZOLE

Therapeutic Function: Antibiotic

Chemical Name: (6R,7R)-8-Oxo-7-(2-(1H-tetrazol-1-yl)acetamido)-3-((1,3,4-thiadiazol-2-ylthio)methyl)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

Common Name: Ceftezole; Demethylcefazolin

Structural Formula:



Chemical Abstracts Registry No.: 26973-24-0

Trade Name	Manufacturer	Country	Year Introduced
Ceftezole	Arocor Holdings Inc.	-	-
Ceftezole	DAE HAN NEW PHARM CO., LTD.	-	-
Alomen	Benedetti	-	-
Falomesin	Chugai	-	-

Raw Materials

1H-Tetrazole-1-acetic acid
Triethylamine
Pivaloyl chloride
1,3,4-Thiadiazole-2-thiol

Manufacturing Process

To a solution of 1 equivalent (eq.) of 1H-tetrazole-1-acetic acid and 1 eq. of triethylamine in 20 ml of tetrahydrofuran cooled to -20°C was added 1 eq. of pivaloyl chloride. After thirty-minute stirring of the mixture 20 ml of a chloroform solution containing 1 eq. of and 1 eq. of triethylamine was poured into the solution cooled at -10°C during a period of 30 minutes. The resulting mixed solution was stirred for 30 minutes at the same temperature, for 1 hour in an ice-water mixture and for 3 hours at room temperature. Removal of a solvent from the reaction mixture afforded an oily residue, which was dissolved into 15 ml of 10% sodium bicarbonate aqueous solution. The resulting aqueous layer was adjusted to pH 1.0-2.0 with 10% hydrochloric acid, washed with ether and extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate and concentrated under reduced pressure leaving a residue which was triturated with ethyl acetate to obtain 3-acetoxymethyl-8-oxo-7-(2-tetrazol-1-acetylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

A solution of 1 eq. of sodium salt of 3-acetoxymethyl-8-oxo-7-(2-tetrazol-1-acetylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid (it may be prepared with equivalent of sodium bicarbonate and above named acid) and 1 eq. of [1.3.4]-thiadiazole-2-thiol in 20 ml of phosphate buffer (pH 6.4) was stirred for 5.5 hours at 60°C. The reaction mixture was adjusted to pH 2.0 with 5% hydrochloric acid and treated with ethyl acetate to form a title compound - ceftezole.

References

Takano T. et al.; US Patent No. 3,516,997; June 23, 1970; Assigned to Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan

CEFTIBUTEN

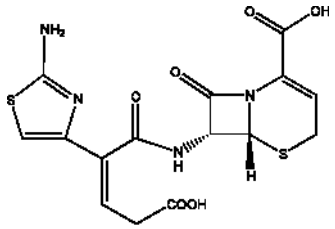
Therapeutic Function: Antibiotic

Chemical Name: 5-Thia-1-azabicyclo(4.2.0)oct-2-ene-2-carboxylic acid, 7-(((2Z)-2-(2-amino-4-thiazolyl)-4-carboxy-1-oxo-2-butenyl)amino)-8-oxo-, (6R,7R)-

Common Name: Ceftibuten

Chemical Abstracts Registry No.: 97519-39-6

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Cedax	Schering-Plough	-	-
Keimax	Essex Pharma GmbH	Germany	-
Procef	Bristol-Myers Squibb	USA	-

Raw Materials

8-Oxo-7-phenylacetylamino-5-thia-1-aza-bicyclo[4.2.0]oct-1-ene-2-carboxylic acid benzhydryl ester
Phosphorus pentachloride/pyridine reagent
4-(3-Aminothiophen-2-yl)-5-oxohex-3-enoic acid 3-methylbut-2-enyl ester
Diphenylmethyl thiazoleacetate
Ethyl formate
Aluminum chloride
Phosphorane from benzyl 2-triphenylphosphonium acetate
Trifluoroacetic acid
Desmethyl cephalosporin

Manufacturing Process

The 1st method of synthesis

The 8-oxo-7-phenylacetylamino-5-thia-1-aza-bicyclo[4.2.0]oct-1-ene-2-carboxylic acid benzhydryl ester is reacted with phosphorus pentachloride/pyridine reagent in methylene dichloride, and the reaction mixture is thereafter cooled to -35°C and treated with methanol to produce hydrochloride of 7-amino-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid benzhydryl ester. This hydrochloride is reacted with 4-(3-aminothiophen-2-yl)-5-oxohex-3-enoic acid 3-methylbut-2-enyl ester. Then 7-[2-(2-benzoylamino-thiazol-5-yl)(3-tert-butyl-4,4-dimethylpent-2-enoxycarbonyl)-pent-2-enoylamino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid synthesized is reacted with aluminum chloride in anisole and diluted hydrochloric acid and then with dimethylmalonate to give 5-thia-1-azabicyclo(4.2.0)oct-2-ene-2-carboxylic acid, 7-(((2Z)-2-(2-amino-4-thiazolyl)-4-carboxy-1-oxo-2-butenyl)amino)-8-oxo-, (6R,7R)- (Ceftibuten).

The 2st method of synthesis

Formulation of the diphenylmethyl thiazoleacetate with ethyl formate leads to 2-(2-aminothiazol-5-yl)-3-hydroxyacrylic acid benzhydryl ester. Condensation of 2-(2-aminothiazol-5-yl)-3-hydroxyacrylic acid benzhydryl ester with the phosphorane from benzyl 2-triphenylphosphonium acetate leads to the 2-(2-aminothiazol-5-ylmethylene)succinic acid 1-benzhydryl ester 4-benzyl ester. Exposure of this ester to trifluoroacetic acid selectively cleaves the diphenylmethyl group over the benzyl ester to give 2-(2-aminothiazol-5-ylmethylene)succinic acid 4-benzyl ester. Condensation of the acid with free amino group in the desmethyl cephalosporin affords the amide of 7-[3-(2-aminothiazol-5-yl)-2-benzoylcarbonylmethylacryloylamino)-8-oxo-5-thia-1-azabicyclo[4.2.1]oct-2-ene-2-carboxylic acid benzyl ester. The remaining benzyl ester protecting groups are removed by means of aluminum chloride to afford 7-[3-(2-aminothiazol-5-yl)-2-benzoylcarbonylmethylacryloylamino)-8-oxo-5-thia-1-azabicyclo[4.2.1]oct-2-ene-2-carboxylic acid or ceftibuten

References

Torii S. et al.; US Patent No. 6,576,761; Nov. 21, 2000; Assignee to Otsuka Kagaku Kabushiki Kaisha (Osaka, JP)
Hamashima Y. et al.// J. Antibiot., 1987, 40, 1468

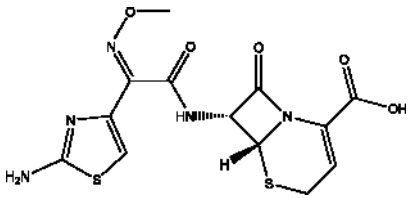
CEFTIZOXIME

Therapeutic Function: Antibacterial

Chemical Name: 7-[2-Methoxyimino-2-(2-amino-1,3-thiazol-4-yl)acetamido]-cephalosporanic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 68401-81-0; 68401-82-1 (Sodium salt)

Trade Name	Manufacturer	Country	Year Introduced
Eposelin	Fujisawa	Japan	1982
Cefizox	SKF	US	1983
Ceftix	Boehringer Mannheim	W. Germany	1983
Cefizox	Eurroughs Wellcome	UK	-

Raw Materials

Phosphorus oxychloride
2-Methoxyimino-2-(2-amino-1,3-thiazol-4-yl)acetic acid
Bis(trimethylsilyl)acetamide
7-Aminocephalosporanic acid

Manufacturing Process

Phosphorus oxychloride (2.0 g) was added at one time at 5°C to 10°C to a suspension of 2-methoxyimino-2-(2-amino-1,3-thiazol-4-yl)acetic acid (syn isomer) (2 g) in dry ethyl acetate (20 ml). After stirring for 20 minutes at 7°C to 10°C, bis(trimethylsilyl)acetamide (0.4 g) was added thereto at the same temperature. After stirring for 10 minutes at 7°C to 10°C, phosphorus oxychloride (2.0 g) was dropwise added thereto at the same temperature. The resulting mixture was stirred for 10 minutes at 7°C to 10°C, and dry dimethylformamide (0.8 g) was dropwise added thereto at the same temperature. The mixture was stirred for 30 minutes at 7°C to 10°C to give a clear solution. On the other hand, trimethylsilylacetamide (7.35 g) was added to a suspension of 7-aminocephalosporanic acid (2.45 g) in dry ethyl acetate (8 ml), after which the mixture was stirred at 40°C to give a clear solution.

To this solution was added at one time the above-obtained ethyl acetate solution at -15°C, and the resulting mixture was stirred for 1 hour at -10°C to -15°C. The reaction mixture was cooled to -30°C, and water (80 ml) was added thereto. The aqueous layer was separated, adjusted to pH 4.5 with sodium bicarbonate and subjected to column chromatography on Diaion HP-20 resin (Mitsubishi Chemical Industries Ltd.) using 25% aqueous solution of isopropyl alcohol as an eluent. The eluate was lyophilized to give 7-[2-methoxyimino-2-(2-amino-1,3-thiazol-4-yl)acetamido]cephalosporanic acid (syn isomer) (1.8 g), MP 227°C (decomp.).

References

Merck Index 1915
DFU 5 (5) 226 (1980)
PDR p. 1704
OCDS Vol. 3 p. 218 (1984)
DOT 19 (3) 133 (1983)
I.N. p. 200
REM p. 1189
Takaya, T., Masugi, T., Takasugi, H. and Kochi, H.; US Patent 4,166,115; assigned to Fujisawa Pharmaceutical Co., Ltd.

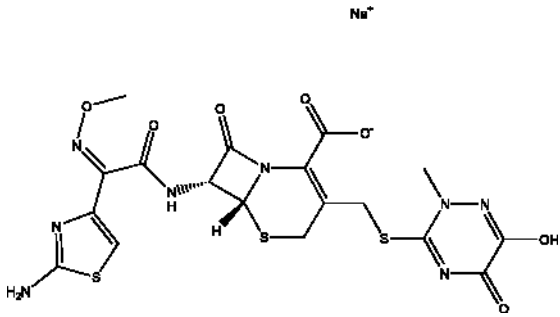
CEFTRIAXONE SODIUM

Therapeutic Function: Antibacterial

Chemical Name: Sodium salt of (6R,7R)-7-[2-(2-amino-4-thiazolyl)-2-(methoxyimino)acetamido]-8-oxo-3-[[(1,4,5,6-tetrahydro-4-methyl-5,6-dioxo-as-triazin-3-yl)thio]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 75478-69-1; 73384-59-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Rocephin	Roche	Switz.	1982
Rocephin	Roche	W. Germany	1983
Acantex	Roche	-	-

Raw Materials

(6R,7R)-7-[2-[2-(2-Chloroacetamido)-4-thiazolyl]-2-(methoxyimino) acetamido]-8-oxo-3-[[(1,4,5,6-tetrahydro-4-methyl-5,6-dioxo-as-triazin-3-yl)thio]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid
Formic acid

Manufacturing Process

19 g of (6R,7R)-7-[2-[2-(2-chloroacetamido)-4-thiazolyl]-2-(methoxyimino) acetamido]-8-oxo-3-[[(1,4,5,6-tetrahydro-4-methyl-5,6-dioxo-as-triazin-3-yl)thio]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid are suspended in 150 ml of water together with 9.5 g of thiourea. The pH is adjusted to 6.8 with 5% sodium hydrogen carbonate solution while gassing with nitrogen and stirring, there being obtained a yellow-orange solution. The pH of the solution is held constant at 6.8-7.0 for 6 hours by adding sodium hydrogen carbonate solution by means of an autotitrator. 100% formic acid is added to the orange colored solution until the pH is 3.5. The precipitated material is filtered off under suction and washed with 100 ml of 10% formic acid. This material is denoted as (1). The filtrate is adjusted to pH 2.5 by adding 100% formic acid, whereby additional substance precipitates out. The mixture is held in an ice-bath for 1 hour, the precipitated substance is then filtered off and washed with a small amount of ice-water. This material is denoted as fraction I. The aforementioned orange-brown material (1) is suspended in 250 ml of water. The suspension is adjusted to pH 7 with 2 N sodium hydroxide, there being obtained an orange-brown solution. Additional 100% formic acid is added to this solution until the pH is 3.5. The material

which thereby precipitates out is filtered off under suction and discarded. The filtrate is adjusted to pH 2.5 with 100% formic acid, whereby additional substance precipitates out. The mixture is held in an ice-bath for 1 hour, the precipitated substance is then filtered off under suction and washed with a small amount of ice-water. This material is denoted as fraction II. Fractions I and II are suspended together in 500 ml of ethanol and evaporated in a rotary evaporator in order to remove water. After adding ether, the mixture is filtered under suction and the precipitate is washed successively with ether and low-boiling petroleum ether. There is thus obtained the title substance in the form of a yellowish solid material which is denoted as A.

The mother liquors and washings of fractions I and II are concentrated from a volume of about 1.7 liters to 250 ml, the pH is adjusted to 2.5 with 100% formic acid and the solution is stored overnight in a refrigerator, whereby further substance crystallizes. This is filtered off under suction and washed with a small amount of water. The residue on the suction filter is azeotropically distilled with ethanol. There is obtained solid, almost colorless title substance which is denoted as B. B is purer than A according to thin-layer chromatography.

In order to obtain pure title substance, the acid B is suspended in 150 ml of methanol and treated while stirring with 10 ml of a 2 N solution of the sodium salt of 2-ethylcaproic acid in ethyl acetate. After about 10 minutes, there results a solution which is treated with 100 ml of ethanol. The mixture is extensively concentrated at 40°C in vacuo. The sodium salt precipitates out in amorphous form after adding ethanol. This salt is filtered off under suction, washed successively with ethanol and low-boiling petroleum ether and dried at 40°C in a high vacuum. There is obtained the title substance in the form of an almost colorless amorphous powder.

References

Merck Index 1916
PDR D. 1499
DOT 19 (12) 653 (1983)
I.N. p. 200
REM p. 1189
Montavon, M. and Reiner, R.; British Patent 2,022,090; December 12, 1979; assigned to F. Hoffman - La Roche and Co. A.G. (Switz.)

CEFUROXIME

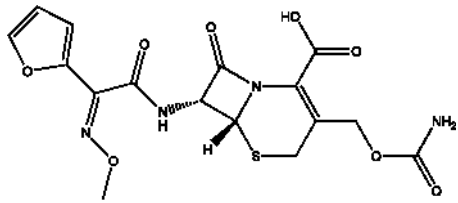
Therapeutic Function: Antibiotic

Chemical Name: (6R,7R)-3-Carbamoyloxymethyl-7-[2-(2-furyl)-2-(methoxyimino)acetamido]-ceph-3-em-4-carboxylic acid

Common Name: -

Chemical Abstracts Registry No.: 55268-75-2; 56238-63-2 (Sodium salt)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Ultroxim	Duncan	Italy	1978
Curoxime	Glaxo	Italy	1978
Zinacef	Hoechst	W. Germany	1978
Zinacef	Glaxo	UK	1978
Zinacef	Glaxo	Switz.	1978
Ceroxime	Glaxo	France	1980
Zinacef	Glaxo	Japan	1982
Zinacef	TANABE SEIYAKU	Japan	1982
Zinacef	Glaxo	US	1983
Altacel	Pulitzer	Italy	-
Biociclin	Del Saz and Filippini	Italy	-
Bioxima	Italsuisse	Italy	-
Cefamar	Firma	Italy	-
Cefoprim	Esseti	Italy	-
Cefumax	Locatelli	Italy	-
Cefur	Tiber	Italy	-
Cefurex	Sarm	Italy	-
Cefurin	Magis	Italy	-
Cefurox	Glaxo	-	-
Colifossim	Coli	Italy	-
Curisef	Glaxo	Italy	-
Duxima	Dukron	Italy	-
Furex	Lafare	Italy	-
Gibicef	Gibipharma	Italy	-
Itorex	Ausonia	Italy	-
Kefox	C.T.	Italy	-
Kesint	Proter	Italy	-
Ketocef	Glaxo	-	-
Lamposporin	Von Boch	Italy	-
Medoxin	Medici	Italy	-
Polixima	Sierochimica	Italy	-
Supero	Farmochimica	Italy	-
Ultroxim	Sigma Tau	Italy	-

Raw Materials

(6R,7R)-7-Amino-3-carbamoyloxymethylceph-3-em-4-carboxylic acid
Phosphorus pentachloride
2-(Fur-2-yl)-2-methoxyiminoacetic acid
Hydrogen chloride

Manufacturing Process

A stirred mixture of N,N-dimethylacetamide (75 ml), acetonitrile (75 ml), triethylamine (42 ml, 0.3 mol) and (6R,7R)-7-amino-3-carbamoyloxy-methylceph-3-em-4-carboxylic acid was immersed in an ice-bath and water (10 ml) was added. The mixture was stirred at 0°C to 2°C for 45 minutes, the solid slowly dissolving to give a yellow solution.

Meanwhile a stirred suspension of phosphorus pentachloride (14.99 g, 0.072 mol) in dry dichloromethane (150 ml) was cooled to 0°C, and N,N-dimethylacetamide (27.5 ml) was added. The resulting solution was recooled to -10°C and 2-(fur-2-yl)-2-methoxyiminoacetic acid (synisomer) (12.17 g, 0.072 mol) was added. The mixture was stirred at -10°C for 15 minutes and crushed ice (35 g) was added. The mixture was stirred at 0°C for 10minutes, where after the lower dichloromethane phase was added over 10 minutes to the cephalosporin solution prepared above, cooled to -10°C so that the reaction temperature rose steadily to 0°C. The mixture was stirred at 0°C to 2°C for 1 hour, where after the cooling bath was removed and the reaction temperature allowed to rise to 20°C over 1 hour. The reaction mixture was then added slowly to 2 N hydrochloric acid (100 ml) diluted with cold water (1.15 l) at 5°C. The pH of the two phase mixture was adjusted to below 2 with 2 N hydrochloric acid (10 ml), and the mixture was stirred and recooled to 5°C. The solid which precipitated was filtered, washed with dichloromethane (100 ml) and water (250 ml), and dried in vacuo at 40°C overnight to give the title compound (22.04 g, 86.6%).

References

Merck Index 191
DFU 3 (4) 266 (1978)
Kleeman and Engel p. 177
PDR p. 922
OCDS Vol. 3 p. 216 (1984)
DOT 12 (5) 189 (1976) and 15 (1) 10 (1979)
I.N. p. 200
REM p. 1187
Cook, M.C., Gregory, G.I. and Bradshaw, J.; US Patent 3,966,717; June 29, 1976; assigned to Glaxo Laboratories, Ltd.
Cook, M.C., Gregory, G.I. and Bradshaw, J.; US Patent 3,974,153; August 10, 1976; assigned to Glaxo Laboratories, Ltd.

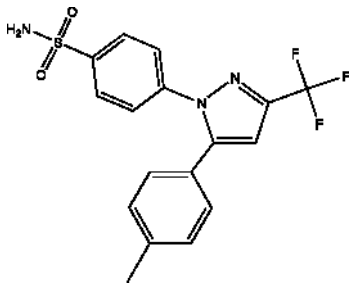
CELECOXIB

Therapeutic Function: Antiinflammatory

Chemical Name: Benzenesulfonamide, 4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)-

Common Name: Celecoxib

Structural Formula:



Chemical Abstracts Registry No.: 169590-42-5; 184007-95-2

Trade Name	Manufacturer	Country	Year Introduced
Celact	Sun Pharmaceuticals Industries Ltd.	India	-
Celcib	Khandelwal Laboratories Ltd.	India	-
Celebrex	Searle Ltd.	-	-
Celebrex	Pfizer	-	-
Celebrex	Bayer	-	-
Celecap	Centaur Laboratories (P) Ltd.	India	-
Celecoxib	Pharmacia	-	-
Colcibra	Crosland Research Laboratories	India	-
Celedol	IPCA laboratories Ltd.	India	-
Celetop	Sarabhai Piramal Pharmaceuticals Ltd.	India	-
Celib	Unichem Laboratories Ltd.	India	-
Cobix	Cipla Limited	India	-
Cobix	Brown and Burk Pharmaceuticals Ltd.	India	-
Eloxib	Emcure Pharmaceuticals Ltd.	India	-
Orthocel	Biochem Pharma Industries	-	-
Revibra	Dr. Reddy's Laboratories Ltd.	India	-

Trade Name	Manufacturer	Country	Year Introduced
Sionara	Alembic Ltd.	India	-
Zecoxib	Win Medicare	India	-
Zycel	Zydus Cadila	India	-

Raw Materials

Ethyl trifluoroacetate
Sodium methoxide
4-Chloroaceteophenone
4-Sulphonamidophenylhydrazine hydrochloride
Hydrochloric acid

Manufacturing Process

4-(5-(4-Methylphenyl)-3-trifluoromethyl-N-pyrazol-1-yl)benzenesulfonamide

To a solution of ethyl trifluoroacetate (1.90 ml, 16.0 mmol) in 7 ml of methyl tert-butyl ether was added 25% NaOMe (3.62 ml, 16.8 mmol). Next 4-chloroaceteophenone (2.08 ml, 16.0 mmol) in 2 ml of methyl tert-butyl ether was added. The mixture was stirred at room temperature overnight. To above solution was added 100 ml of 90% EtOH, followed by 4 N HCl (4.0 ml, 16 mmol) and 4-sulphonamidophenylhydrazine hydrochloride (3.58 g, 16 mmol). The mixture was heated to reflux for 3 hours. The mixture was concentrated. When 30 ml of water was added, a solid formed. The solid was filtered and washed with 20 ml of 60% EtOH to give 4.50 g of white solid. The filtrate was evaporated and taken up in ethyl acetate (100 ml), washed with saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated. Heptane was added at boiling point of the mixture. After cooling down to 0°C, 1.01 g more product was obtained. The combined yield of the 4-(5-(4-methylphenyl)-3-trifluoromethyl-N-pyrazol-1-yl)benzenesulfonamide (Celecoxib) was 86%.

References

Zhi Benxin et al.; WO 96/37476, Nov. 28, 1996; Applicante Searle and Co. (US)

CELIPROLOL

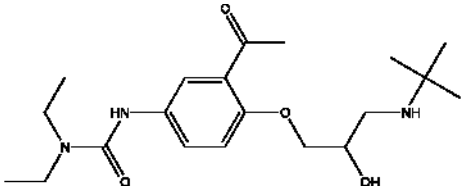
Therapeutic Function: Beta-adrenergic blocker

Chemical Name: N'-[3-Acetyl-4-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]phenyl]-N,N-dimethylurea

Common Name: -

Chemical Abstracts Registry No.: 56980-93-9

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Selectol	Chemie Linz	Austria	1983
Selectol	Chemie Linz	W. Germany	1983

Raw Materials

3-Acetyl-4-hydroxyaniline
Dimethylcarbamoyl chloride
Epichlorohydrin
t-Butylamine

Manufacturing Process

3-Acetyl-4-hydroxyaniline, in solution in pyridine, is reacted with dimethylcarbamoyl chloride at room temperature to give N-(3-acetyl-4-hydroxy)phenyl-N'-dimethylurea, which after evaporating the pyridine, taking up the residue in chloroform and evaporating the latter, is obtained in a crystalline form. Melting point: 160°-162°C. After reaction of the product in alkaline aqueous solution, with epichlorohydrin, N-[3-acetyl-4-(2',3'-epoxy)-propoxy]-phenyl-N'-dimethylurea (melting point: 98°-102°C) is obtained, and this, in turn, is reacted with excess tert-butylamine in aqueous solution at room temperature to give N-[3-acetyl-4-(3'-tert-butylamino-2'-hydroxy)-propoxy)-phenyl-N'-dimethylurea of melting point: 120°-122°C.

References

Merck Index 1921
DFU 4 (3) 181 (1979)
DOT 18 (12) 632 (1982)
I.N. p. 201
Zolss, G., Pittner, H., Stormann-Menninger-Lerchenthal, H. and Lindner, I.; US Patent 3,983,169; September 28, 1976; assigned to Chemie Linz AG (Austria)

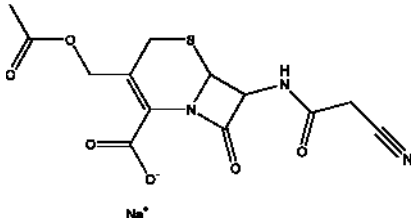
CEPHACETRILE SODIUM

Therapeutic Function: Antibiotic

Chemical Name: 7-(2-Cyanoacetamido)-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylic acid acetate monosodium salt

Common Name: Sodium 7-(2-cyanoacetamido)-cephalosporanic acid

Structural Formula:



Chemical Abstracts Registry No.: 23239-41-0; 10206-21-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Celospor	Ciba Geigy	Switz.	1969
Celospor	Ciba	France	1973
Clospor	Gruenenthal	W. Germany	1974
Celospor	Ciba	Italy	1974
Celospor	Ciba	W. Germany	1974
Celtol	Takeda	Japan	1978
Celospor	Ciba Geigy	Japan	1978
Flunicef	Alfa Farm.	Italy	-

Raw Materials

7-Aminocephalosporanic acid
Cyanoacetyl chloride
Sodium hydroxide

Manufacturing Process

13.6 g (0.05 mol) of 7-aminocephalosporanic acid are taken up in a mixture of 150 ml of methylene chloride and 19.5 ml of tributylamine (0.12 mol) and at 0°C a solution of 8.4 g of cyanoacetylchloride (0.07 mol) in 100 ml of methylene chloride is stirred in. The bath is then stirred for ½ hour at 0°C and for ½ hour at 20°C, the reaction solution is evaporated under vacuum and the residue taken up in 10% aqueous dipotassium hydrogenphosphate solution. This aqueous phase is washed with ethyl acetate, acidified to pH 2.0 with concentrated hydrochloric acid and extracted with ethyl acetate.

After having been dried over sodium sulfate and evaporated under vacuum, this extract gives as a solid residue 14.7 g of crude 7-cyanoacetylamino-cephalosporanic acid which is purified by chromatography on 30 times its own weight of silica gel. The fractions eluted with chloroform plus acetone (7:3) furnish a product which crystallizes from acetone plus ether in the form of needles melting at 168° to 170°C with decomposition.

5.10 g (15 mmol) of 7-cyanoacetyl-aminocephalosporanic acid are suspended

in 102 ml of distilled water and converted into the sodium salt by stirring in dropwise 15 ml of N sodium hydroxide solution.

References

Merck Index 1934
Kleeman and Engel p. 159
DOT 7 (5) 181 (1971) 9 (2) 50 (1973) and 10 (7) 239 (1974)
I.N. p. 193
Bickel, H., Bosshardt, R., Fechtig, B., Schenker, K. and Urech, J.; US Patent 3,483,197; December 9, 1969; assigned to Ciba Corporation

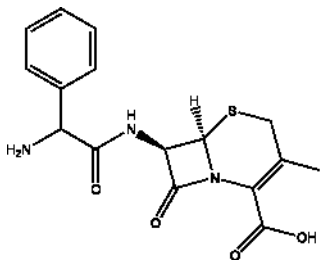
CEPHALEXIN

Therapeutic Function: Antibiotic

Chemical Name: 7-[(Aminophenylacetyl)amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 15686-71-2; 23325-78-2 (Monohydrate)

Trade Name	Manufacturer	Country	Year Introduced
Ceporex	Glaxo	UK	1970
Ceprorexine	Glaxo	France	1970
Cepol	Torii	Japan	1970
Keflex	Shionogi	Japan	1970
Keflex	Lilly	UK	1970
Keflex	Lilly	US	1971
Ceporex	Glaxo	Italy	1971
Keforal	Lilly	France	1971
Keforal	Lilly	Italy	1971
Oracef	Lilly	W. Germany	1971

Trade Name	Manufacturer	Country	Year Introduced
Keflex	Serum Impfinst.	Switz.	1974
Acaxina	Martin Santos	Spain	-
Acinipan	Aldon	Spain	-
Ambal	Medical	Spain	-
Amplicefal	Miluy	Spain	-
Ampligram	Hermes	Spain	-
Ausocef	Ausonia	Italy	-
Basporin	Basileos	Spain	-
Bilatox	Biopharma	Spain	-
Bioporina	Biologia Marina	Spain	-
Brisoral	Bristol-Myers	-	-
Cefabiot Oral	Galepharma Iberica	Spain	-
Cefadina	Antibioticos	Spain	-
Cefadros	Proter	Italy	-
Cefa-Iskia	Iskia	Spain	-
Cefaleh Ina	Alvarez-Gomez	Spain	-
Cefalekey	Pereira	Spain	-
Cefalex-Gobens	Normon	Spain	-
Cefalival	Valles Mestre	Spain	-
Cefaloto	Lifepharma	Spain	-
Cefa-Reder	Reder	Spain	-
Cefaxin	Bristol	Italy	-
Cefibacter	Rubio	Spain	-
Ceflon	Mulda	Turkey	-
Ceflor	Coli	Italy	-
Ceforal	Teva	Israel	-
Cepexin	Glaxo	-	-
Cephalomax	Daisan	Japan	-
Cephazal	Hokuriku	Japan	-
Cepol	Torii	Japan	-
Cepoven	Glaxo	Italy	-
CEX	Glaxo	Japan	-
Chemosporal	Erba	Italy	-
Cilicef Oral	Hortel	Spain	-
Ciponium	Nippon Kayaku, Co.	Japan	-
Derantel	Nippon Chemiphar	Japan	-
Devaleksin	Deva	Turkey	-
Diabeton	Teknofarma	Italy	-
Erifalecin	Dreikehl	Spain	-

Trade Name	Manufacturer	Country	Year Introduced
Erocetin	Roemmers	Argentina	-
Esmezin	Sawai	Japan	-
Falecina	Italquimica	Spain	-
Farexin	Lafare	Italy	-
Fergon	Alfar	Spain	-
Garasin	Wakamoto	Japan	-
Grafalex	Graino	Spain	-
Huberlexina	Hubber	Spain	-
Ibilex	I.B.I.	Italy	-
Iwalexin	Iwaki	Japan	-
Janocilin	Janovich	Spain	-
Keflex	Shionogi	Japan	-
Kelfison	Davur	Spain	-
Larixin	Toyama	Japan	-
Latoral	Dukron	Italy	-
Lefosporina	Bicsa	Spain	-
Lexibiotico	Llano	Spain	-
Libesporal	Liberman	Spain	-
Llenas Biotic	Llenas	Spain	-
Lorexina	Crosara	Italy	-
Madlexin	Meiji	Japan	-
Maksipor	Fako	Turkey	-
Mamalexin	Showa	Japan	-
Mepilacin	Kanto	Japan	-
Neolexina	Asia	Spain	-
Nilexina	Pental	Spain	-
Ohlexin	Ohta	Japan	-
Oracocin	Tobishi	Japan	-
Oralexine	Novo	Denmark	-
Oroxin	Otsuka	Japan	-
Ortisporina	Turro	Spain	-
Ospexin	Biochemie	Austria	-
Palitrex	Galenika	Yugoslavia	-
Porinabis	Santos	Spain	-
Pracefal	Pradel	Spain	-
Prindex	Hosbon	Spain	-
Pyassan	Chinoin	Hungary	-
Rinesal	Kissei Pharmaceutical Co., Ltd.	Japan	-
Rogeridina	Roger	Spain	-

Trade Name	Manufacturer	Country	Year Introduced
Salitex	Banyu	Japan	-
Sargetina	Sarget	France	-
Sartosona	Sanomed	Spain	-
Sasperos	Schiapparelli	Italy	-
Sayra	Legem	Spain	-
Sefaleksin	Ilsan	Turkey	-
Segoramin	Takata	Japan	-
Sencephalin	Takeda	Japan	-
Septilisin	Bago	Argentina	-
Syncel	Toyo Jozo	Japan	-
Taicelexin	Taiyo	Japan	-
Talinsul	Ester	Spain	-
Testaxina	Bryan	Spain	-
Tokilexin	Isei	Japan	-
Torlasporin	Torlan	Spain	-
Wasserporina	Wassermann	Spain	-
Xahl	S.S. Seiyaku	Japan	-

Raw Materials

Soidum-D-α-phenylglycine
Zinc
Methyl acetoacetate
Hydrogen chloride
p-Nitrobenzyl-7-aminodesacetoxycephalosporanate

Manufacturing Process

To a 1 liter flask containing dimethylformamide at 0°C, was added 24.8 g sodium N-(2-methoxycarbonyl-1-methylvinyl)-D-α-phenylglycine (prepared from sodium D-α-phenylglycine and methyl acetoacetate). The mixture was cooled to -40°C and methyl chloroformate (7.5 ml) and dimethylbenzylamine (0.26 ml) added. After stirring for 25 minutes, p-nitrobenzyl 7-aminodesacetoxycephalosporanate (32.8 g) in the form of its hydrochloride salt was added, followed by triethylamine (12.1 ml) and dimethylformamide (140 ml) over a period of 20 minutes. The reaction mixture was stirred for 2 hours at -25°C to -35°C, then warmed to 0°C and water (32 ml) added. To the resultant solution, hydrochloric acid (54 ml) was added followed by zinc (21.8 g) in portions over a period of 5 minutes, the temperature being maintained at 5°C to 10°C. Further hydrochloric acid (35 ml) was added and the solution stirred at 15°C to 20°C for 7 hours.

The pH was adjusted to 3.3 with triethylamine and semicarbazidehydrochloride (9.5 g) added. The mixture was brought back to pH 3 with further triethylamine, then stirred for 30 minutes at pH 3. The resultant mixture was adjusted slowly over 4 hours to pH 6.8 by addition of triethylamine, seeding being carried out when pH 4.5 was reached. The

precipitated cephalexin was filtered off, washed with dimethylformamide (200 ml) and the cephalexin recovered, yield 75%.

References

Merck Index 1936
Kleeman and Engel p. 161
PDR p. 841
OCDS Vol. 1 p.417 (1977) and 2 p. 439 (1980)
DOT 5 (1) 29 (1969) and 6 (5) 165 (1970)
I.N. p. 194
REM p. 1189
Davison, M., Frankham, D.B., Spence, T.W.M.; US Patent 3,946,002; March 23, 1976; assigned to Lilly Industries Ltd.

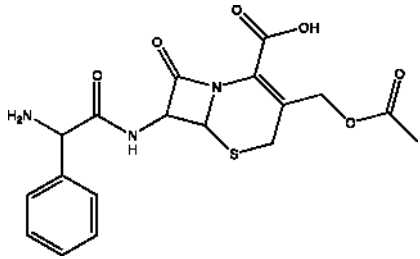
CEPHALOGLYCIN

Therapeutic Function: Antibacterial

Chemical Name: 3-[(Acetyloxy)methyl]-7-[(aminophenylacetyl)amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

Common Name: 7-(D-α-Aminophenylacetylamido)-caphalosporanic acid

Structural Formula:



Chemical Abstracts Registry No.: 3577-01-3

Trade Name	Manufacturer	Country	Year Introduced
Kefglycin	Shionogi	Japan	1969
Kafocin	Lilly	US	1970

Raw Materials

D-Phenylglycine
7-Aminocephalosporanic acid
Isobutyl chloroformate
Carbobenzoxy chloride
Hydrogen

Manufacturing Process

dl-Phenylglycine is resolved in a conventional manner by reaction with cinchonine, fractional crystallization of the resulting diastereoisomers, and acidification to release the phenylglycine enantiomorphs. D-phenylglycine, thus prepared, is reacted with carbobenzoxy chloride in a conventional manner to produce N-carbobenzoxy-D-phenylglycine.

A 0.60 g portion of N-carbobenzoxy-D-phenylglycine is dissolved in 10 ml of dry tetrahydrofuran. The solution is cooled in an ice-salt bath, and to it is added 0.29 ml of triethylamine with stirring over a period of 10 minutes, followed by 0.29 ml of isobutyl chloroformate, after which stirring is continued for 10 minutes at -5°C. During this time, 0.57 g of 7-aminocephalosporanic acid and 0.29 ml of triethylamine are dissolved in 5 ml of tetrahydrofuran and 5 ml of water, and the solution is centrifuged to remove a dark sludge. The clarified solution is cooled in ice and slowly added to the reaction mixture, and stirring is continued in the ice bath for 0.5 hour, followed by one hour at room temperature.

The reaction product mixture is a homogenous solution having a pH of about 6. It is evaporated under vacuum to a semisolid residue. To the residue are added 35 ml of water and a few drops of triethylamine to raise the pH to 8. The aqueous solution obtained thereby is extracted successively with 50 ml and 35 ml portions of ethyl acetate, the pH being adjusted to 2 at each extraction with hydrochloric acid. The extracts are combined, filtered, dried over sodium sulfate, stripped of solvent, and evaporated under vacuum. The product is 7-(N-carbobenzoxy-D-α-aminophenylacetamido)cephalosporanic acid in the form of a yellow-white amorphous solid weighing 1.10 g.

Of this material 1.0 g is dissolved in 150 ml of warm 95% ethyl alcohol. To the solution is added 1.0 g of 5% palladium on carbon catalyst, and the mixture is hydrogenated at room temperature and atmospheric pressure by bubbling hydrogen into it for 3 hours with stirring. The hydrogenation product is filtered. The solid phase, comprising the catalyst and the desired product, is suspended in ethyl acetate and water and adjusted to pH 2 with hydrochloric acid. The suspension is filtered to remove the catalyst. The aqueous phase is separated from the filtrate, and is evaporated under vacuum to recover the desired product, 7-(D-α-aminophenylacetamido)cephalosporanicacid.

References

Merck Index 1938
Kleeman and Engel p. 163
OCDS Vol. 1 p.417 (1977)
DOT 6 (5) 169 (1970)
I.N. p. 195
British Patent 1,017,624; January 19,1966; assigned to Merck and Co., Inc.
British Patent 985,747; March 10, 1965; assigned to Eli Lilly and Company
Wall, W.F., Fatherey, M. and Boothroyd, B.; US Patent 3,422,103; January 14, 1969; assigned to Glaxo Laboratories, Ltd.
Pfeiffer, R.R. and Bottorff, E.M.; US Patent 3,497,505; February 24, 1970; assigned to Eli Lilly and Co.
Jackson, B.G.; US Patent 3,671,449; June 20, 1972; assigned to Eli Lilly and Co.

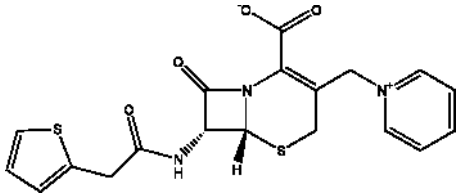
CEPHALORIDINE

Therapeutic Function: Antibacterial

Chemical Name: (6R-trans)-1-[[2-Carboxy-8-oxo-7-[(2-thienylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]pyridinium hydroxide inner salt

Common Name: Cefaloridin

Structural Formula:



Chemical Abstracts Registry No.: 50-59-9

Trade Name	Manufacturer	Country	Year Introduced
Ceporin	Glaxo	UK	1964
Ceporin	Glaxo	Switz.	1965
Cepaloridin	Glaxo	W. Germany	1965
Kefiodin	Lilly	France	1967
Loridine	Lilly	US	1968
Ceporin	Glaxo	Italy	1976
Acaporina	Martin Santos	Spain	-
Aliporina	Asla	Spain	-
Amplicerina	Miluy	Spain	-
Ampligram	Hermes	Spain	-
Basporidina	Basileos	Spain	-
Bioporina	Biologia Marina	Spain	-
Cefabena	Jebena	Spain	-
Cefabiot	Galepharma Iberica	Spain	-
Cefaclox	Sigma Tau	Italy	-
Cefalescord	Callol	Spain	-
Cefalisan	Lifepharma	Spain	-
Cefalobiotic	Wolner	Spain	-
Cefalogobens	Normon	Spain	-
Cefalomiso	Oftalmiso	Spain	-
Cefamusel	De La Cruz	Spain	-

Trade Name	Manufacturer	Country	Year Introduced
Cefaresan	Alacan	Spain	-
Ceflorin	Glaxo	-	-
Cepalorin	Glaxo	-	-
Ceporan	Glaxo	-	-
Ceporan	Torii	Japan	-
Ceproduc	Glaxo	Italy	-
CER	Glaxo	Japan	-
Cidan-Cef	Cidan	Spain	-
Cilicef	Hortel	Spain	-
Cobalcina	Pradel	Spain	-
Cusisporina	Norte De Espana	Spain	-
Diclocef	Medici	Italy	-
Dinasint	Proter	Italy	-
Eldia	Legem	Spain	-
Endosporol	Cantabria	Spain	-
Enebiotico	Llano	Spain	-
Faredina	Lefare	Italy	-
Filoklin	Lifasa	Spain	-
Floridin	Coli	Italy	-
Gencefal	Morgens	Spain	-
Glaxoridin	Glaxo	-	-
Huberlexina	Hubber	Spain	-
Intrasporin	Torlan	Spain	-
Janosina	Janovich	Spain	-
Keflodin	Shionogi	Japan	-
Kefspor	Lilly	-	-
Kelfison	Davur	Spain	-
Latorex	Durron	Italy	-
Lauridin	Crosara	Italy	-
Lexibiotico	Llano	Spain	-
Libesporina	Liberman	Spain	-
Liexina	ICN	-	-
Llenas Biotic	Llenas	Spain	-
Lloncefal	Castillon	Spain	-
Poricefal	Santos	Spain	-
Prinderin	Hosbon	Spain	-
Rogeridina	Roger	Spain	-
Rolex ins	Fedal	Spain	-
Sargefal	Sarget	France	-

Trade Name	Manufacturer	Country	Year Introduced
Sintoridyn	I.S.F.	Italy	-
Sporanicum	Incasa-Wolff	Spain	-
Talinsul	Ester	Spain	-
Tapiola	Guadalupe	Spain	-
Testadina	Bryan	Spain	-
Totalmicina	Emyfar	Spain	-
Wasser idina	Wassermann	Spain	-

Raw Materials

7-Aminocephalosporanic acid
2-Thienylacetyl chloride
Pyridine

Manufacturing Process

7-Aminocephalosporanic acid (5.00 g) which passed through a 100-mesh sieve was suspended in boiling ethyl acetate (200 ml), and 2-thienylacetyl chloride (Cagniant, Bull. Soc. Chim. France, 1949, 847) (4.42 g, 1.5 equiv.) was added in ethyl acetate (20 ml). The mixture was boiled under reflux for 40 minutes, cooled, and filtered. Aniline (5.03 ml) was added, and after 1 hour the mixture was extracted with 3% sodium hydrogen carbonate solution (1 x 150 ml, 2 x 100 ml, 1 x 50 ml) and the alkaline extracts washed with ethyl acetate (3 x 100 ml). The aqueous solution was acidified to pH 1.2, and extracted with ethyl acetate (2 x 150 ml). The ethyl acetate extract was washed with water (4 x 40 ml), dried ($MgSO_4$), and concentrated in vacuo to low volume. The crude 7-2'-thienylacetamidocephalosporanic acid (2.5 g) which separated was collected by filtration. Evaporation of the filtrate gave a further 2.68 g (71%) of the product, which was purified by crystallization from ethyl acetate, then aqueous acetone, MP 150°C to 157°C (decomp.).

7-2'-Thienylacetamidocephalosporanic acid (7.0 g) was suspended in water (60 ml) and stirred with pyridine (7 ml) until the acid dissolved. The resulting solution (pH 5.9) was kept at 35°C for 3 days, then filtered and extracted with methylene chloride (4 x 60 ml). The methylene chloride extract was back-extracted with a little water and the total aqueous solutions were then percolated through a column of Dowex 1 x 8 resin, (100 to 200 mesh, 150 g) in the acetate form at pH 4.3. The column was washed with water until the optical rotation of the eluate fell to zero and the eluate (500 ml) was freeze-dried. The residual white solid was dissolved in the minimum volume of methanol and after a few minutes the pyridine derivative crystallized; this is the cephaloridine product.

References

Merck Index 1940
Kleeman and Engel p. 164
OCDS Vol. 1 p. 417 (1977)
DOT 1 (3) 88 (1965)
I.N. p. 195

Arkley, V., Eardley, S. and Long, A.G.; British Patent 1,030,630; May 25, 1966; assigned to Glaxo Laboratories, Ltd.
Higgins, H.M. Jr.; US Patent 3,270,012; August 30, 1966; assigned to Eli Lilly and Co.

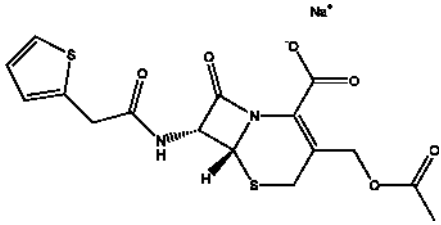
CEPHALOTHIN SODIUM

Therapeutic Function: Antibacterial

Chemical Name: 6R-trans-3-[(Acetyloxy)methyl]-8-oxo-7-[(2-thienylacetyl) amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-carboxylic acid sodium salt

Common Name: 7-(2-Thienyiacetamido)cephalosporanic acid

Structural Formula:



Chemical Abstracts Registry No.: 58-71-9; 153-61-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Keflin	Lilly	US	1964
Cepovenin	Hoechst/Glaxo	W. Germany	1965
Keflin	Lilly	France	1965
Keflin	Serum Impfinst.	Switz.	1965
Kefiin	Shionogi	Japan	1966
Keflin	Lilly	Italy	1967
Keflin	Lilly	UK	1969
Seffin	Glaxo	US	1983
Averon	Alfar	Spain	-
Averon-I	Alfa Farm.	Italy	-
Cephalotin	Lilly	W. Germany	-
Cephation	Meiji	Japan	-
Ceporacin	Glaxo	W. Germany	-
Cepovenin	Hoechst	-	-
CET	Glaxo	Japan	-
Coaxin	Tobishi	Japan	-
Loccalline	Showa	Japan	-

Trade Name	Manufacturer	Country	Year Introduced
Lospoven	Hoechst	Japan	-
Restin	Ono	Japan	-
Sodium Cephalotin	Green Cross	Japan	-
Sucira N	Mohan	Japan	-
Synclotin	Toyo Jozo	Japan	-
Toricelosin	Torii	Japan	-

Raw Materials

2-Thienylacetic acid
Sodium hydroxide
Thionyl chloride
7-Aminocephalosporanic acid

Manufacturing Process

7-(2'-Thienylacetamido)cephalosporanic acid sodium salt may be produced from 2-thienylacetyl chloride, obtainable by treatment of 2-thienylacetic acid [Ernst, Berichte, 19 (1886) 3281] with thionyl chloride in a conventional manner. The 2-thienylacetyl chloride is then reacted with 7-aminocephalosporanic acid and then converted to the sodium salt using sodium hydroxide.

References

Merck Index 1943
Kleeman and Engel p. 165
PDR pp. 911, 1056
OCDS Vol. 1 pp. 417, 420 (1977)
DOT 2 (2) 44 (1966)
I.N. p. 196
REM p. 1187
British Patent 982,252; February 3, 1965; assigned to Eli Lilly and Company

CEPHAPIRIN SODIUM

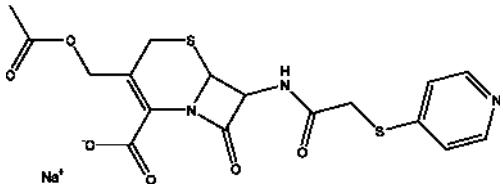
Therapeutic Function: Antibacterial

Chemical Name: 3-[(Acetyloxy)methyl]-8-oxo-7-([(4-pyridinylthio)acetyl] amino)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monosodium salt

Common Name: Sodium 7-(pyrid-4-ylthioacetamido)cephalosporanate

Chemical Abstracts Registry No.: 24356-60-3; 21593-23-7 (Acid)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Cefadyl	Bristol	US	1974
Bristocef	Bristol	W. Germany	1974
Cephaloject	Bristol	France	1974
Cefatrexyl	Essex	Switz.	1974
Brisporin	Bristol	Italy	1976
Cefatrexyl	Bristol	Japan	1977
Brisfirina	Bristol-Myers	-	-
Cefa-Lak	Bristol	-	-
Cefatrex	Bristol-Myers	-	-
Cefatrexil	Mead Johnson	-	-
Cefatrexyl	Galenika	Yugoslavia	-
Piricef	C.T.	Italy	-
Today	Bristol-Myers	-	-

Raw Materials

Aminocephalosporanic acid
Sodium-2-ethylhexanoate
2-Mercaptopyrimidine
Sodium bicarbonate
Bromoacetyl bromide

Manufacturing Process

One route is that described in US Patent 3,422,100 as follows, starting with aminocephalosporanic acid (ACA): 27.2 g (0.1 mol) of 7-ACA, 33.2 g (0.3 mol) of $NaHCO_3$, 200 ml of water and 100 ml of acetone were mixed together, cooled to 0°C and stirred rapidly while 20.1 g (0.1 mol) of bromoacetyl bromide dissolved in 100 ml of acetone was added in one fast addition. The temperature was kept at 0 to 5°C for ten minutes, then the ice-salt bath was removed and stirring continued for one hour as the temperature approached 25°C. The mixture was concentrated in vacuo at 20°C to one-half volume and 200 ml of water added. Two 400 ml ether extracts were made and discarded. The aqueous solution was covered with 200 ml of ethyl acetate and vigorously stirred and cooled while being acidified to pH 2 with 40% phosphoric acid.

The mixture was filtered, the ethyl acetate layer separated and washed with three 100 ml portions of water, dried over Na_2SO_4, filtered and treated with 30 ml of sodium 2-ethylhexanoate in n-butanol (34 ml = 0.1 mol). The oil which settled out was scratched to induce crystallization. After stirring for 20

minutes the product, sodium 7-(α-bromoacetamido)cephalosporanate, was scraped from the sides of the flask and collected. The filter cake was washed with several portions of acetone, air dried, and dried in vacuo over P_2O_5.The yield was 22.5 g and decomposed at 193°C.

A solution of 1.13 g (0.01 mol) of 2-mercaptopyrimidine and 1.06 g (0.01 mol) of sodium carbonate dissolved in 25 ml of water was added dropwise over a period of an hour at room temperature, to a stirred solution of 4.15 g (0.01 mol) of sodium 7-(α-bromoacetamido)cephalosporanate in 25 ml of water.

Stirring was continued an additional 90 minutes and then 50 ml of ethyl acetate was added, Forty percent H_3PO_4 was added dropwise with vigorous stirring until pH 2.5 to 3 was obtained. The product crystallized immediately and was filtered off, washed several times with water and then three times with 25 ml portions of ethyl acetate, following which it was air dried. The yield was 2.9 g of crystals that decomposed at 167 to 168°C. The IR and NMR spectra were consistent with the desired product, 7-[α-(2-pyrimidinylthio) acetamido]-cephalosporanic acid monohydrate.

An alternate route is that described in US Patent 3,503,967 which uses ACA in the last step.

Another alternative route is that described in US Patent 3,578,661 uses bromomethylcephalosporin as one raw material.

However the acid is prepared, the sodium salt may be prepared as described in US Patent 3,503,967: Five liters of methylene chloride were added to a clean dry vessel equipped with stirrer. 7-[α(4-pyridylthio)acetamido] cephalosporanic acid (1,000 g) was added to the vessel, followed by 350 ml of triethylamine. The resultant solution was treated with decolorizing charcoal for 15 minutes and filtered. A solution of sodium-3-ethyl-hexanoate (27.3%) in butanol-methylene chloride was added to the filtrate with stirring. Seven thousand five hundred milliliters of acetone was added. Crystallization occurred while stirring was continued several hours under dry conditions. The crystals were collected by filtration, washed with large volumes of acetone, and then dried in vacuo at 50°C to yield about 950 g of the title compound.

References

Merck Index 1945
Kleeman and Engel p. 167
PDR p. 695
OCDS Vol. 2 p. 441 (1980)
DOT9 (2) 56 (1973) and 10 (11) 299 (1974)
I.N. p. 197
REM p. 1187
Crast, L.B. Jr.; US Patent 3,422,100; January 14, 1969; assigned to Bristol-Myers Company
Silvestri, H.H. and Johnson, D.A.; US Patent 3,503,967; March 31, 1970; assigned to Bristol-Myers Company
Havranek, R.E. and Crast, L.B. Jr.; US Patent 3,578,661; May 11, 1971; assigned to Bristol-Myers Company

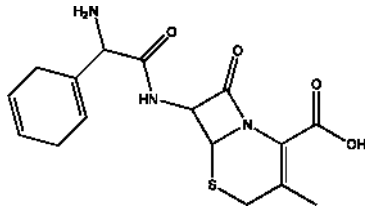
CEPHRADINE

Therapeutic Function: Antibiotic

Chemical Name: 7-[D-2-Amino-2-(1,4-cyclohexadien-1-yl)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 38821-53-3

Trade Name	Manufacturer	Country	Year Introduced
Sefril	Squibb	Switz.	-
Eskacef	SKF	UK	1972
Velosef	Squibb	UK	1972
Sefril	Von Heyden	W. Germany	1973
Velocef	Squibb	Italy	1973
Velosef	Squibb	US	1974
Anspor	SKF	US	1974
Velosef	Squibb	France	1975
Eskacef	SKF	France	1975
Dicefalin	Nippon Squibb	Japan	1978
Cefro	Sankyo	Japan	1980
Lisacef	Lisapharma	Italy	1980
Askacef	SKF	-	-
Cefamid	Gibipharma	Italy	-
Cefosan	San Carlo	Italy	-
Cefradex	Ausonia	Italy	-
Cefrag	Magis	Italy	-
Cefro	Sankyo	Japan	-
Cefrum	San Carlo	Italy	-
Celex	Aristochimica	Italy	-
Cesporan	Errekappa	Italy	-
Citicel	C.T.	Italy	-
Dimacef	Dima	Italy	-
Ecosporina	Ecobi	Italy	-

Trade Name	Manufacturer	Country	Year Introduced
Eskacef	SKF	Italy	-
Eskacef	SK Dauelsberg	W. Germany	-
Forticef	Godecke	W. Germany	-
Lisacef	Lisapharma	Italy	-
Medicef	Medici	Italy	-
Megacef	Beytout	France	-
Noblitina	Juste	Spain	-
Protocef	Ripari-Gero	Italy	-
Samedrin	Savoma	Italy	-

Raw Materials

D-Phenylglycine
Methyl acetoacetate
Lithium
3-Deacetoxy-7-aminocephalosporanic acid
Ammonia

Manufacturing Process

In a first step, D-2-amino-2-(1,4-cyclohexadienyl)acetic acid is obtained as follows. A solution of 11.0 g (72.7 mmol) of D-phenylglycine in 900 ml distilled ammonia (which has been treated with 45 mg lithium after distillation to destroy traces of moisture) is slowly diluted with 370 ml dry ten-butyl alcohol.

Over a period of hours, 1.65 g lithium (3.27 eq) is added in small portions until a permanent blue color is obtained. The blue reaction mixture is then treated with 38 g of triethylamine hydrochloride. The ammonia is allowed to evaporate at room temperature overnight and the residual solvent is evaporated at reduced pressure. The white residue is taken up in a small amount of methanol-water and added to 4 liters of cold 1:1 chloroform-acetone to precipitate the crude product. After 20 minutes stirring the suspension is filtered and the white filter cake dried in vacuo; the filter cake is then pulverized and submitted once more to the precipitation process from 1:1 chloroform-acetone.

The white, crystalline product, 11.8 g, MP 297°C (dec), $[\alpha]_D$ -89.7 (2 N NaOH) is quantitatively obtained but is slightly contaminated with lithium chloride, 0.6% ionic chlorine being found by analysis.

The product of a second step is the methyl acetoacetic ester enamine of N-2-amino-2-(1,4-cyclohexadienyl)acetic acid sodium salt. 306 mg D-2-amino-2-(1,4-cyclohexadienyl)acetic acid (2.00 mmol) are dissolved by warming in a solution of 108 mg of $NaOCH_3$ (2.00 mmol) in 4.3 ml reagent grade MeOH. 255 mg (0.24 ml, 2.20 mmol) methyl acetoacetate are added and the mixture refluxed for 45 minutes. The MeOH is almost totally stripped off in vacuo. Five milliliters benzene are added and distilled off to a small residual volume. The addition and distillation of benzene is repeated to insure complete removal of the MeOH and water. The product crystallizes out overnight from a small residual volume of benzene. It is filtered off, washed with benzene, and dried

in vacuo. Yield 463 mg.

Then 3-deacetoxy-7-aminocephalosporanic acid is condensed with the above described sodium salt in the presence of triethylamine to give cephradine.

References

Merck Index 1947
Kleeman and Engel p. 175
PDR pp. 1703, 1771
OCDS Vol. 2 p. 440 (1980)
DOT 9 (3) 89 (1973)
I.N. p. 199
REM p. 1188
Weisenborn, F.L., Dolfini, J.E., Bach, G.G. and Bernstein, J.; US Patent 3,485,819; December 23, 1969; assigned to E.R. Squibb and Sons, Inc.

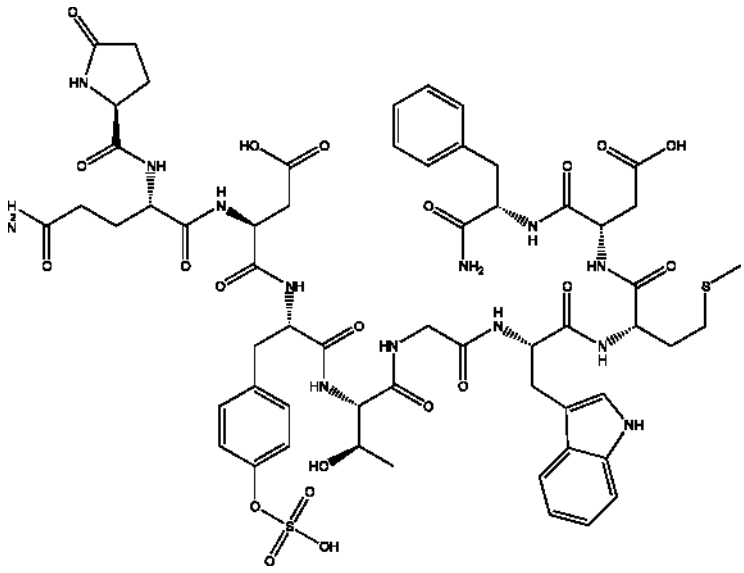
CERULETIDE

Therapeutic Function: Stimulant (gastric secretory)

Chemical Name: Decapeptide of empirical formula $C_{58}H_{73}N_{13}O_{21}S_2$

Common Name: Cerulein; Caerulein

Structural Formula:



Chemical Abstracts Registry No.: 17650-98-5

Trade Name	Manufacturer	Country	Year Introduced
Ceosunin	Kyowa Hakko	Japan	1976
Takas	Carlo Erba	W. Germany	1978
Takus	Essex	Switz.	1981
Tymtran	Adria	US	1982
Cerulex	Farmitalia	France	1983

Raw Materials

L-Pyroglutamyl-L-glutaminyl-L-aspartyl-L-tyrosine azide
L-Threonyl-glycyl-L-tryptophanyl-L-methionyl-L-aspartyl-L-phenylalaninamide
Pyridine sulfuric anhydride
Sodium carbonate

Manufacturing Process

The tetrapeptide, L-pyroglutamyl-L-glutaminyl-L-aspartyl-L-tyrosine-azide (I), is condensed with the hexapeptide, L-threonyl-glycyl-L-tryptophanyl-L-methionyl-L-aspartyl-L-phenylalaninamide (II), having the hydroxyl of the threonyl radical blocked by an acyl radical in a suitable solvent, such as dimethylformamide, to obtain the decapeptide, L-pyroglutamyl-L-glutaminyl-L-aspartyl-L-tyrosyl-L-threonylglycyl-L-tryptophanyl-L-methionyl-L-aspartyl-Lphenylaninamide (III) having the hydroxy group of the threonyl radical blocked by an acyl radical. The decapeptide (III) is treated, at low temperature, with the complex anhydrous pyridine sulfuric anhydride finally to obtain the decapeptide, L-pyroglutamyl-L-glutaminyl-L-aspartyl-L-tyrosyl-L-threonyl-glycyl-L-tryptophanyl-L-methionyl-L-aspartyl-L-phenylalaninamide (IV) having the phenolic group of the tyrosyl radical protected by a sulfate radical and the hydroxyl of the threonyl radical protected by an acyl radical.

Finally, by mild alkaline hydrolysis of the decapeptide (IV) one obtains the decapeptide product.

References

Merck Index 1963
DFU 1 (8) 359 (1976)
Kleeman and Engel p. 178
DOT 15 (11) 13 (1979)
I.N. p. 203
REM p. 1274
Bernardi, L., Bosisio, G., De Castiglione, R. and Goffredo, O.; US Patent 3,472,832; Oct. 14, 1969; assigned to Societa Farmaceutici Italia (Italy)

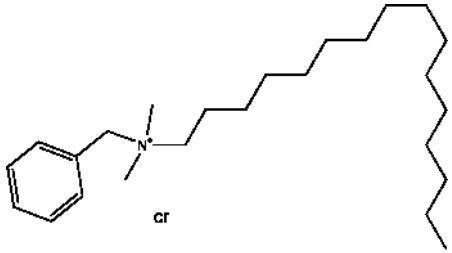
CETALKONIUM CHLORIDE

Therapeutic Function: Antiseptic

Chemical Name: Ammonium, benzyldimethylhexadecyl-, chloride

Common Name: Cetalkonium chloride; Cetol

Structural Formula:



Chemical Abstracts Registry No.: 122-18-9; 10328-34-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Cetalkonium Chloride	Chemische Fabrik Berg	-	-
Baktonium	BODE CHEMIE GMBH and CO.	-	-
Ceetolan	Lannett Company, Inc.	-	-

Raw Materials

Hexadecylamine
Benzyl chloride
Methyl chloride

Manufacturing Process

185 parts of hexadecylamine and 126.5 parts of benzylchloride was stirred at 100°C for 8 hours. After cooling to the crystalline product was added methyl chloride. N-Hexadecyl-N,N-dimethylbenzenemethanaminium chloride was obtained.

References

Merck Index, Monograph number: 2059, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Fr. Patent No. 771,746; Oct. 15, 1934; Assigned to I.G. Farbenindustrie Aktiengesellschaft

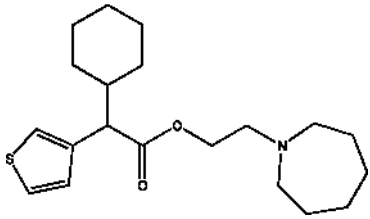
CETIEDIL

Therapeutic Function: Vasodilator

Chemical Name: α-Cyclohexyl-3-thiopheneacetic acid 2-(hexahydro-1H-azepin-1-yl)ethyl ester

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 14176-10-4; 16286-69-4 (Citrate)

Trade Name	Manufacturer	Country	Year Introduced
Stratene	Innothera	France	1973
Stratene	Sigma Tau	Italy	1976
Fusten	Galenika	Greece	-
Huberdilat	Hubber	Spain	-
Vasocet	Winthrop	-	-

Raw Materials

Sodium
(3-Thienyl)acetonitrile
1-(2-Chloroethyl)-hexahydro-1H-azepine
Cyclohexyl bromide

Manufacturing Process

In a 100 ml flask fitted with a mechanical stirrer, a vertical condensor protected by a calcium chloride stopper, a dropping-funnel and a source of nitrogen were introduced 30 ml of hexamethylenephosphotriamide and 2.3 g (0.1 mol) of finely cut sodium wire. A mixture of 12.3 g (0.1 mol) of (3-thienyl)-acetonitrile and 16.3 g (0.1 mol) of cyclohexyl bromide was then quickly added at a temperature of 20 C. The reaction mixture was then maintained under nitrogen atmosphere and stirred for 12 hours at room temperature. The excess of sodium was destroyed by adding 5 ml of ethanol and the organic solution was slowly poured into 100 ml of a 1 N iced solution of hydrochloric acid. The solution was extracted twice with 100 ml ether. The ethereal phases were collected, washed with water, dried and concentrated under reduced pressure. The crude product was then purified by

chromatography on a silica column (150 g of silica) using a 1/1 benzene/cyclohexane mixture as elution agent. The product obtained was rectified by distillation.

In this manner, 3.4 g of alpha(3-thienyl)-alpha-cyclohexylacetonitrile were obtained, which represents a yield of 16%.

The nitrile may then be hydrolyzed to cyclohexyl-(3-thienyl)acetic acid which is reacted with 1-(2-chloroethyl)-hexahydro-1H-azepine to give cetiedil. It is commonly used as the citrate.

References

Merck Index 1976
Kleeman and Engel p. 179
OCDS Vol. 3 p. 42 (1984)
DOT 10 (4) 126 (1974)
I.N.p. 204
Pigerol, C., De Cointet De Fillain, P., Grain, C. and Le Blat, J.; US Patent 4,108,865; August 22, 1978; assigned to Labaz (France)

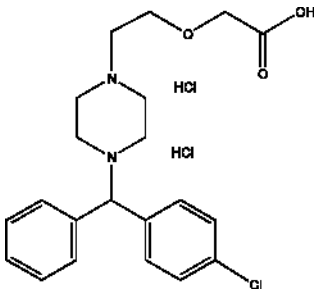
CETIRIZINE DIHYDROCHLORIDE

Therapeutic Function: Antihistaminic; Antiallergic

Chemical Name: Acetic acid, (2-(4-((4-chlorophenyl)phenylmethyl)-1-piperazinyl)ethoxy)-, dihydrochloride

Common Name: Cetirizine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 83881-52-1

Trade Name	Manufacturer	Country	Year Introduced
Cesil	Silva Pharmaceticals Ltd.	India	-
Citizen	Zenith Pharmaceuticals Ltd.	India	-

Trade Name	Manufacturer	Country	Year Introduced
Cetizin	Acme Laboratories Ltd.	India	-
Cetra	Cosmo Pharma Laboratories Ltd.	India	-
Nosemin	Ibn Sina Pharmaceuticals	India	-
Rinitrin	Sigma Laboratories Ltd.	-	-
Riz	Orion Laboratories Ltd.	India	-
Zyrtec	UCB	Belgium	-
Zyrtec	Pfizer	-	-
Zyrtec	Sun Pharma	-	-

Raw Materials

2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]-ethanol
tert-BuOK
Sodium chloracetate

Manufacturing Process

Preparation of 2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]-ethoxy]acetic acid (cetirizine).

To a mixture of 50 g 2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]-ethanol and 225 ml of tert-butanol at 45°C under a nitrogen was added 21 g tert-BuOK. The temperature was raised to 75-80°C and the mixture was kept at this temperature. After 45 min was added 11 g sodium chloracetate; after 1.5 hour was added 5.2 g tert-BuOK; after 2 hours was added 5.64 g sodium chloracetate; after 2.5 hours was added 1.9 g tert-BuOK; after 3 hours was added 1.9 g sodium chloracetate; after 3.5 hours was added 0.8 g tert-BuOK; and after 4 hours was added 1.13 g sodium chloracetate. Then about 150 ml tert-butanol was distilled of, 190 ml of water was added and the distillation of tert-butanol was continued until the temperature of the vapour reaches 100°C. To the reaction mixture was added 60 ml of water and 8 ml concentrated hydrochloric acid to pH 8. Unreacted 2-[4-[(4-chlorophenyl) phenylmethyl]-1-piperazinyl]-ethanol was extracted with diethyl ether. The aqueous phase was acidified to pH 5 by addition of hydrochloric acid and extracted with dichloromethane (200 ml x 3). The extract was dried over $MgSO_4$, filtered and concentrated in a rotary evaporator. An obtained oil was allowed to crystallize by addition of 150 ml of 2-butanone, yields of 2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]-ethoxy]acetic acid 55.5%, M.P. 146-148°C.

32.7 g 2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]-ethoxy]acetic acid was suspended in a mixture of 125 ml of water and 13.8 ml 37% aqueous hydrochloric acid. The mixture was concentrated in a rotary evaporator. An obtained oil was allowed to crystallize by addition of 245 ml of 2-butanone, yields of 2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]-ethoxy]acetic acid dihydrochloride 88%, M.P. 228.22°C.

References

Taj Yong, Kariman Rhoshayar, Tam Tim Fat; US Patent No. 6,046,332; April 4, 2000;
Bodson G. et al.; Canadian Patent 1,320,732

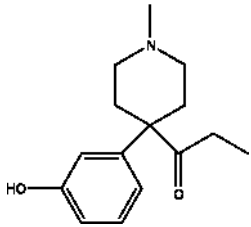
CETOBEMIDONE

Therapeutic Function: Narcotic analgesic

Chemical Name: 1-[4-(3-Hydroxyphenyl)-1-methyl-piperidin-4-yl]-propan-1-one

Common Name: Cetobemidone; Chetobemidone; Ketobemidone

Structural Formula:



Chemical Abstracts Registry No.: 469-79-4

Trade Name	Manufacturer	Country	Year Introduced
Ketobemidone	Shanghai Lancheng Corporation	-	-
Cliradon	Ciba	-	-
Ketogan	Lundbeck	-	-
Ketogin	Lundbeck	-	-
Ketodur	Pfizer	-	-
Ketogan novum	Pharmacia	-	-
Ketorax	Pharmacia	-	-
Ketorax	Pfizer	-	-

Raw Materials

Sodium amide
3-Methoxybenzyl cyanide
Magnesium
Ethyl bromide
N,N-Bis(2-chloroethyl)-N-methylamine

Manufacturing Process

The process includes the following steps:

1. 80 weight parts (w.p.) powder of sodium amide was added to 147 w.p. 3-methoxy-benzylcyanide, 156 w.p. N,N-bis(2-chloroethyl)-N-methylamine and 350 w.p. toluene in 6-8 portions by stirring at 40°-45°C. The mixture was slowly heated to 100°-105°C with stirring for 1 hour at this temperature. Some water was added after cooling, the toluene layer was treated with diluted HCl and it therefrom was adjusted to a alkaline pH by addition of sodium hydroxide, extracted with ether and the ether layer dried over Na_2CO_3. The solvent was removed; the distillation of the residue gave 4-cyan-4-(3-metoxyphenyl)-1-methylpiperidine as a colorless oil; BP 150°C at 2 mm/Hg, hardened by standing; MP 44°C. The yield was 65-68%.

2. The solution of ethyl magnesium bromide from 36 w.p. magnesium and 165 w.p. ethyl bromide in 700 w.p. ether was added to 230 w.p. above cyanide in 330 w.p toluene. The mixture was refluxed for 1 hour. Then the ether was slowly distilled and the residue was stood for 1 hour at water bath temperature. After cooling with an ice the mixture was acidified by addition of HCl to adjust the congo acid pH. 4-(3-Methoxyphenyl-1-methyl-4-propipnylpiperidine was prepared by a saturation of above solution with NH_3 and it therefrom was dried over K_2CO_3 and distilled to give a colorless product BP 184°-185°C at 6 mm/Hg.

3. The mixture 261 w.p 4-(3-methoxyphenyl)-1-methyl-4-propipnylpiperidine and 750 w.p. HBr (BP 126°C) was refluxed for 1 hour. Then 2/3 of acid was distilled on an oil bath and the hot water was added to the rest. The title product was precipitated by NH_3 as the oil that became hard and after recrystallisation from ethylacetate had MP 156°-157°C.

References

Eisleb O.E.; D.R. Patent No. 752,755; 10 Nov. 1952; Assigned to I.G. Farbenindustrie A.G., Frankfurt/Main

CETYL ALCOHOL

Therapeutic Function: Pharmaceutic aid

Chemical Name: n-Hexadecanol

Common Name: 1-Hexadecanol; Ethal; Ethol; Palmityl alcohol

Structural Formula:

Chemical Abstracts Registry No.: 36653-82-4

Trade Name	Manufacturer	Country	Year Introduced
Hexadecyl alcohol	Esso Res. And Eng. Co.	-	-
Ego Skin Cream	Ego	-	-

Raw Materials

Sodium bicarbonate
Hydrochloric acid
Palmitoyl chloride
Hexadecyl bromide
Calcium oxide
Sodium borohydride

Manufacturing Process

1). A slurry of sodium bicarbonate comprising 39.8 g sodium bicarbonate and 254 ml water was placed in an autoclave. 96.3 g hexadecyl bromide and 635 ml acetone were then added. The autoclave was sealed and while stirring (590 r.p.m.) it was heated to a temperature of 218°C over a period of 1 hour 15 min. The temperature was maintained at 218-220°C for an additional hour. At the end of the reaction the autoclave was cooled to about 50°C, that is, to a temperature at which the alcohol remains molten. The autoclave was then rinsed with acetone and 1 N hydrochloric acid add to neutralize the sodium bicarbonate. The reaction mixture was diluted with an equivalent volume of water and then extracted with n-pentane. (Other suitable water insoluble solvents such as benzene, carbon tetrachloride, chloroform, petroleum ether and the like can be used for extraction). The pentane extract was washed with water and then dried over magnesium sulfate. The dried solution was filtered and evaporated. The residue was melted and a vacuum applied to remove the last traces of pentane. On distillation a yield of 94.8% of the theoretical yield white crystals of hexadecanol was recovered; M.P. 49°C, B.P. 344°C, n_D^{79} = 1.4283.

2). 5.80 g of hexadecyl bromide, 36 ml of 60% aqueous dioxane and 0.73 g of calcium oxide were placed in an ampoule. The ampoule was then heated, while shaking, to a temperature of 220°C over a period of 0.5 hours, and maintained at this temperature for 1 hour. After the reaction the ampoule was cooled and the products worked up as in method 1. Analysis for alcohol content by Zerewitinoff active hydrogen determination showed the yield to be 92.5%; M.P. 49°C, B.P. 344°C, n_D^{79} = 1.4283.

3). A solution of palmitoyl chloride in dioxane was added dropwise to a cooled dispersion of sodium borohydride.The mixture was heated on the steam bath for a short time and then, after cooling, water was added. On distillation a yield of hexadecanol 87%, M.P. 49°C, B.P. 344°C.

References

Levine I. E., Uppinger E. C.; US Patent No. 3,018,308; Jan.23, 1962; Assigned to California Research Corporation, San Francisco, Calif., a corporation of Delaware
Caikin, Brown; J. Am. Chem. Soc.; 1949, 71, 122

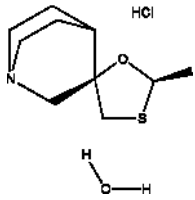
CEVIMELINE HYDROCHLORIDE

Therapeutic Function: Salivation stimulant

Chemical Name: Spiro(1-azabicyclo(2.2.2)octane-3,5'-(1,3)oxathiolane), 2'-methyl-, hydrochloride, hemihydrate, cis-

Common Name: Cevimeline hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 153504-70-2

Trade Name	Manufacturer	Country	Year Introduced
Evoxac	SnowBrand Pharmaceuticals	-	-
Evoxac	Daiichi	-	-

Raw Materials

3-Hydroxy-3-mercaptomethylquinuclidine
Acetaldehyde
Sodium sulfate
Hydrogen chloride
Stannic chloride
Sodium hydroxide

Manufacturing Process

(1) Into a 500 ml four-necked flask equipped with a stirrer, a thermometer and a calcium chloride tube, 10.6 g of 3-hydroxy-3-mercaptomethylquinuclidine (purity: 98.3%), 222.8 g of chloroform, 31.7 g of toluene and 2.2 g of dimethylsulfoxide were charged, and 17.3 g of acetaldehyde was added thereto at 10-15°C. While maintaining the temperature at the same level, 12.2 g of anhydrous sodium sulfate was added thereto. Then, 9.8 g of hydrogen chloride gas was blown thereinto over a period of two hours, and then the mixture was maintained at room temperature for 6 hours with stirring.

To the reaction mixture, 125.7 g of a 15% sodium hydroxide aqueous solution was dropwise added to make the reaction mixture strongly alkaline. Then, undissolved inorganic salts were separated by filtration, and the inorganic

salts were washed with 18.9 g of chloroform. The filtrate was subjected to liquid separation, and the aqueous layer was re-extracted with chloroform. These chloroform layers were put together, and 100.5 g of 5% sulfuric acid was added thereto to obtain desired 2-methylspiro(1,3-oxathiolane-5,3')quinuclidine sulfate. Then, it was again made alkaline with 54.6 g of a 10% sodium hydroxide aqueous solution to free the desired 2-methylspiro(1,3-oxathiolane-5,3')quinuclidine, which was then extracted four times with 33 g of n-hexane. The n-hexane layer was dried over anhydrous sodium sulfate, and then, sodium sulfate was filtered off to obtain a n-hexane solution of 2-methylspiro(1,3-oxathiolane-5,3')quinuclidine. To this n-hexane solution, 18.0 g of an iso-propyl alcohol solution containing 20% of hydrochloric acid was dropwise added to obtain 2-methylspiro(1,3-oxathiolane-5,3')quinuclidine hydrochloride. After stirring for 3 hours, precipitated white crystals were collected by filtration to obtain 10.1 g of a mixture of hydrochlorides of trans- and cis-2-methylspiro(1,3-oxathiolane-5,3')quinuclidine (purity: 95.8%, yield of pure product 68.5%).

(2) Into a 500 ml four-necked flask equipped with a stirrer and a thermometer, 4.9 g (0.02 mol) of the mixture of hydrochlorides of trans- and cis-2-methylspiro(1,3-oxathiolane-5,3')quinuclidine obtained in the above step (1) (the weight ratio of cis-and trans-isomers was 50.5/49.5) and 34 ml of chloroform (this chloroform contained 0.5 wt % of ethyl alcohol) were charged, and 17 ml of a chloroform solution containing 0.2 g of hydrogen chloride (this chloroform also contained 0.5 wt % of ethyl alcohol) was added thereto with stirring. Then, 7.8 g of stannic chloride was dropwise added thereto over a period of 30 min, and an isomerization reaction was carried out with stirring at room temperature for 24 hours. To the reaction product, 50 ml of water was added, and a 48% sodium hydroxide aqueous solution was added thereto with stirring to make the reaction mixture strongly alkaline. Then, the chloroform layer was separated. To the aqueous solution, 10 ml of chloroform was added for re-extraction. These chloroform layers were put together, and 24.0 g of 5% sulfuric acid was added thereto to convert 2-methylspiro(1,3-oxathiolane-5,3')quinuclidine in the reaction mixture to a sulfate, which was then dissolved in water. To this aqueous layer, a 10% sodium hydroxide aqueous solution was again added to make it strongly alkaline and to free 2-methylspiro(1,3-oxathiolane-5,3')quinuclidine in the reaction mixture. Then, it was extracted four times with 15 ml of n-hexane. The extracted n-hexane layer was dried over anhydrous sodium sulfate. Then, an iso-propyl alcohol solution containing 20% of hydrochloric acid was dropwise added thereto to convert 2-methylspiro(1,3-oxathiolane-5,3')quinuclidine in the reaction mixture to a hydrochloride, and precipitated white crystals were collected by filtration and dried to obtain 4.4 g of a mixture containing hydrochlorides of cis- and trans-2-methylspiro(1,3-oxathiolane-5,3')quinuclidine (yield hydrochlorides: 92.1%). The ratio of cis- and trans-2-methylspiro(1,3-oxathiolane-5,3')quinuclidine was 98.6/1.4 (was analyzed by liquid chromatography).

References

Hayashi K. et al.; US Patent No. 5571918; Nov. 5, 1996; Assigned to Ishihara Sangyo Kaisha Ltd. (Osaka, JP)

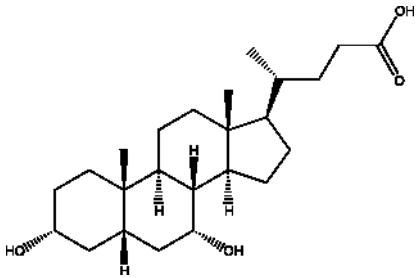
CHENODIOL

Therapeutic Function: Gallostone dissolving agent

Chemical Name: 3,7-Dihydroxycholan-24-oic acid

Common Name: Chenodeoxycholic acid; Chenic acid

Structural Formula:



Chemical Abstracts Registry No.: 474-25-9

Trade Name	Manufacturer	Country	Year Introduced
Chenofalk	Fa1k	W. Germany	1974
Chenofalk	Pharmacolor	Switz.	1974
Chenossil	Giuliani	Italy	1975
Chenodex	I.S.H.	France	1977
Chendol	Weddell	UK	1978
Regalen	Eisai	Japan	1982
Chenocol	Yamanouchi	Japan	1982
Chenix	Reid-Rowell	US	1983
Aholit	Vetprom	Yugoslavia	-
Bilo	Iltas	Turkey	-
Calcolise	Prodes	Spain	-
Carbilcolina	Ralay	Spain	-
Chelobil	Oftalmiso	Spain	-
Chemicolina	Ern	Spain	-
Chenar	Armour-Montagu	-	-
Chendal	Tika	Sweden	-
Chendix	Weddell	UK	-
Chendol	Weddell	UK	-
Chenoacid	Falk	W. Germany	-
Chenodecil	Aldon	Spain	-
Chenodex	Houde	France	-
Chenomas	Guadalupe	Spain	-
Chenotar	Armour	-	-
Cholonorm	Gruenenthal	W. Germany	-

Trade Name	Manufacturer	Country	Year Introduced
Cholasa	Tokyo Tanabe	Japan	-
Cholestex	Ikapharm	Israel	-
Duanox	Roche	-	-
Fluibil	Zambon	Italy	-
Gamiquenol	Gamir	Spain	-
Hekbilin	Hek	W. Germany	-
Henohol	Galenika	Yugoslavia	-
Kebilis	Hoechst-Roussel	-	-
Kenolite	Leurquin	France	-
Quenobilan	Estedi	Spain	-
Soluston	Rafa	Israel	-
Ulmenid	Roche	-	-

Raw Materials

7-Acetyl-12-ketochenodeoxycholic acid
Hydrazine hydrate
Potassium hydroxide

Manufacturing Process

To 1,400 ml of an approximately 50% water/triglycol solution of the potassium salt of chenodeoxycholic acid, obtained by the Wolff-Kishner reduction (using hydrazine hydrate and potassium hydroxide) from 50 g of 7-acetyl-12-ketochenodeoxycholic acid, 220 ml of dilute hydrochloric acid is added to bring the pH to 2. The solution is stirred and the crude chenodeoxycholic acid precipitates. The precipitate is recovered and dried to constant weight at about 60°C. About 36 g of the crude chenodeoxycholic acid, melting in the range of 126°-129°C, is obtained.

25 g of crude chenodeoxycholic acid so obtained is dissolved in 750 ml of acetonitrile while stirring and heating. 3 g of activated charcoal is added and then removed by suction filtering. The resulting liquid filtrate is cooled, the pure chenodeoxycholic acid crystallizing out. The crystals are recovered by suction filtering and the recovered crystals dried under vacuum. The yield is 19 g of pure chenodeoxycholic acid with a melting range of 168°-171°C.

References

Merck Index 2007
Kleeman and Engel p. 181
PDR p. 1446
DOT 8 (7) 273 (1972) and 12 (2) 52 (1976)
I.N. p. 17
REM p. 812
Maeke, S. and Rambacher, P.; US Patent 4,163,017; July 31, 1979; assigned to Diamalt A.G. (Germany)

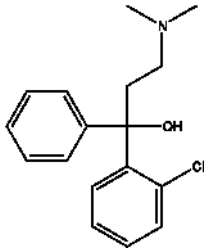
CHLOPHEDIANOL

Therapeutic Function: Antitussive

Chemical Name: 2-Chloro-α-[2-(dimethylamino)ethyl]-α-phenylbenzenemethanol

Common Name: Clofedanol

Structural Formula:



Chemical Abstracts Registry No.: 791-35-5

Trade Name	Manufacturer	Country	Year Introduced
Detigon	Bayer	W. Germany	1958
Detigon	Bayer	Italy	1959
Ulo	Riker	US	1960
Tussiplegyl	Bayer	France	1969
Colorin	Nippon Shinyaku	Japan	1981
Abehol	Pliva	Yugoslavia	-
Anayok	Chibi	Italy	-
Baltix	Kobanyai	Hungary	-
Demax	Orma	Italy	-
Dencyl	Bencard	UK	-
Eletuss	Serpero	Italy	-
Eutus	Eupharma	Italy	-
Farmatox	Cifa	Italy	-
Fugatox	Ifisa	Italy	-
Gen-Tos	Morgens	Spain	-
Gutabex	Russi	Italy	-
Pectolitan	Kettelhack Riker	W. Germany	-
Prontosed	Francia	Italy	-
Refugal	Bayer	-	-
Tigonal	I.B.P.	Italy	-
Tuxidin	Gazzini	Italy	-
Tuxinil	Bieffe	Italy	-
Ulone	Riker	-	-

Raw Materials

o-Chlorobenzophenone
Acetonitrile
Sodium amide
Hydrogen
Methyl sulfate

Manufacturing Process

This compound may be produced by reacting o-chlorobenzophenone with acetonitrile in the presence of sodium amide or another strongly basic condensing agent, to form the nitrile of beta-phenyl-beta-o-chlorophenyl-hydracrylic acid, which is then hydrogenated to yield 1-phenyl-1-o-chlorophenyl-3-aminopropanol-1. The latter intermediate compound is subsequently dimethylated with an agent such as methyl sulfate to provide the desired end product 1-o-chlorophenyl-1-phenyl-3-dimethylaminopropanol.

References

Merck Index 2018
Kleeman and Engel p. 226
I.N. p. 244
REM p. 871
Lorenz, R., Gosswald, R. and Henecka, H.; US Patent 3,031,377; April 24, 1962; assigned to Farbenfabriken Bayer AG, Germany

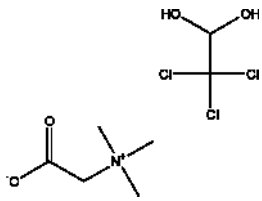
CHLORAL BETAINE

Therapeutic Function: Sedative

Chemical Name: Adduct of chloral hydrate with betaine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 2218-68-0

Trade Name	Manufacturer	Country	Year Introduced
Beta-Chlor	Mead Johnson	US	1963

Raw Materials

Betaine hydrate
Chloral hydrate

Manufacturing Process

An intimate mixture of betaine hydrate (67.5 g) and chloral hydrate (100 g) was warmed to ca. 60°C when an exothermic reaction occurred and the mixture became pasty. It was then stirred at 60°C for 30 minutes. The residue solidified on cooling and was crystallized from a small amount of water. The product separated in hard, colorless prisms of MP 122.5 to 124.5°C (corr).

References

Merck Index 2026
Kieeman and Engel p. 184
Petrow, V., Thomas, A.J. and Stephenson, O.; US Patent 3,028,420; April 3, 1962; assigned to The British Drug Houses Limited, England

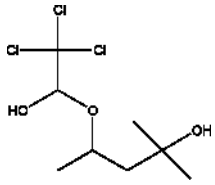
CHLORALODOL

Therapeutic Function: Hypnotic

Chemical Name: 2-Methyl-4-(2,2,2-trichloro-1-hydroxyethoxy)-2-pentanol

Common Name: Chloralodol; Chlorhexadol

Structural Formula:



Chemical Abstracts Registry No.: 3563-58-4

Trade Name	Manufacturer	Country	Year Introduced
Chloralodol	Shanghai Lancheng Corporation	-	-
Lora (formerly)	Wallace Labs	-	-
Medodorm	Medo	-	-

Raw Materials

2-Methyl-2,4-pentanediol
Chloral hydrate

Manufacturing Process

472 g of 2-methyl-2,4-pentanediol (4 moles) are heated to 70°-80°C in a bowl, and 660 g of chloral hydrate (4 moles) are added under stirring until all of chloral hydrate is dissolved. The temperature, which decreases during the addition, then increased to 60° to 70°C. When reaction mixture has become a nearly dry crystal powder, the powder is subjected to further drying by slight heating. Yield of raw product is about 1060 g. Recrystallization is carried out from tetrachloromethane, and the yield is 980 g (about 92 %).

References

Christensen J.E.T.; US Patent No. 2,931,838; Apr. 5, 1960; Assigned to Det Danske Medicinal and Keminkalle-Kompagni A-S, Copenhagen, Denmark

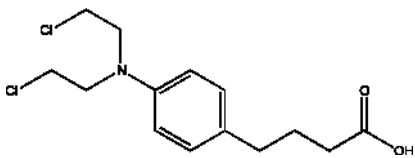
CHLORAMBUCIL

Therapeutic Function: Antineoplastic

Chemical Name: 4-[Bis(2-chloroethyl)amino]benzenebutanoic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 305-03-3

Trade Name	Manufacturer	Country	Year Introduced
Leukeran	Burroughs-Wellcome	US	1957
Leukeran	Wellcome	W. Germany	-
Leukeran	Wellcome	Switz.	-
Amboclorin	Simes	Italy	-
Chloraminophene	Techni-Pharma	France	-
Linfolysin	I.S.M.	Italy	-

Raw Materials

Acetanilide
Maleic acid
Phosphorus oxychloride
Hydrogen
Ethylene oxide

Manufacturing Process

Acetanilide and maleic acid are condensed to give beta-(p-acetaminobenzoyl) acrilic acid which is hydrogenated to give methyl-gamma-(p-aminophenyl) butyrate. That is reacted with ethylene oxide and then with phosphorus oxychloride to give the methyl ester which is finally hydrolyzed to give chlorambucil.

References

Merck Index 2031
Kleeman and Engel p. 184
PDR p. 752
DOT 16 (5) 70 (1980)
I.N. p. 208
REM p. 1145
Phillips, A.P. and Mentha, J.W.; US Patent 3,046,301; July 24, 1962; assigned to Burroughs Wellcome and Co. (USA.) Inc.

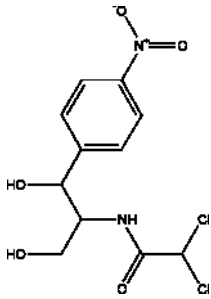
CHLORAMPHENICOL

Therapeutic Function: Antimicrobial

Chemical Name: D(-)-threo-2,2-Dichloro-N-[β-hydroxy-α-(hydroxymethyl)-p-nitrophenethyl]acetamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 56-75-7

Trade Name	Manufacturer	Country	Year Introduced
Leukomycin	Bayer	W. Germany	-
Chloromycetin	Warner Lambert	Switz.	-
Chloromycetin	Parke Davis	US	1949
Chloramphenicol	MSD-Chibret	France	1954
Econochlor Sol	Alcon	US	1975
Amboken	Gedeon Richter	Mexico	-
Amphicol	McKesson	US	-
Antacin	Sumitomo	Japan	-
Aquamycin	Winzer	W. Germany	-
Bemacol	Int'l. Multifoods	US	-
Berlicetin	Ankerwerk	E. Germany	-
Biocetin	Tasman Vaccine	UK	-
Biophenicol	Biochemie	Austria	-
Cafenolo	Benvegna	Italy	-
Catilan	Hoechst	W. Germany	-
Cebenicol	Chauvin-Blache	France	-
Chemicetina	Erba	Italy	-
Chemyzin	S.I.T.	Italy	-
Chlomin	Knoll	W. Germany	-
Chloramex	Dumex	Denmark	-
Chloramol	Protea	Australia	-
Chloramphenicol-POS	Ursapharm	W. Germany	-
Chlorasol	Evsco	US	-
Chlora-Tabs	Evsco	US	-
Chloricol	Evsco	US	-
Chlornitromycin	Farmakhim	Bulgaria	-
Chlorocid	EGYT	Hungary	-
Chloromycetin	Sankyo	Japan	-
Chloronitrin	Jenapharm	E. Germany	-
Chloroptic	Allergan	US	-
Chlorsig	Sigma	Australia	-
Chloramidina	Arco	Switz.	-
Clorbiotina	Wassermann	Spain	-
Clorofenicina	Antibioticos	Spain	-
Clorosintex	Angelini	Italy	-
Cylphenicol	Trent	US	-
Desphen	Despopharm	Switz.	-
Detreomine	Polfa	Poland	-
Devamycetin	Deva	Turkey	-

Trade Name	Manufacturer	Country	Year Introduced
Dextromycin	V.N.I.Kh.F.J.	USSR	-
Doctamicina	Docta	Switz.	-
Farmicetina	Erba	Italy	-
Globenicol	Gist Brocades	-	-
Glorous	Sanwa	Japan	-
Halomycetin	Kwizda	Austria	-
Hortfenicol	Hortel	Spain	-
Ismicetina	I.S.M.	Italy	-
Isophenicol	Bouchara	France	-
Kamaver	Engelhard	W. Germany	-
Kemicetin	Aesca	Austria	-
Kernicetine	Fujisawa	Japan	-
Kernicetine	Erba	Italy	-
Kemicetine	Vifor	Switz.	-
Kemicetine	I.C.N.	Canada	-
Kemicotine	Erba	UK	-
Kloromisin	Biofarma	Turkey	-
Labamicol	Labatec	Switz.	-
Levomycetin	Provita	Austria	-
Lomecitina	Locatelli	Italy	-
Loromisin	Atabay	Turkey	-
Medichol	Copanos	US	-
Micochlorine	Continental Pharma	Belgium	-
Misetin	Dif-Dogu	Turkey	-
Mycetin	Farmigea	Italy	-
Mychel	Rachelle	US	-
Mycinol	Horner	Canada	-
Neocetin	Uranium	Turkey	-
Novochlorcap	Novopharm	Canada	-
Novaphenicol	Nova	Canada	-
Novophenicol	Solac	France	-
Oftakloram	Tan	Turkey	-
Oftalent	Weifa	Norway	-
Oleomycetin	Winzer	W. Germany	-
Ophtaphenicol	Faure	France	-
Oralmisetin	Mulda	Turkey	-
Otachron	Alpine	Austria	-
Otomycin	Pliva	Yugoslavia	-
Pantovernil	Heyden	W. Germany	-

Trade Name	Manufacturer	Country	Year Introduced
Paraxin	Boehringer Mannheim	W. Germany	-
Paraxin	Yamanouchi	Japan	-
Pedimycetin	T.E.M.S.	Turkey	-
Pentamycetin	Pentagone	Canada	-
Pentocetine	Ibsa	Switz.	-
Rivomycin	Rivopharm	Switz.	-
Romphenil	Zeria	Japan	-
Septicol	Streuli	Switz.	-
Serviclofen	Servipharm	Switz.	-
Sificetina	Sifi	Italy	-
Sno-Paenicol	Smith and Nephew	UK	-
Sopamycetin	Pharbec	Canada	-
Spersanicol	Dispersa	Switz.	-
Suismycetin	Lagap	Switz.	-
Synthomycetin	Abic	Israel	-
Tevocin	Tevcon	US	-
Thilocanfol	Thilo	W. Germany	-
Tifomycine	Roussel	France	-
Veticol	Copanos	US	-
Viceton	Int'l. Multifoods	US	-
Viklorin	Ilsan	Turkey	-
Vitaklorinlltas	Iltas	Turkey	-

Raw Materials

Sodium
Methyl dichloroacetate
Benzaldehyde
Hydrogen
beta-Nitroethanol
Acetic anhydride
Nitric acid

Manufacturing Process

Chloramphenicol may be prepared by fermentation or by chemical synthesis. The fermentation route to chloramphenicol is described in US Patents 2,483,871 and 2,483,892. To quote from US Patent 2,483,892: The cultivation of Streptomyces venezuelae may be carried out in a number of different ways. For example, the microorganism may be cultivated under aerobic conditions on the surface of the medium, or it may be cultivated beneath the surface of the medium, i.e., in the submerged condition, if oxygen is simultaneously supplied.

Briefly stated, the production of chloramphenicol by the surface culture method involves inoculating a shallow layer, usually less than about 2 cm, of a sterile, aqueous nutrient medium with Streptomyces venezuelae and incubating the mixture under aerobic conditions at a temperature between about 20° and 40°C, preferably at room temperature (about 25°C), for a period of about 10 to 15 days. The mycelium is then removed from the liquid and the culture liquid is then treated by methods described for isolating there

from the desired chloramphenicol.

The synthetic route to chloramphenicol is described in US Patent 2,483,884 as follows: 1.1 g of sodium is dissolved in 20 cc of methanol and the resulting solution added to a solution of 5 g of benzaldehyde and 4.5 g of beta-nitroethanol in 20 cc of methanol. After standing at room temperature for a short time the gel which forms on the mixing of the reactants changes to a white insoluble powder. The precipitate is collected, washed with methanol and ether and then dried. The product thus produced is the sodium salt of 1-phenyl-2-nitropropane-1,3-diol.

Eighteen grams of the sodium salt of 1-phenyl-2-nitropropane-1,3-diolis dissolved in 200 cc of glacial acetic acid. 0.75 g of palladium oxide hydrogenation catalyst is added and the mixture shaken at room temperature under three atmospheres pressure of hydrogen overnight. The reaction vessel is opened, 2.5 g of 10% palladium on carbon hydrogenation catalyst added and the mixture shaken under three atmospheres pressure of hydrogen for 3 hours. The catalyst is removed from the reaction mixture by filtration and the filtrate concentrated under reduced pressure. Fifty cubic centimeters of n-propanol is added to the residue and the insoluble inorganic salt removed by filtration.

The filtrate is treated with excess hydrochloric acid and evaporated to obtain a pale yellow oil. Five grams of the oil thus obtained is treated with 15 cc of saturated potassium carbonate solution and the mixture extracted with 50 cc of ether, then with 30 cc of ethyl acetate and finally with two 30 cc portions of ethanol. Evaporation of the solvent from the extract gives the following quantities of the desired 1-phenyl-2-aminopropane-1,3-diol: 0.5 g, 1.0 g and 3.1 g.

1.7 g of 1-phenyl-2-aminopropane-1,3-diol is treated with 1.6 g of methyl dichloroacetate and the mixture heated at 100°C for 1.25 hours. The residue is washed with two 20 cc portions of petroleum ether and the insoluble product collected. Recrystallization from ethyl acetate yields the desired (dl)-reg.-1-phenyl-2-dichloroacetamidopropane-1,3-diol in pure form; MP 154° to 156°C.

Five hundred milligrams of (dl)-reg.-1-phenyl-2-dichloroacetamidopropane-1,3-diolis added to a solution consisting of 1 cc of pyridine and 1 cc of acetic anhydride and the resulting reaction mixture heated at 100°C for 1/2 hour. The reaction mixture is evaporated to dryness under reduced pressure and the residue taken up in and crystallized from methanol. Recrystallization from methanol produces the pure diacetate of (dl)-reg.-1-phenyl-2-dichloro-acetamidopropane-1,3-diol (MP 94°C).

Two hundred milligrams of the diacetate of (dl)-reg.-1-phenyl-2-dichloroacetamidopropane1,3-diol is added to a mixture consisting of 0.25 cc of concentrated nitric acid and 0.25 cc of concentrated sulfuric acid at 0°C. The reaction mixture is stirred until solution is complete, poured onto 25 g of ice and the mixture extracted with ethyl acetate. The ethyl acetate extracts are evaporated under reduced pressure and the diacetate of (dl)-reg.-1-pnitrophenyl-2-dichloroacetamidopropane-1,3-diol so produced purified by recristallization from ethanol; MP 134°C.

Five hundred milligrams of the diacetate of (dl)-reg.-1-p-nitrophenyl-2-dichloroacetamidopropane-1,3-diol is dissolved in a mixture consisting of 25 cc of acetone and an equal volume of 0.2 N sodium hydroxide solution at 0°C and the mixture allowed to stand for one hour. The reaction mixture is neutralized with hydrochloric acid and evaporated under reduced pressure to dryness. The residue is extracted with several portions of hot ethylene dichloride, the extracts concentrated and then cooled to obtain the crystalline (dl)-reg.-1- p-nitrophenyl-2-dichloroacetamidopropane-1,3-diol; MP 171°C.

References

Merck Index 2035
Kleeman and Engel p. 185
PDR PP. 1321, 1379, 1606, 1999
OCDS Vol. 1 p. 75 (1977) and 2 pp. 28, 45 (1980)
I.N. p. 209
REM p. 1208
Bartz, Q.R.; US Patent 2,483,871; October 4, 1949; assigned to Parke, Davis and Company
Crooks, H.M., Jr., Rebstock, M.C., Controulis, J. and Bartz, Q.R.; US Patent 2,483,884; October 4, 1949; assigned to Parke, Davis and Company
Ehrlich, J., Smith, R.M. and Penner, M.A.; US Patent 2,483,892; October 4, 1949; assigned to Parke, Davis and Company
Carrara, G.; US Patent 2,776,312; January 1, 1957
Slack, R.; US Patent 2,786,870; March 26, 1957; assigned to Parke, Davis and Company

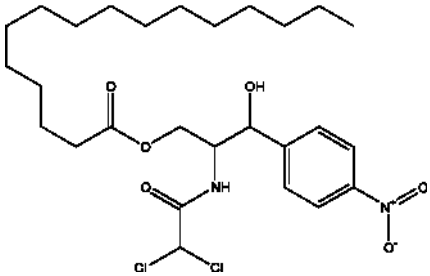
CHLORAMPHENICOL PALMITATE

Therapeutic Function: Antibacterial; Antirickettsial

Chemical Name: D(-)-threo-1-p-Nitrophenyl-2-dichloroacetamido-3-palmitoyloxypropane-1-ol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 530-43-8

Trade Name	Manufacturer	Country	Year Introduced
Chloromycetin	Parke Davis	US	1951
B-CP	Biokema	Switz.	-
Berlicetin	Ankerwerk	E. Germany	-
Chlorambon	Biokema	Switz.	-
Chloromisol	Maipe	Spain	-
Colimycin	Biofarma	Turkey	-
Detreopal	Polfa	Poland	-
Hortfenicol	Hortel	Spain	-
Levomicetina	Lepetit	Italy	-
Paidomicetina	Lafare	Italy	-
Protophenicol	Arco	Switz.	-
Sintomicetina	Lepetit	-	-

Raw Materials

Palmitoyl chloride
Chloramphenicol

Manufacturing Process

1,674 g of palmitoyl chloride is added to 1,870 g of D(-)-threo-1-p-nitrophenyl-2-dichloroacetamidopropane-1,3-diol (chloramphenicol) in 2,700 cc of pyridine and the solution stirred for 1 hour. The mixture is poured into 16 liters of water and the solid collected. Recrystallization of the crude product from benzene yields the desired D(+)-threo-1-p-nitrophenyl-1dichloroacetamido-3-palmitoyloxypropane-1-ol in pure form: MP 90°C.

References

Merck Index 2036
PDR p. 1324
I.N. p. 210
REM p. 1209
Edgerton, W.H.; US Patent 2,662,906; December 15, 1953; assigned to Parke, Davis and Co.

CHLORAZANIL HYDROCHLORIDE

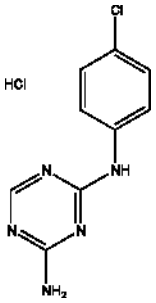
Therapeutic Function: Diuretic

Chemical Name: 1,3,5-Triazine-2,4-diamine, N-(4-chlorophenyl)-, hydrochloride

Common Name: Chloramanozinum; Chlorazanil hydrochloride

Chemical Abstracts Registry No.: 2019-25-2; 500-42-5 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Chlorazanil hydrochloride	Shanghai Lancheng Corporation	-	-
Diuretico	Sol	-	-
Orpidan	Heumann	-	-

Raw Materials

(4-Chlorophenyl)biguanidine hydrochloride
Formic acid

Manufacturing Process

31.2 g (4-chlorophenyl)biguanidine hydrochloride and 35 ml of concentrated formic acid were refluxed for 4 hours. The hot solution was cooled and mixed with 200 ml of diluted hydrochloric acid. The falling crystals were filtered off. The yield of chlorazanil was 24 g (74%). MP 258°C.

In practice it is usually used as hydrochloride.

References

Bauereis R.; D.B.Patent No. 1,008,303; 31 August 1955; Assigned to Heumann and Co Chem. pharm. Fabrik, Nürnberg

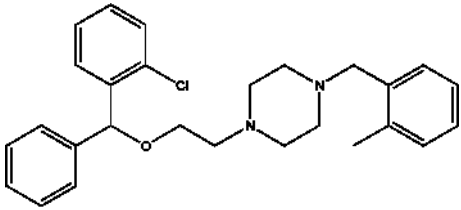
CHLORBENZOXAMINE

Therapeutic Function: Anticholinergic, Antiulcer

Chemical Name: 1-[2-[(2-Chlorophenyl)phenylmethoxy]ethyl]-4-[(2-methylphenyl)methyl]piperazine

Common Name: Chlorbenzoxamine; Chlorbenzoxyethamine

Structural Formula:



Chemical Abstracts Registry No.: 522-18-9

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

Raw Materials

1-m-Methylbenzyl-4-(2-hydroxyethyl)-piperazine
o-Chlorobenzhydrile chloride

Manufacturing Process

A mixture of 0.1 mol of 1-m-methylbenzyl-4-(2-hydroxyethyl)-piperazine and 0.1 mol of o-chlorobenzhydrile chloride was heated at 160°C for 3 hours. After cooling the product obtained was dissolved in benzene. The solution was washed with 20% aqueous solution of sodium carbonate and then with water. Chlorbenzoxamine was distilled in vacuo, B.P. 240°C/0.1 mm Hg. Yield 50%.

References

Merck Index, Monograph number: 2125, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Morren H.; Belg. Patent No. 549,420; July 10, 1956

CHLORCYCLIZINE

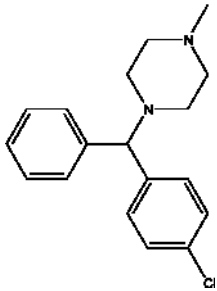
Therapeutic Function: Antihistaminic

Chemical Name: 1-[(4-Chlorophenyl)phenylmethyl]-4-methylpiperazine

Common Name: Histachlorazine

Chemical Abstracts Registry No.: 82-93-9; 1620-21-9 (Hydrochloride salt)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Perazil	Burroughs-Wellcome	US	1949
Di-Paralene	Abbott	US	1950
Histantin	Burroughs-Wellcome	-	-
Histofax	Burroughs-Wellcome	UK	-
Mantadil	Burroughs-Wellcome	US	-
Prurisedine	Couvreur	Belgium	-
Trihistan	Revit	Switz.	-
Trihistan	Gea	Denmark	-
Trihistan	Weifa	Norway	-

Raw Materials

4-Chlorobenzhydryl chloride
Methyl piperazine

Manufacturing Process

0.08 mol (19 9) of 4-chlorobenzhydryl chloride and 0.16 mol (16 g) of methylpiperazine were mixed in about 20 cc of dry benzene. The flask containing the reaction mixture was covered by a watch glass and set in a steam bath, and heating was continued for 6 hours. The contents of the flask were partitioned between ether and water and the ethereal layer was washed with water until the washings were neutral. The ethereal layer was extracted successively with 30 and 10 cc portions of 3 N hydrochloric acid. On evaporation of the ether layer there remained a residue of 2.5 9. The aqueous extracts were united and basified with concentrated alkali. The oily base was taken into ether and dried over potassium carbonate. On evaporation of the ether, N-methyl-N'-(4-chlorobenzhydryl) piperazine was recovered in the form of a viscous oil in 75% yield. The N-methyl-N'-(4-chlorobenzhydryl) piperazine was dissolved in absolute alcohol and ethanolic hydrogen chloride added in excess. The dihydrochloride crystallized on addition of absolute ether and was recrystallized from the same solvent mixture in the form of longish prisms melting at about 216°C.

References

Merck Index 2045
Kleeman and Engel p. 188
PDR p. 754
OCDS Vol. 1 p. 58 (1977)
I.N. p. 211
REM p.1132
Baltzly, R. and Castillo, J.C.; US Patent 2,630,435; March 3, 1953; assigned to Burroughs-Wellcome and Co. (USA.) Inc.

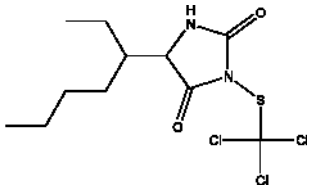
CHLORDANTOIN

Therapeutic Function: Topical antifungal

Chemical Name: 5-(1-Ethylpentyl)-3-[(trichloromethyl)thio]-2,4-imidazolidinedione

Common Name: Clodantoin

Structural Formula:



Chemical Abstracts Registry No.: 5588-20-5

Trade Name	Manufacturer	Country	Year Introduced
Sporostacin	Ortho	US	1960
Sporostacin	Ortho	UK	-
Gynelan	Eisai	Japan	-

Raw Materials

Perchloromethyl mercaptan
5-(1-Ethylpentyl)hydantoin sodium salt

Manufacturing Process

Perchloromethylmercaptan is reacted with the sodium salt of 5-(1-ethylpentyl)hydantoin.

References

Merck Index 2047
Kleeman and Enael P. 225
I.N. p. 243
Kittleson, A.R.; US Patent 2,553,770; May 22, 1951; assigned to Standard Oil Development Company
Hawley, R.S., Kittleson, A.R. and Smith, P.V. Jr.; US Patent 2,553,775; May 22, 1951; assigned to Standard Oil Development Company

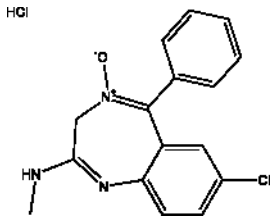
CHLORDIAZEPOXIDE HYDROCHLORIDE

Therapeutic Function: Tranquilizer

Chemical Name: 7-Chloro-N-methyl-5-phenyl-3H-1,4-benzodiazepin-2-amino-4-oxide hydrochloride

Common Name: Metaminodiazepoxide hydrochloride; Methaminodiazepoxide hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 438-41-5; 58-25-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Librium	Roche	W. Germany	1960
Librium	Roche	US	1960
Librium	Roche	Switz.	1960
Librium	Sauter	UK	1960
Librium	Roche	France	1961
Librium	Roche	Italy	1961
SK-Lygen	SKF	US	1976
Diazachel	Rachelle	US	1976
A-Poxide	Abbott	US	1977
Zetran	Hauck	US	1978
Balance	Yamanouchi	Japan	-
Bent	Pharma. Farm. Spec.	Italy	-

Trade Name	Manufacturer	Country	Year Introduced
Benzodiapin	Lisapharma	Italy	-
Binomil	Uriach	Spain	-
Cebrum	Cifa	Italy	-
Chemdipoxide	Chemo-Drug	Canada	-
Chlordiazachel	Rachelle	US	-
Contol	Takeda	Japan	-
Diapax	Therapex	Canada	-
Dolibrax	Roche	France	-
Elenium	Polfa	Poland	-
Endequil	Panther-Osfa	Italy	-
Equibral	Ravizza	Italy	-
Gene-Poxide	Franca	Canada	-
Huberplex	Hubber	Spain	-
I-Liberty	I-Pharmacal	US	-
Labican	Boniscontro-Gazzone	Italy	-
Lentotran	Farm Patria	Portugal	-
Lixin	I.S.M.	Italy	-
Medilium	Medic	Canada	-
Murcil	Reid-Provident	US	-
Napoton	Chemimportexport	Rumania	-
Normide	Inibsa	Spain	-
Novopoxide	Novopharm	Canada	-
Omnalio	Estedi	Spain	-
Peast C	Sawai	Japan	-
Protensin	Elliott-Marion	Canada	-
Psicofar	Terapeutico	Italy	-
Psicoterina	Francia	Italy	-
Radepur	Arzneimittelwerk Dresden	E. Germany	-
Reliberan	Geymonat Sud	Italy	-
Relium	Riva	Canada	-
Risolid	Dumex	Denmark	-
Sakina	Causyth	Italy	-
Sereen	Foy	US	-
Smail	Saita	Italy	-
Solium	Horner	Canada	-
Sophiamin	Santen	Japan	-
Trakipearl	Hishiyama	Japan	-
Tropium	D.D.S.A.	UK	-
Untensin	Pharmador	S. Africa	-
Via-Quil	Denver	Canada	-

Raw Materials

2-Amino-5-chlorobenzophenone
Chloroacetyl chloride
Hydrogen chloride
Hydroxylamine
Methylamine

Manufacturing Process

A mixture of 202 g 2-amino-5-chlorobenzophenone, 190 g hydroxylamine hydrochloride, 500 cc pyridine and 1,200 cc alcohol was refluxed for 16 hours, then concentrated in vacuo to dryness. The residue was treated with a mixture of ether and water. The water was separated, the ether layer containing a considerable amount of precipitated reaction product was washed with some water and diluted with petroleum ether. The crystalline reaction product, 2-amino-5-chlorobenzophenone-alpha-oxime, was filtered off. The product was recrystallized from a mixture of ether and petroleum ether forming colorless prisms, MP 164 to 167°C.

To a warm solution (50°C) of 172.5 g (0.7 mol) of 2-amino-5-chlorobenzophenone-alpha-oxime in one liter glacial acetic acid were added 110 cc (1.47 mols) chloroacetyl chloride. The mixture was heated for 10 minutes at 50°C and then stirred at room temperature for 15 hours. The precipitated yellow prisms, 2-chloromethyl-4-phenyl-6-chloroquinazoline 3-oxide hydrochloride, were filtered off, melting range 128° to 150°C with dec.

The acetic acid mother liquor, containing the rest of the reaction product, was concentrated in vacuo. The residue was dissolved in methylene chloride and washed with ice cold sodium carbonate solution. The organic solution was dried, concentrated in vacuo to a small volume and diluted with ether and petroleum ether. Fine yellow needles of 2-chloromethyl-4-phenyl-6-chloroquinazoline 3-oxide precipitated. The pure base was recrystallized from a mixture of methylene chloride, ether and petroleum ether, MP 133° to 134°C.

Ninety-eight grams of 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide hydrochloride were introduced into 600 cc of ice cold 25% methanolic methylamine. The mixture was initially cooled to about 30°C and then stirred at room temperature. After 15 hours the reaction product which precipitated was filtered off. The mother liquor was concentrated in vacuo to dryness. The residue was dissolved in methylene chloride, washed with water and dried with sodium sulfate. The methylene chloride solution was concentrated in vacuo and the crystalline residue was boiled with a small amount of acetone to dissolve the more soluble impurities. The mixture was then cooled at 5°C for 10 hours and filtered. The crystalline product, 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide, was recrystallized from ethanol forming light yellow plates, MP 236° to 236.5°C.

A solution of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide in an equivalent amount of methanolic hydrochloric acid was diluted with ether and petroleum ether.

The precipitated hydrochloride was filtered off and recrystallized from methanol, MP 213°C.

References

Merck Index 2049
Kleeman and Engel p. 188
PDR pp. 993, 1510, 1606, 1723, 1999
OCDS Vol. 1 p. 365 (1977) and 2 p. 401 (1980)
DOT 9 (6) 236 (1973)
REM p. 1061
Sternbach, L.H.; US Patent 2,893,992; July 7, 1959; assigned to Hoffmann-La Roche, Inc.

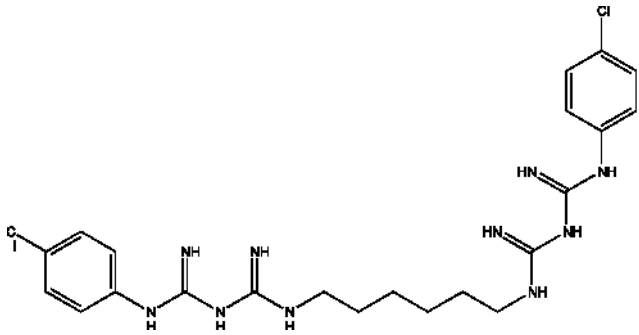
CHLORHEXIDINE

Therapeutic Function: Antimicrobial

Chemical Name: N,N''-Bis(4-chlorophenyl)-3,12-diimino-2,4,11,13-tetraazatetradecanediimidamide

Common Name: 1,6-di(4'-Chlorophenyldiguanido)hexane

Structural Formula:



Chemical Abstracts Registry No.: 55-56-1

Trade Name	Manufacturer	Country	Year Introduced
Hibiclens	Stuart	US	1976
Hibitane	I.C.I.	France	1976
Corsodyl	I.C.I.	UK	1977
Souplens	Chauvin-Blache	France	1978
Hibitane	Stuart	US	1979
Hibistat	ICI	US	1980
Abacil	Polfa	Poland	-
Aseptigel	Medicornea	France	-

Trade Name	Manufacturer	Country	Year Introduced
Bactigras	Smith and Nephew	UK	-
Biotensid	Arcana	Austria	-
Cetal	Orapharm	Australia	-
Chlorhexamed	Blendax	W. Germany	-
Chlorohex	Geistlich	Switz.	-
Dacrine	Chibret	France	-
Dentosmin	VEB Leipziger Arz.	E. Germany	-
Desmanol	Schulke and Mayr	W. Germany	-
Desocort	Chauvin-Blache	France	-
Dialens	Chauvin-Blache	France	-
Eludril	Inava	France	-
Hexadol	Green Cross	Japan	-
Hibiscrub	ICI Pharma	France	-
Hibiscrub	ICI	Japan	-
Hibitane	Sumitomo	Japan	-
Larylin	Beiersdorf	W. Germany	-
Lisium	Brunton Chemists	UK	-
Manusan	Polfa	Poland	-
Maskin	Maruishi	Japan	-
Nolvasan	Fort Dodge Labs	US	-
Oronine	Otsuka	Japan	-
Pabron	Taisho	Japan	-
Plac Out	Bernabo	Argentina	-
Plak-Out	Hawe-Neos	Switz.	-
Plurexid	Sythemedica	France	-
Rhino-Blache	Chauvin-Blache	France	-
Rotersept	Roter	Netherlands	-
Scarlene	Chauvin-Blache	France	-
Secalan	Zyma	Switz.	-
Septalone	Abic	Israel	-
Sterilone	Roter	Netherlands	-
Trachitol	Engelhard	W. Germany	-
Vitacontact	Faure	France	-

Raw Materials

Hexamethylene bis-dicyandiamide
p-Chloroaniline hydrochloride

Manufacturing Process

25 parts of hexamethylene bis-dicyandiamide, 35 parts of p-chloroaniline hydrochloride and 250 parts of beta-ethoxyethanol are stirred together at

130°C to 140°C for 2 hours under reflux. The mixture is then cooled and filtered and the solid is washed with water and crystallized from 50% aqueous acetic acid. 1,6-di(N_1,N_1'-p-chlorophenyldiguanido-N_5,N_5')hexane dihydrochloride is obtained as colorless plates of MP 258°C to 260°C.

The following is an alternative route: 19.4 parts of p-chlorophenyldicyandiamide, 9.4 parts of hexamethylene diaminedihydrochloride and 100 parts of nitrobenzene are stirred together and heated at 150 C to 160°C for 6 hours. The mixture is cooled, diluted with 200 parts of benzene and filtered. The solid residue is washed with benzene and crystallized from 50% acetic acid. 1,6-di(N_1,N_1'-p-chlorophenyldiguanido-N_5,N_5')hexane dihydrochloride is obtained.

References

Merck Index 2057
Kleeman and Engel p. 189
PDR p. 1781
I.N. p. 212
REM p. 1159
Rose, F.L. and Swain, G.; US Patent 2,684,924; July 27, 1954; assigned to Imperial Chemical Industries, Ltd.

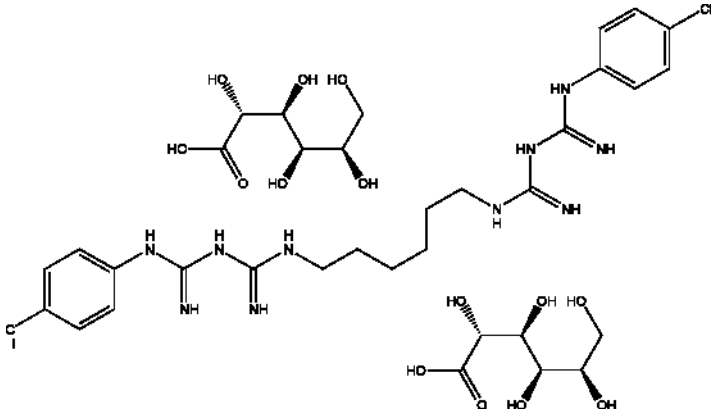
CHLORHEXIDINE DIGLUCONATE

Therapeutic Function: Antiseptic

Chemical Name: D-Gluconic acid, compd. with N,N''-bis(4-chlorophenyl)-3,12-diimino-2,4,11,13-tetraazatetradecane diimidamide (2:1)

Common Name: Chlorhexidine gluconate; Clorexidina gluconato

Structural Formula:



Chemical Abstracts Registry No.: 18472-51-0

Trade Name	Manufacturer	Country	Year Introduced
Abacil	Polfa-Lodz SA	Poland	-
Aseptinol S	PFC SNC	France	-
Betasept	The Purdue Frederick Company	-	-
Chlorhexidine gluconate	Xttrium Laboratories	USA	-
Corsodyl	GlaxoSmithKline Consumer Healthcare	USA	-
Elugel	Pierre Fabre Medicament	France	-
Hibiclens	Medical Supply, Inc.	-	-
Hibiclens	Zeneca	-	-
Peridex	Zila Pharmaceuticals	Canada	-
Periochip	Dexcel Pharma Ltd.	-	-
Periochip	Dexcel Pharma Ltd.	-	-
Periogard Oral Rinse	Colgate Oral Care	-	-
Plivasept	Pliva	Horvatia	-
Sensisept	Diversey Lever	France	-

Raw Materials

Hexamethylene bis-dicyandiamide
p-Chloroaniline hydrochloride

Manufacturing Process

35 parts of hexamethylene bis-dicyandiamide, 35 parts of p-chloroaniline hydrochloride and 250 parts of β-etoxyethanol are stirred together at 130-140°C for 2 hours under reflux. The mixture is then cooled and filtered. The solid is washed with water and crystallised from 50% aqueous acetic acid. 1,1'-Hexamethylene bis(5-(p-chlorophenyl)biguanide) is obtained as colorless plates, melting point 258-260°C. By addition of D-gluconic acid to aqueous solution of chlorhexidine base is prepared 1,1'-hexamethylenebis(5-(p-chlorophenyl)biguanide)digluconate (1:2).

References

Leslie F. et al.; US Patent No. 2,684,924; July 27, 1954; Assigneed to Imperial Chemical Industries Limited
Werie P. et al.; US Patent No. 6,500,466; Dec.31, 2002; Assigneed to Degussa AG, Dusseldorf (DE)

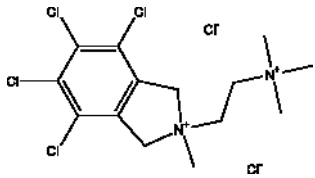
CHLORISONDAMINE CHLORIDE

Therapeutic Function: Antihypertensive

Chemical Name: 4,5,6,7-Tetrachloro-1,3-dihydro-2-methyl-2-[2-(trimethylammonio)ethyl]-2H-isoindolium dichloride

Common Name: Chlorisondamine dimethochloride

Structural Formula:



Chemical Abstracts Registry No.: 69-27-2

Trade Name	Manufacturer	Country	Year Introduced
Ecolid Chloride	Ciba	US	1956

Raw Materials

3,4,5,6-Tetrachlorophthalic anhydride
2-Dimethylaminoethyl amine
Lithium aluminum hydride
Methyl iodide
Silver chloride

Manufacturing Process

50 parts by weight of 3,4,5,6-tetrachlorophthalic anhydride is added with stirring and cooling to 30 parts by volume of 2-dimethylaminoethyl amine. The mixture is heated at 170°C for 4 minutes and the oily residue then dissolved in 200 parts by volume of hot ethanol. On cooling, N-(2'-dimethylaminoethyl)-3,4,5,6-tetrachlorophthalimide separates. It crystallizes from ethanol and melts at 184°-186°C.

6 parts by weight of N-(2'-dimethylaminoethyl)-3,4,5,6-tetrachlorophthalimide is extracted continuously with 300 parts by volume of dry ether in which have been dissolved 3.1 parts by weight of lithium aluminum hydride. After 48 hours the excess lithium aluminum hydride is destroyed by cautious addition of 9 parts by volume of ethyl acetate while stirring. There is then added in succession with stirring 3 parts by volume of water, 6 parts by volume of 15% aqueous sodium hydroxide and 9 parts by volume of water. The granular precipitate of lithium and aluminum salts are filtered and washed with ether. The ether is distilled off, yielding the crude, oily 4,5,6,7-tetrachloro-2-(2'-dimethylaminoethyl)-isoindoline. The above base is dissolved in 25 parts by volume of 90% ethanol and refluxed 2 hours with 6 parts by volume of methyl iodide. 4,5,6,7-tetrachloro-2-(2'-dimethylaminoethyl)-isoindoline dimethiodide separates during the reaction. It is collected by filtration and recrystallized

from a mixture of ethanol and water; MP 244°-246°C.

4,5,6,7-tetrachloro-2-(2'-dimethylaminoethyl)-isoindoline dimethochloride is prepared by shaking an aqueous solution of the dimethiodide with an excess of freshly prepared silver chloride and evaporating to dryness the aqueous solution after removal of the silver salts. 4,5,6,7-tetrachloro-2-(2'-dimethylaminoethyl)-isoindoline dimethochloride is recrystallized from ethanol-ethylacetate; MP 276°-280°C.

References

Merck Index 2068
I.N. p. 213
Huebner, C.F.; US Patent 3,025,294; March 13, 1962;assigned to Ciba Pharmaceutical Products, Inc.

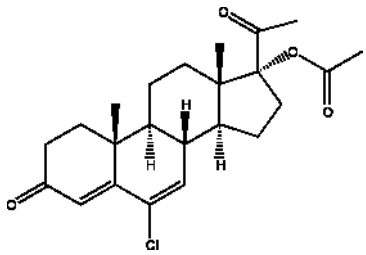
CHLORMADINONE ACETATE

Therapeutic Function: Progestin

Chemical Name: Pregna-4,6-diene-3,20-dione, 6-chloro-17-hydroxy-, acetate

Common Name: Chlormadinone acetate; Clormadinone aceteto

Structural Formula:



Chemical Abstracts Registry No.: 302-22-7

Trade Name	Manufacturer	Country	Year Introduced
Chlormadinone Acetate	Teikoku Hormone Mfg. Co., Ltd.	-	-
Chlormadinone Acetate	Taizhou Baida Pharmaceutical Co., Ltd.	-	-
Chlormadinone Acetate	Lansheng Crop. Pharm Chemical	-	-
Hypostat	Kyowa	-	-
Lutoral	Shionogi	-	-

Trade Name	Manufacturer	Country	Year Introduced
Lutoral	Syntex	-	-
Prostal	Teikoku Hormone Mfg. Co., Ltd.	-	-

Raw Materials

6-Dehydro-17α-acetoxy-progesterone
Succinimide, N-chloro-
Perchloric acid
Aluminum oxide

Manufacturing Process

10 g 6-dehydro-17α-acetoxy-progesterone was dissolved in 400 ml dioxane and 40 ml water. The solution was added to 4 g N-chlorosuccinimide and 2.4 ml 70% perchloric acid. The mixture was left at ambient temperature for 24 hours, whereupon it was poured in water, a dropping precipitate was filtered off, washed with water and dried. It was filtered through aluminum oxide and recrystallized from ether to give 6-chloro-6-dehydro-17α-acetoxy-progesterone (chlormadinone acetate). MP: 204°-206°C. $[\alpha]_D$= +54.6° (chloroform).

References

Merck Index, Monograph number: 3876, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Brueckner K. et al.; D.B. Patent No. 1,075,114; April, 29, 1958

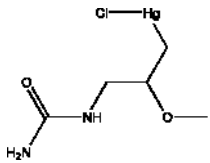
CHLORMERODRIN

Therapeutic Function: Diuretic

Chemical Name: 1-[3-(Chloromercuri)-2-methoxypropyl]urea

Common Name: Chlormeroprin

Structural Formula:



Chemical Abstracts Registry No.: 62-37-3

Trade Name	Manufacturer	Country	Year Introduced
Neohydrin	Lakeside	US	1952
Asahydrin	Pharmacia	Sweden	-
Bucohydral	Vifor	Switz.	-
Mercloran	Parke Davis	US	-
Merilid	Pharmacia	Sweden	-
Oricur	Medix	Denmark	-
Orimercur	Reder	Spain	-
Ormerdan	Parke Davis	US	-

Raw Materials

Allyl urea
Mercury acetate
Sodium chloride

Manufacturing Process

To a refluxing solution of 100 g of allyl urea and 600 ml of absolute methanol there was added with stirring a suspension of 319 g of mercuric acetate and 600 ml of absolute methanol and 60 ml of glacial acetate acid; complete solution resulted. After 6 hours of refluxing, the solution was cooled and clarified by filtration. To this solution there were added 50 g of sodium chloride and 240 ml of water. After a short time a heavy white precipitate settled out. This precipitate, which was 3-chloromercuri-2-methoxy-propylurea, was filtered, washed and dried.

References

Merck Index 2071
Kleeman 81 Engel p. 191
I.N. p.213
REM p. 489
Foreman, E.L; US Patent 2,635,983; April 21, 1953; assigned to Lakeside Laboratories, Inc.

CHLORMEZANONE

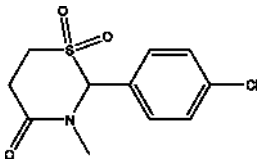
Therapeutic Function: Tranquilizer

Chemical Name: 2-(4-Chlorophenyl)tetrahydro-3-methyl-4H-1,3-thiazin-4-one-1,1-dioxide

Common Name: Chloromethazanone

Chemical Abstracts Registry No.: 80-77-3

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Trancopal	Winthrop-Breon	US	1958
Supotran	Winthrop	France	1965
Alinam	Lucien	France	-
Chlomedinon	Taiyo	Japan	-
Lumbaxol	Aldo Union	Spain	-
Metsapal	Leiras	Turkey	-
Muxotal	Farmos	Finland	-
Muskel	Winthrop	W. Germany	-
Myolespen	Dojin	Japan	-
Relizon	Mochida	Japan	-
Rexan	Labif	Italy	-
Rilaquil	Guidotti	Italy	-
Tanafol	A.M.S.A.	Italy	-
Trancote	Sawai	Japan	-
Transanate	Teikoku	Japan	-

Raw Materials

4-Chlorobenzaldehyde
β-Mercaptopropionic acid
Methylamine
Potassium permanganate

Manufacturing Process

A solution of 4-chlorobenzaldehyde is reacted with beta-mercaptopropionic acid and with methylamine. The mixture is refluxed in benzene and water is removed from an overhead separator. The reaction mixture was cooled, washed with dilute ammonium hydroxide and water, and the benzene was removed by distillation in vacuo. The oily residue was taken up in ether from which it crystallized. The precipitate was recrystallized twice from ether to yield 2-(4-chlorophenyl)-3-methyl-4-metathiazanone.

A solution of 11.2 g of potassium permanganate in 100 ml of warm water was added dropwise to a well stirred solution of 10 g of 2-(4-chlorophenyl)-3-methyl-4-metathiazanone in 50 ml of glacial acetic acid. The temperature was kept below 30°C with external cooling. An aqueous sodium bisulfite solution was then added to remove the manganese dioxide. The thick whitish oil which separated was taken up in chloroform and the extract was washed with water. Removal of the chloroform by distillation in vacuo yielded an oily residue which solidified. The solid was recrystallized from isopropyl alcohol to give 5 g

of the product, 2-(4-chlorophenyl)-3-methyl-4-metathiazanone-1,1-dioxide, MP 116.2° to 118.6°C (corr.).

References

Merck Index 2072
Kleeman and Engel p. 191
PDR p. 1934
DOT 9 (6) 243 (1973)
I.N. p. 214
REM p. 1074
British Patent 815,203; June 17, 1959; assigned to Sterling Drug, Inc.

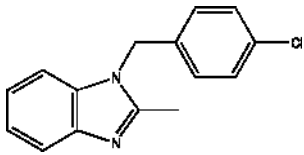
CHLORMIDAZOLE

Therapeutic Function: Antifungal

Chemical Name: 1-p-Chlorobenzyl-2-methylbenzimidazole

Common Name: Chlormidazole; Clomidazolum

Structural Formula:



Chemical Abstracts Registry No.: 3689-76-7

Trade Name	Manufacturer	Country	Year Introduced
Diamyceline	Diamant	-	-
Polfungicid zasypka	ICN	-	-
Futrican	Astra	-	-
Myco-Polycid	Zdr	-	-
Unifungicid	Unia	-	-
Polfungicid plyn	ICN	-	-

Raw Materials

2-Methylbenzimidazole
Sodium amide
p-Chlorobenzylbromide
p-Chlorobenzyl-o-phenylene diamine
Acetic acid

Manufacturing Process

The first method synthesis of 1-p-chlorobenzyl-2-methylbenzimidazole:

26.4 g of 2-methylbenzimidazole are dissolved in 350 ml of dioxane, 10 g of sodium amide are added there to. After about 5 min 41,2 g of p-chlorobenzylbromide are added to the resulting mixture which is then boiled under reflux for 6 hours. Dioxane is removed by distillation. The residue is triturated with dilute hydrochloric acid. The resulting crystalline mass representing the crude hydrochloride of 1-p-chlorobenzyl-2-methylbenzimidazole is filtered off by suction and recrystallized from water. On cooling, colorless crystals are obtained which are dissolved in hot water. Dilute ammonia solution is added to the resulting aqueous solution to render it weakly alkaline. The base of 1-p-chloro-benzyl-2-methylbenzimidazole precipitates, first in liquid form, and gradually solidifies to a white mass of its hydrate. After recyrstallization from aqueous ethanol, the product has a melting point of 67-68°C. The base of 1-p-chlorobenzyl-2-methylbenzimidazole distills in the form of a colorless oil at 240-242°C/12 mm. Its hydrate of the melting point 67-68°C is obtained by trituration with water.

The second method of synthesis of 1-p-chlorobenzyl-2-methylbenzimidazole:

23.3 g of p-chlorobenzyl-o-phenylenediamine are boiled under reflux with 75 ml of glacial acetic acid for 3 hours. Most of the acetic acid is then removed by distillation. Dilute sodium hydroxide solution is added to the residue to render it weakly alkaline. The resulting base of 1-p-chlorobenzyl-2-methylbenzunidazole is purified as such by recrystallization from aqueous ethanol. It may also be converted into its hydrochloride which is then worked up as described hereinabove in the first method of synthesis.

References

Merck Index, Monograph number: 2156, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.

Herrling S. et al.; US Patent No. 2,876,233; Mar. 3, 1959; Assigned to Chemie Gruenenthal G.m.b.H., Rhineeland, Germany, Stolberg, a corporation of Germany

CHLOROBUTANOL

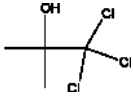
Therapeutic Function: Hypnotic, Anesthetic, Antiseptic, Pharmaceutic aid, Ophthalmologic

Chemical Name: 2-Propanol, 1,1,1-trichloro-2-methyl-

Common Name: Acetone chloroform; Alcohol trichlorisobutylicus; Chlorbutanol; Chlorbutol(un); Trichlorbutanolum

Chemical Abstracts Registry No.: 57-15-8

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Chlorobutanol	Narchem Corporation	-	-
Lacri-Lube	Allergan	-	-
Coliquifilm	Allergan	-	-
Chloretone	Parke Davis	-	-

Raw Materials

Acetone
Chloroform
Potassium hydroxide

Manufacturing Process

33 g (0.59 mol) of powdered potassium hydroxide was added in small amounts to a solution of 50 g (0.86 mol) of acetone in 100 g (0.84 mol) of chloroform to form a reaction mixture containing approximately 0.7 mol of KOH per mol of chloroform. The mixture was chilled to a temperature below 0°C, thoroughly agitated, and than allowed to stand at temperature of about 0°C for 24 hours. The mixture was then filtered and the filtrate was distilled. The fraction boiling within the range of 165-175°C was poured into an equal amount of water to precipitate the 1,1,1-trichloro-tert-butyl alcohol. The precipitated 1,1,1-trichloro-tert-butyl alcohol was filtered and recrystallized from an ethanol-water mixture and air dried. The yield of 1,1,1-trichloro-tert-butyl alcohol was 6 g, that is, somewhat less than 4% of the theoretical yield based on chloroform charged. When calculated on the basis of chloroform consumed the yield was about 15%.

References

Merck Index, Monograph number: 2180, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Harrington G.A.; US Patent No. 2,462,389; Feb. 22, 1949; Assigned to Socony-Vacuum Oil Company, Incorporated. New York, N.Y., a corporation of New York

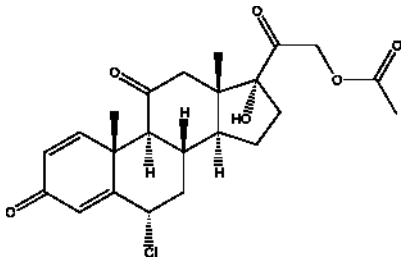
CHLOROPREDNISONE ACETATE

Therapeutic Function: Glucocorticoid

Chemical Name: 6α-Chloro-17,21-dihydroxypregna-1,4-diene-3,11,20-trione 21-acetate

Common Name: Chloroprednisone acetate; Chlorprednisoni acetas

Structural Formula:



Chemical Abstracts Registry No.: 140066-79-6

Trade Name	Manufacturer	Country	Year Introduced
Topilan	Syntex	-	-
Localyn	Recordati Industria Chimica e Farmaceutica S.p.A.	-	-

Raw Materials

6-α-Chlorocortisone
Selenium oxide
Aluminum oxide

Manufacturing Process

A suspension of 500 mg 6-α-chlorocortisone (or 6-α-chloro-17-α-hydroxy 21 acetoxy-δ^4-pregnene-3,11,20-trione) 25 ml dry tert-butanol, 150 mg selenium oxide and 0.05 ml pyridine were heated to reflux for 70 hours in a nitrogen atmosphere. On cooling the mixture was diluted with 50 ml ethyl acetate, filtered through Cilite and thoroughly washed with ethyl acetate. Ethyl acetate was distilled to a dryness, the dry residue was adsorbed on 25 g of aluminum oxide and eluated with mixture of benzene, ethyl acetate and ether. The obtained fractions were distilled to dryness and recrystallized from acetone-hexane. 105 mg of 6α-chloro-17,21-dihydroxypregna-1,4-diene-3,11,20-trione 21-acetate (or 6-α-chloro 17,21-α-hydroxy 21-acetoxy-$\delta^{1,4}$-pregnadiene-3,11,20-trione) was obtained. MP: 217°-219°C. λ_{max} 238 mμ.

References

Djerassi C. et al.; DB Patent No. 1,079,042; March 4, 1958; Mexico

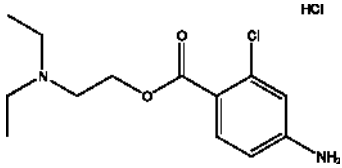
CHLOROPROCAINE HYDROCHLORIDE

Therapeutic Function: Local anesthetic

Chemical Name: 4-Amino-2-chlorobenzoic acid 2-diethylaminoethyl ester hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 3858-89-7; 133-16-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Nesacaine	Astra	US	1956
Nesacaine	Pennwalt	US	-
Nesacaine	Strasenburgh	US	-
Piocaine	Teikoku-Nagase	Japan	-

Raw Materials

2-Chloro-4-amino benzoic acid
beta-Diethyl amino ethanol
Thionyl chloride
Hydrogen chloride

Manufacturing Process

In the first step, 2-chloro-4-aminobenzoyl chloride hydrochloride is prepared by refluxing a mixture of 25 cc of purified thionyl chloride and 10 g of 2-chloro-4-aminobenzoic acid until all of the solid has gone into solution. To the cooled solution is added 150 cc of dry ethyl ether. A brisk stream of dry hydrogen chloride is passed into the solution until the precipitation of 2-chloro-4-aminobenzoylchloride hydrochloride is complete. The acyl halide is removed by filtration and dried in a vacuum desiccator.

In the second step, the diethylaminoethyl 2-chloro-4-aminobenzoate hydrochloride is prepared by refluxing equimolar proportions of the hydrochloride of beta-diethylaminoethanol in a suitable inert solvent such as a mixture of dry toluene and tetrachloroethane and the hydrochloride of 2-chloro-4-aminobenzoyl chloride until the reaction as indicated by the cessation of hydrogen chloride evolution is complete. The supernatant solvents are decanted from the reaction product which can be conveniently purified by crystallization from absolute ethanol.

An alternative purification can be effected by dissolving the reaction product in water. The ester base is liberated by rendering the clarified aqueous solution alkaline. Removal of the base from the alkaline solution is achieved by extraction with a suitable solvent such as benzene or ether. The pure hydrochloride of diethylaminoethyl 2-chloro-4-aminobenzoate is then precipitated from the dried extract by the addition of dry hydrogen chloride. After removal by filtration and recrystallization from ethanol it is found to have a melting point of 173° to 174°C.

References

Merck Index 2131
Kleeman and Engel p. 193
PDR p. 594
OCDS Vol. 1 p. 11 (1977)
I.N. p. 220
REM p. 1050
Marks, H.C. and Rubin, M.I.; US Patent 2,460,139; January 25, 1949; assigned to Wallace and Tiernan Products, Inc.

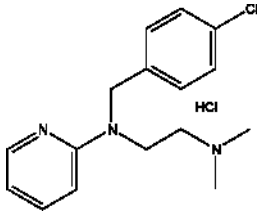
CHLOROPYRAMINE HYDROCHLORIDE

Therapeutic Function: Antihistaminic

Chemical Name: 1,2-Ethanediamine, N-((4-chlorophenyl)methyl)-N',N'-dimethyl-N-2-pyridinyl-, hydrochloride

Common Name: Chlortripelennamine hydrochloride; Halopyramine hydrochloride; Chloropyramine hydrochloride; Chlorpyraminum hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 6170-42-9; 59-32-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Chloropyramine hydrochloride	Vramed	-	-
Chloropyramine hydrochloride	Sopharma	-	-

Trade Name	Manufacturer	Country	Year Introduced
Allergosan	Sopharma	-	-
Antiapin	Pharmachim	-	-
Antiapin	Balkanpharma - Troyapharm	-	-
Avapena	Novartis Farmaceutica, S. A. de C. V.	-	-
Suprastin	Egis Pharmaceuticals Ltd.	-	-
Synopen	Pliva	-	-

Raw Materials

2-Bromopyridine
Quinoline
Sodium hydroxide
Ammonia
N,N-Dimethyl-N'-(4-chlorobenzyl) ethylenediamine
Potassium

Manufacturing Process

A solution comprising 40 parts of 2-bromopyridine, 100 parts of N,N-dimethyl-N'-(4-chlorobenzyl)ethylenediamine and 100 parts of quinoline is heated at 140-145°C for 5 hours. The oil layer after washing with 30% sodium hydroxide solution is distilled, and the fraction which distills at 142-170°C/1 mm is collected. This oil is converted to the monohydrochloride and recrystallized from a mixture of amyl alcohol and ether. The monohydrochloride salt of N,N-dimethyl-N'-(4-chlorobenzyl)-N'-(2-pyridyl) ethylenediamine is obtained which melts at 167-168.4°C.

N,N-Dimethyl-N'-(4-chlorobenzyl)-N'-(2-pyridyl)ethylenediamine may be prepared by another method:

To a mixture of 100 ml of liquid ammonia and about 80 mg of black iron oxide was added 0.78 g (0.02 atom) of potassium. When all of the potassium had reacted, 3.3 g of N,N-dimethyl-N'-(2-pyridyl)ethylenediamine was added. After the addition of 75 ml of dry toluene the ammonia was removed on the steam bath. To the cooled and stirred mixture was added 4.26 g of p-chlorobenzyl chloride, and the reaction mixture was stirred on the steam bath for 11 hours. It was then filtered and concentrated to an oil. This concentrate was taken up in ether, and the ethereal solution was washed with water, dried over sodium sulfate, and concentrated. Distillation gave 2.96 g of yellow liquid. Treatment of this distillate with an equivalent quantity of hydrogen chloride in absolute alcohol and precipitation by the addition of anhydrous ether gave 2.33 g of the N,N-dimethyl-N'-(4-chlorobenzyl)-N'-(2-pyridyl)ethylenediamine hydrochloride.

References

Merck Index, Monograph number: 2214, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Howard K.L.; US Patent No. 2,569,314; Sept. 25, 1951; Assigned to American Cyanamid Company, New York, N.Y., a corporation of Maine

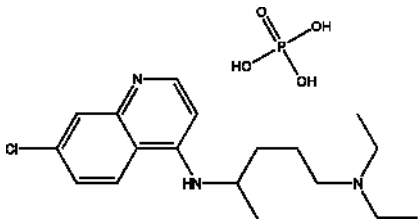
CHLOROQUINE PHOSPHATE

Therapeutic Function: Antimalarial

Chemical Name: N^4-(7-Chloro-4-quinolinyl)-N',N'-diethyl-1,4-pentanediamine phosphate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 50-63-5; 54-05-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Nivaquine	Specia	France	1949
Aralen	Winthrop	US	-
Arthrochin	Arcana	Austria	-
Artri	Badrial	France	-
Aspiquinol	Bayer	France	-
Avloclor	I.C.I.	UK	-
Chemochin	Pliva	Yugoslavia	-
Clorochina	Bayer	Italy	-
Cidanchin	Cidan	Spain	-
Delagil	EGYT	Hungary	-
Dichinalex	Savoma	Italy	-
Elestol	Bayer	France	-
Heliopar	Farmos	Finland	-
Imagon	Astra	-	-
Lagaquin	Legap	Switz.	-
Letaquine	Letap	Switz.	-
Malarex	Dumex	Denmark	-
Quinachlor	Cophar	Switz.	-
Quinercil	Robert and Carriere	France	-
Quinilon	Sumitomo	Japan	-
Resochin	Bayer	Japan	-
Rivoquine	Rivopharm	Switz.	-

Trade Name	Manufacturer	Country	Year Introduced
Serviquin	Servipharm	Switz.	-
Silbesan	Atmos	W. Germany	-
Siragon	Biochemie	Austria	-
Tresochin	Bayer	-	-

Raw Materials

4,7-Dichloroquinoline
1-Diethylamino-4-aminopentane
Phosphoric acid

Manufacturing Process

105 g of 4,7-dichloroquinoline (MP 93 to 94°C) are heated with 200 g of 1-diethylamino-4-aminopentane for 7 hours in an oil bath to 180°C while stirring, until a test portion dissolved in diluted nitric acid does not show a precipitation with sodium acetate solution. The mixture is dissolved in diluted acetic acid and made alkaline by adding sodium lye.

The base is extracted with ether, dried with potassium carbonate, the ether removed by distillation and the residue fractionated. The 4-(5'-diethylaminopentyl-2'-amino)-7-chloroquinoline (BP 212 to 214C/0.2 mm) is obtained. On cooling the compound solidifies crystalline. It melts, recrystallized from benzene, at 88°C. The base combines with phosphoric acid to yield a diphosphate salt.

References

Merck Index 2136
Kleeman and Engel p. 194
PDR p. 1902
OCDS Vol. 1 p. 341 (1977)
I.N. p. 220
REM p. 1218
Andersag, H., Breitner, S. and Jung, H.; US Patent 2,233,970; March 4, 1941; assigned to Winthrop Chemical Company, Inc.

CHLOROTHIAZIDE

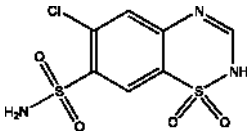
Therapeutic Function: Diuretic; Antihypertensive

Chemical Name: 6-Chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide

Common Name: -

Chemical Abstracts Registry No.: 58-94-6

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Diuril	Merck Sharp and Dohme	US	1957
Diurilix	Theraplix	France	1959
Aldoclor	MSD	US	-
Azide	Fawns and McAllan	Australia	-
Chlorosal	Teva	Israel	-
Chloroserpine	Schein	US	-
Chlotride	Sharp and Dohme	W. Germany	-
Clotride	MSD	Italy	-
Diubram	Bramble	Australia	-
Diupres	MSD	US	-
Diuret	Protea	Australia	-
Diurone	Knoll	Australia	-
Fenuril	Pharmacia	Sweden	-
Lyovac	MSD	US	-
Niagar	Cimes	Belgium	-
Ro-Chlorozide	Robinson	US	-
Salisan	Ferrosan	Denmark	-
Saluren	Croce Bianca	Italy	-
Saluretil	Gayoso Wellcome	Spain	-
Saluric	MSD	UK	-
Salutrid	Leiras	Finland	-
SK-Chlorothiazide	SK and F	US	-
Urinex	Orion	Finland	-

Raw Materials

m-Chloroaniline
Ammonia
Chlorosulfonic acid
Formic acid

Manufacturing Process

(A) m-Chloroaniline (64 g, 0.5 mol) was added dropwise with stirring to 375 ml of chlorosulfonic acid in a 3-liter round bottom, 3-necked flask cooled in an ice bath. Sodium chloride (350 g) was added portionwise over a period of 1 to

2 hours and the mixture then heated gradually in an oil bath to 150°C. After 3 hours at 150° to 160°C, the flask was cooled thoroughly in an ice bath and the contents treated with a liter of cold water. The product was extracted with ether and the extract washed with water and dried over sodium sulfate.

After removal of ether on the steam bath, the residual 5-chloroaniline-2,4-disulfonyl chloride, which may be crystallized from benzene-hexane MP 130° to 132°C, was cooled in an ice bath and treated with 150 ml of 28% ammonium hydroxide in a 2-liter Erlenmeyer flask. The mixture was heated on the steam bath for 1 hour, cooled and the product collected on the filter, washed with water and dried. Upon crystallization from dilute alcohol 5-chloro-2,4-disulfamylaniline was obtained as colorless needles, MP 251° to 252°C.

(B) A solution of 88 g of 5-chloro-2,4-disulfamylaniline in 1.1 liters of 88% formic acid was heated under reflux for 2 hours. After removal of 200 ml of solvent by distillation, one liter of water was added and the product collected, washed with water and dried. Crystallization from dilute alcohol afforded 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide as colorless needles, MP 342.5° to 343°C, as described in US Patent 2,809,194.

References

Merck Index 2143
Kleeman and Engel p. 194
PDR pp. 830, 993, 1133, 1168, 1606, 1723
OCDS Vol. 1 pp. 321, 355 (1977) and 2 p. 395 (1980)
I.N. p. 221
REM p.938
Novello, F.C.; US Patent 2,809,194; October 8, 1957; assigned to Merck and Co., Inc.
Hinkley, D.F.; US Patent 2,937,169; May 17, 1960; assigned to Merck and Co., Inc.

CHLOROTRIANISENE

Therapeutic Function: Estrogen

Chemical Name: 1,1',1''-(1-Chloro-1-ethenyl-2-ylidene)tris[4-methoxybenzene]

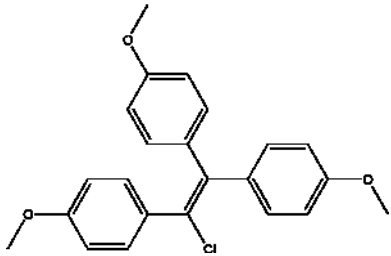
Common Name: Tri-p-anisylchloroethylene

Chemical Abstracts Registry No.: 569-57-3

Raw Materials

Tris-p-methoxyphenyl ethylene
Chlorine

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
TACE	Merrell	US	1952
TACE FN	Merrell	France	1959
Anisene	Farmila	Italy	-
Clorotrisin	Courtois	Italy	-
Merbentul	Merrell	W. Germany	-
Triagen	Gentili	Italy	-

Manufacturing Process

The following method is described in US Patent 2,430,891. To a solution of 10 parts of tris-p-methoxyphenyl ethylene in 35 to 40 parts of carbon tetrachloride is added a solution of 2.0 parts of chlorine in 50 parts of carbon tetrachloride, with stirring, and over a period of ½ hour. The carbon tetrachloride is then removed by distillation on a steam bath and the residual oil is recrystallized from 250 to 400 parts of methanol, decolorizing with charcoal or the like if necessary. Tris-p-methoxyphenyl chloroethylene is obtained in a yield of 65 to 75%. It melts at 113° to 114°C.

References

Merck Index 2149
Kleeman and Engel p. 195
PDR p. 1239
OCDS Vol. 1 p. 104 (1977)
I.N.p. 221
REM p. 988
Shelton, R.S. and Van Campen, M.G. Jr.; US Patent 2,430,891; November 18, 1947; assigned to the Wm. S. Merrell Company

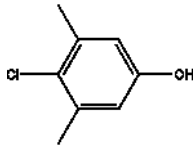
4-CHLORO-3,5-XYLENOL

Therapeutic Function: Topical antiseptic; Disinfectant

Chemical Name: 4-Chloro-3,5-dimethylphenol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 88-04-0

Trade Name	Manufacturer	Country	Year Introduced
Septiderm	Fougera	US	1960
Anti-Sept	Seamless	US	-
Bacillotox	Bode	W. Germany	-
Baktol	Bode	W. Germany	-
Cruex	Pharmacraft	US	-
Dettol	Reckitt and Coleman	UK	-
Fungoid	Pedinol	US	-
Ice-O-Derm	Wampole	US	-
Metasep	Marion	US	-
Micro-Guard	Sween	US	-
Orlex	Baylor	US	-
Otall	Saron Pharmacal	US	-
Pedi-Pro Foot Powder	Pedinol	US	-
Rezamid	Dermik	US	-
Rocapyol	Plurosan	Austria	-
Roxenol	Saunders	Canada	-
Satinasept	Mack	W. Germany	-
Sween-Soft	Sween	US	-
Valvanol	Asid	W. Germany	-
Zetar	Dermik	US	-

Raw Materials

Sulfuryl chloride
m-5-Xylenol

Manufacturing Process

546 g of intermediate xylenol fraction having a crystallizing point of 45°C mixed with an equal weight of m-5-xylenol are placed in a suitable vessel, equipped with stirring gear, and 273 g of sulfuryl chloride are added slowly. The temperature rises in the course of the reaction to about 40°C. When all the sulfuryl chloride is added the reaction mixture is heated to 80°C and the

acid gases removed as far as possible by air-blowing or any other suitable means. On cooling a quantity of the required chlor-xylenol separates out and is removed from the mother liquor. Further quantities of the material required can be isolated by vacuum distillation of the mother liquors and further crystallization. In all, 200 to 208 g of material substantially 2-chlor-m-5-xylenol can be obtained having a melting point of 112°C to 115°C. The material can be purified if desired by crystallization from a solvent such as a hydrocarbon.

References

Merck Index 2152
Kleeman and Engel p. 196
PDR pp. 1397, 1662, 1790
I.N. p. 222
REM p. 1168
Gladden, G.W.; US Patent 2,350,677; June 6, 1944: assigned to W.W. Cocker

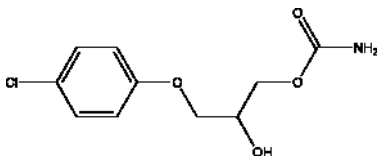
CHLORPHENESIN CARBAMATE

Therapeutic Function: Muscle relaxant

Chemical Name: 3-(4-Chlorophenoxy)-1,2-propanediol-1-carbamate

Common Name: 3-p-Chlorophenoxy-2-hydroxypropyl carbamate

Structural Formula:



Chemical Abstracts Registry No.: 886-74-8

Trade Name	Manufacturer	Country	Year Introduced
Maolate	Upjohn	US	1967
Kolpicortin	Doetsch Grether	Switz.	-
Rinlaxer	Taisho	Japan	-

Raw Materials

p-Chlorophenol
Glyceryl monochlorohydrin
Phosgene
Ammonia

Manufacturing Process

1.0 mol of 3-p-chlorophenoxy-1,2-propanediol (chlorphenesin) is suspended in 1,000 ml of benzene in a 5-liter flask equipped with a dropping funnel, thermometer and stirrer. 1.0 mol of phosgene in 500 ml of cold, dry benzene is then added dropwise over a period of 45 minutes, the resulting mixture being maintained at 30°C until all solid material is dissolved. 1.0 mol of triethylamine is added dropwise and the resulting reaction mixture stirred for 45 minutes at 30°C following the addition. The reaction mixture is then cooled to 5°C and extracted repeatedly with 600 ml portions of cold water to remove the triethylamine hydrochloride.

The benzene fraction, containing the intermediate 3-p-chlorophenoxy-3-hydroxypropyl chlorocarbonate, is added to 600 ml of cold concentrated ammonium hydroxide and the resulting reaction mixture agitated vigorously at 5°C for 7 hours. The crude 3-p-chlorophenoxy-2-hydroxypropylcarbamate solid is then filtered off, dissolved in hot benzene, dried to remove all traces of water, and permitted to crystallize out. Several recrystallirations from solvent mixtures of benzene and toluene, with small amounts of acetone, produced a crystalline white solid in about 65% yield. The product is 3-p-chlorophenoxy-2-hydroxypropyl carbamate, melting at 89° to 91°C. The chlorphenesin starting material is made by reacting p-chlorophenol with glyceryl monochlorohydrin as noted in US Patent 3,214,336.

References

Merck Index 2156
Kleeman and Engel p. 198
PDR p. 1850
OCDS Vol. 1 p. 118 (1977)
DOT 2 (4) 138 (1966)
I.N. p. 223
REM p. 927
Collins, R.J. and Matthews, R.J.; US Patent 3,161,567; December 15, 1964; assigned to The Upjohn Company
Parker, H.E.; US Patent 3,214,336; October 26, 1965; assigned to The Upjohn Company

CHLORPHENIRAMINE MALEATE

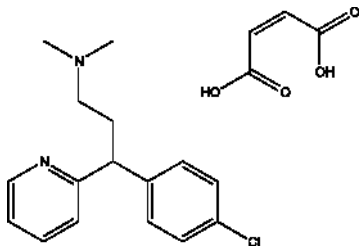
Therapeutic Function: Antihistaminic

Chemical Name: γ-(4-Chlorophenyl)-N,N-dimethyl-2-pyridinepropanamine maleate

Common Name: Chlorophenyl pyridyl propyldimethylamine maleate; Chlorphenamine maleate; Chlorprophen-pyridamine maleate

Chemical Abstracts Registry No.: 113-92-8; 132-22-9 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Chlor-Trimeton	Schering	US	1949
Teldrin	SKF	US	1954
Drize	Ascher	US	1967
Histaspan	U.S.V.	US	1968
Allerbid	Amfre-Grant	US	1971
Antagonate	Dome	US	1973
Animing	Nisshin Seiyaku	Japan	1981
Ahiston	Ikapharm	Israel	-
Alaspan	Almay	US	-
Alermine	Reid-Provident	US	-
Allerdor	Fellows-Testagar	US	-
Allergex	Protea	Australia	-
Allergin	Dellsberger	Switz.	-
Allergin	Sankyo	Japan	-
Allergisan	Pharmacia	Sweden	-
Allersan	Pharmacia	Sweden	-
Allertab	Tri-State	Italy	-
Allerton	Scalari	Italy	-
Anaphyl	Sam-On	Israel	-
Anthistamin-Sigletten	Rohm Pharma	W. Germany	-
Atalis-D	Kanto	Japan	-
Bismilla	Fuso	Japan	-
Chlo-Amine	Hollister-Stier	US	-
Chlodamine	Maruko	Japan	-
Chloramate	Reid-Provident	US	-
Chloramin	Langley	Australia	-
Chlor-Hab	Danbury	US	-
Chlor-Mal	Rugby	US	-
Chlormene	Robinson	US	-
Chloroton	Cenci	US	-
Chlorphen	Pro Doc	Canada	-
Chlor-Tel	Garden	US	-

Trade Name	Manufacturer	Country	Year Introduced
Chlortrone	Barlow Cote	Canada	-
Clorten	Panthox and Burck	Italy	-
C-Meton	S.S. Pharm	Japan	-
Cotuxinf	Sauba	France	-
Dallergy	Laser	US	-
Decongestant Elixir	Schein	US	-
Demazin	Schering	US	-
Donatussin	Laser	US	-
Dow-Chlorpheniramine	Dow	US	-
Hexapneumine	Doms	France	-
Histachlor	Vitamix	US	-
Histadur	Wynn	US	-
Histaids	Ohio Medical	US	-
Histalen	Len-Tag	US	-
Histamic	Metro Med	US	-
Histapen	Douglas	New Zealand	-
Histol	Blaine	US	-
Isoclor	Arnar-Stone	US	-
Kloromin	Halsey	US	-
Lekrica	Yoshitomi	Japan	-
Lorphen	Geneva	US	-
Neoallermin	Taiyo	Japan	-
Neorestamin	Kowa	Japan	-
Niratron	Progress	US	-
Novahistine	Dow	US	-
Novopheniram	Novopharm	Canada	-
Piriton	Allen and Hanburys	UK	-
Pneumopan	Sauba	France	-
Polaronic	Byk-Essex	W. Germany	-
Poracemin	Horita	Japan	-
Probahist	Legere	US	-
Propofan	Lepetit	France	-
Pyridamal	Bel Mar	US	-
Pyrroxate	Upjohn	US	-
Quadrahist	Schein	US	-
Rachelamine	Rachelle	US	-
Rumicine	Cetrane	France	-
Singlet	Dow	US	-
Synistamine	Sigmapharm	Austria	-
Trimeton	Essex	Italy	-
Trymegen	Medco	US	-
U.R.I.	ICN	US	-
Vitac	Egnaro	France	-

Raw Materials

4-Chlorobenzyl cyanide
Dimethylaminoethyl chloride
Sulfuric acid
2-Chloropyridine
Sodium amide

Manufacturing Process

See "Brompheniramine Maleate." The starting material is simply a chlorophenyl compound.

References

Merck Index 2157
Kleeman and Engel p. 196
PDR pp. 992, 1033, 1246, 1606
OCDS Vol. 1 p. 77 (1977)
I.N. p. 222
Sperber, N., Papa, D. and Schwenk, E.; US Patents 2,567,245; September 11, 1951; and 2,676,964; April 27, 1954; both assigned to Schering Corporation

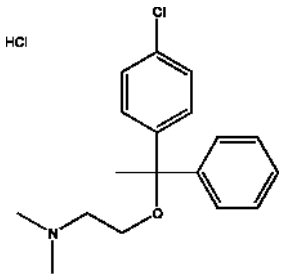
CHLORPHENOXAMINE HYDROCHLORIDE

Therapeutic Function: Muscle relaxant; Antiparkinsonian

Chemical Name: 2-[1-(4-Chlorophenyl)-1-phenylethoxy]-N,N-dimethylethanamine hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 562-09-4: 77-38-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Phenoxene	Dow	US	1959
Systral	Lucien	France	1963

Trade Name	Manufacturer	Country	Year Introduced
Clorevan	Evans	UK	-
Contristamine	Noristan	S. Africa	-
Rodavan	Asta	W. Germany	-
Systral	Asta	W. Germany	-
Svstral	Kyorin	Japan	-

Raw Materials

Methyl chloride
4-Chlorobenzophenone
Sodium amide
Magnesium
Dimethylaminoethyl chloride
Hydrogen chloride

Manufacturing Process

A Grignard solution is prepared by introducing methyl chloride into a boiling suspension of 36 g of magnesium in 1,000 cc of absolute ether until all the magnesium has reacted. 216 grams of 4-chloro-benzophenone are slowly added to the Grignard solution with ice cooling and stirring; after 15 hours, the thus-obtained product is poured into a mixture of 200 g of ammonium chloride and ice, whereupon it is separated with ether. The separated ether layer is dried with sodium sulfate, and the ether is distilled. The residual carbinol is added to a suspension of 45 g of sodium amide in 500 cc of toluene. To the thus-obtained mixture there are added 125 g of dimethylaminoethyl chloride, and the mixture is heated at boiling temperature for 3 hours with stirring.

The mixture is taken up with water and the base is extracted from the toluene with dilute hydrochloric acid. The hydrochloric solution is rendered alkaline with caustic soda, the base is separated with ether, dried, and after distillation of the ether fractionated in vacuo, BP at 0.05 mm Hg, 150° to 153°C. The basic ether is then dissolved in dry ether, and ether saturated with dry hydrogen chloride is added dropwise with stirring. An excess of hydrogen chloride must be avoided as it may produce decomposition to the corresponding diphenyl ethylene. The ether-moist hydrochloride is preferably dried at once in vacuo and subsequently reprecipitated from acetone-ether and then again dried in vacuo over phosphorus pentoxide. Hydrochloride, MP 128°C.

References

Merck index 2159
Kleeman and Engel p. 198
OCDS Vol. 1 p. 44 (1977)
I.N. p. 223
REM p.931
Arnold, H., Brock, N. and Kuhas, E.; US Patent 2,785,202; March 12, 1957; assigned to Asta-Werke A.G. Chemische Fabrik, Germany

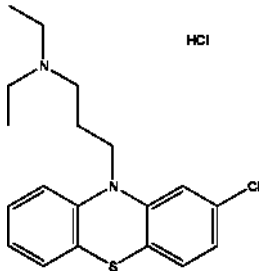
CHLORPROETHAZINE HYDROCHLORIDE

Therapeutic Function: Muscle relaxant; Tranquilizer

Chemical Name: 2-Chloro-N,N-diethyl-10H-phenothiazine-10-propanamine hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 84-01-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Neuriplege	Genevrier	France	1961

Raw Materials

2-Bromo-2'-(3''-dimethylaminopropyl)-amino-4'-chlorodiphenyl sulfide
Copper
Potassium carbonate
Hydrogen chloride

Manufacturing Process

2-Bromo-2'-(3''-dimethylaminopropyl)-amino-4'-chlorodiphenylsulfide (10 g) is dissolved in dimethylformamide (80 cc). To this solution is added potassium carbonate (5 g) and copper powder (0.4 g). It is then heated under reflux for 48 hours, cooled, and the insoluble matter filtered off. After washing with dimethylformamide (20 cc), the filtrate is taken up in distilled water (200cc). The base formed is extracted with ether (3 times with 50 cc), the ethereal solution is dried over sodium sulfate, the ether driven off on a water-bath and the residue distilled. In this way there is obtained 3-chloro-10-(3'-dimethylaminopropyl)-phenothiazine (6.4 g) which boils at 210 C to 225°C under 0.7 mm of mercury. The hydrochloride is made by the action of ethereal hydrogen chloride on the base dissolved in acetone; this hydrochloride melts at 180°C.

References

Merck Index 2161
OCDS Vol. 1 p. 379 (1977)
I.N. p. 224
Buisson, P.J.C., Gaillot, P. and Gaudechon, J.; US Patent 2,769,002; October 30, 1956; assigned to Societe des Usines Chimiques Rhone-Poulenc (France)

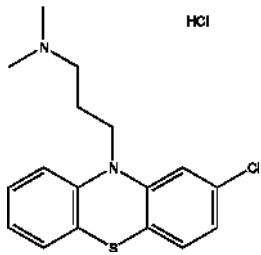
CHLORPROMAZINE HYDROCHLORIDE

Therapeutic Function: Tranquilizer

Chemical Name: 2-Chloro-N,N-dimethyl-10H-phenothiazine-10-propanamine hydrochloride

Common Name: N-(3-Dimethylaminopropyl)-3-chlorophenothiazine

Structural Formula:



Chemical Abstracts Registry No.: 69-09-0; 50-53-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Thorazine	SKF	US	1954
Chlor-PZ	U.S.V	US	1973
Promapar	Parke Davis	US	1973
Prochel	Rachelle	US	1975
Acemin	Sankyo	Japan	-
Chloractil	D.D.S.A.	UK	-
Chlorazin	Streuli	Switz.	-
Chlorpromados	Holz	W. Germany	-
Chlor-Promanyl	Paul Maney	Canada	-
Chlorprom-Ez-Ets	Barlow Cote	Canada	-
Contomin	Yoshitomi	Japan	-
Copormin	Kaken	Japan	-

Trade Name	Manufacturer	Country	Year Introduced
Cromedazine	Fellows-Testagar	US	-
Doimazin	Nippon Shinyaku	Japan	-
Elmarine	Elliott-Marion	Canada	-
Epokuhl	Kyowa	Japan	-
Esmind	Otsuka	Japan	-
Fenactil	Polfa	Poland	-
Hibanil	Mekos	Sweden	-
Hibernal	Leo	Sweden	-
Ishitomin	Kanto	Japan	-
Klorazin	Star	Finland	-
Klorproman	Orion	Finland	-
Klorpromex	Dumex	Denmark	-
Largactil	Specia	France	-
Megaphen	Bayer	W. Germany	-
Neurazine	Misr. Co-Pharm.	Egypt	-
Norcozine	Iwaki	Japan	-
Procalm	Bramble	Australia	-
Promachlor	Geneva	US	-
Promacid	Knoll	Australia	-
Promactil	Wassermann	Spain	-
Promexin	Meiji	Japan	-
Promosol	Horner	Canada	-
Propafenin	Deutsches Hydrierwerk	E. Germany	-
Protran	Protea	Australia	-
Prozil	Dumex	Denmark	-
Prozin	Lusofarmaco	Italy	-
Psychozine	O'Neal, Jones and Feldman	US	-
Psylkatil	Farmos	Finland	-
Repazine	Lennon	S. Africa	-
Taroctyl	Taro	Israel	-
Wintermin	Shionogi	Japan	-

Raw Materials

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

Manufacturing Process

To a boiling suspension of 11.6 g of chlorophenothiazine (consisting of a mixture of two isomers melting at 196° to 198°C and 116° to 117°C, respectively, the latter in minor proportion) and 2.4 g of sodium amide (80%) in 60 cc of xylene, there are added over a period of one hour 7.5 g of 3-

dimethylamino-1-chloropropane in solution in its own weight of xylene. At the end of the addition, heating is continued for one hour under reflux. After cooling, the contents are taken up in acidified water and the xylene separated. The aqueous layer is made strongly alkaline by means of sodium hydroxide in order to liberate the base and this is extracted with ether. On distillation of the ethereal extract there is obtained 10-(3'-dimethylamino-propyl)-chlorophenothiazine which distills at 200° to 205°C under a pressure of 0.8 mm Hg. Its hydrochloride, recrystallized from chlorobenzene, melts at 177° to 178°C. The chlorophenothiazine may be prepared by reacting m-chlorodiphenylamine with sulfur in the presence of an iodine catalyst.

References

Merck Index 2163
Kleeman and Engel p. 199
PDR p. 1728
OCDS Vol. 1 pp. 319, 378 (1977), 2 p. 409 (1980) and 3p. 72 (1984)
I.N.p. 224
REM p. 1086
Charpentier, P.; US Patent 2,645,640; July 14, 1953; assigned to Societe des Usines Chimiques Rhone-Poulenc, France

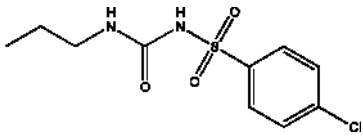
CHLORPROPAMIDE

Therapeutic Function: Oral hypoglycemic

Chemical Name: 4-Chloro-N-[(propylamino)carbonyl]benzenesulfonamide

Common Name: 1-(p-Chlorobenzenesulfonyl)-3-propylurea

Structural Formula:



Chemical Abstracts Registry No.: 94-20-2

Trade Name	Manufacturer	Country	Year Introduced
Diabinese	Pfizer	US	1958
Diabinese	Pfizer	France	1960
Dynalase	Pharmadyne	US	1980
Insulase	Premo	US	1980
Abemide	Kabayashi	Japan	-
Adiaben	Belupo Ltd.	Yugoslavia	-
Arodoc-C	Sawai	Japan	-

Trade Name	Manufacturer	Country	Year Introduced
Biadibe	Guidotti	Italy	-
Bioglumin	Uriach	Spain	-
Catanil	De Angeli	Italy	-
Chloronase	Hoechst	W. Germany	-
Chloronase	Hoechst	Japan	-
Clordiabet	Carulla-Vekar	Spain	-
Clordiasan	Santos	Spain	-
Cloro-Hipoglucina	Lefa	Spain	-
Diabemide	Guidotti	Italy	-
Diabet	Pages Maruny	Spain	-
Diabetabs	Wolfs	Belgium	-
Diabetasi	Biagini	Italy	-
Diabetoral	Boehringer Mannheim	W. Germany	-
Diabexan	Crosara	Italy	-
Diabitex	Irapharm	Israel	-
Diamel-Ex	Ibsa	Switz.	-
Diamide	Kanto	Japan	-
Gliconorm	Gentili	Italy	-
Glucamide	Lemmon	US	-
Glucosulfina	Infale	Spain	-
Meldian	Pliva	Yugoslavia	-
Melisar	Beolet	Italy	-
Melitase	Berk	UK	-
Mellitos	Ono	Japan	-
Melormin	Farmos	Finland	-
Normoglic	Salfa	Italy	-
Novopropamide	Novopharm	Canada	-
Orabet	Deva	Turkey	-
Orabines	Biofarma	Turkey	-
Orbin	Biles	Turkey	-
Prodiaben	Labif	Italy	-
Promide	Protea	Australia	-
Shuabate	Toyama	Japan	-
Stabinol	Horner	Canada	-
Toyomelin	Toyo Jozo	Japan	-

Raw Materials

Propyl isocyanate
p-Chlorobenzene sulfonamide
Triethylamine

Manufacturing Process

A solution of 54 g (0.64 mol) of propyl isocyanate in 60 ml of anhydrous

dimethylformamide was added to a cold, well-stirred suspension of 81 g (0.42 mol) of dry p-chlorobenzenesulfonamide in 210 ml of anhydrous triethylamine during the course of 20 to 30 minutes. The mildly exothermic reaction was completed by allowing it to stand at room temperature for about 5 hours. The reaction mixture was then slowly added to 3 liters of cold 20% acetic acid during the course of about one hour, constant agitation being maintained throughout the addition.

After the addition was complete, the desired product, which had crystallized out, was filtered and washed well with about 2 liters of cold water. The crude material was then dissolved in 1 liter of cold 5% sodium carbonate and the resulting solution was immediately filtered from an insoluble gum. The product was then reprecipitated, by slowly adding the filtrate to 3 liters of 20% acetic acid. The precipitate, which is very nearly pure N-(p-chlorobenzenesulfonyl)-N'-propylurea, was then dried and subsequently recrystallized from about 800 ml of benzene to give a 59% yield of pure product, MP 129.2 to 129.8°C.

References

Merck Index 2164
Kleeman and Engel p. 200
PDR pp. 830, 993, 1034, 1417, 1999
OCDS Vol. 1 p. 137 (1977)
I.N.p. 225
REM p. 976
McLamore, W.M.; US Patent 3,349,124; October 24, 1967; assigned to Chas. Pfizer Co., Inc.

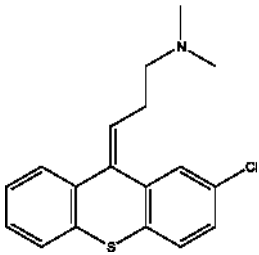
CHLORPROTHIXENE

Therapeutic Function: Tranquilizer

Chemical Name: 3-(2-Chloro-9H-thioxanthen-9-ylidene)-N,N-dimethyl-1-propanamine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 113-59-7; 6469-93-8 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Taractan	Roche	France	1960
Taractan	Roche	US	1962
Clothixen	Yoshitomi	Japan	-
Cloxan	Orion	Finland	-
Minithixen	Spofa	Czechoslovakia	-
Paxyl	Ikapharm	Israel	-
Tra-Quilan	Eisai	Japan	-
Truxal	Tropon	W. Germany	-
Truxal	Toyama	Japan	-
Truxaletten	Tropon	W. Germany	-

Raw Materials

3-Dimethylaminopropyl chloride
2-Chlorothiaxanthone
Acetyl chloride
Magnesium
Ethyl bromide

Manufacturing Process

Chlorprothixene may be prepared as described in US Patent 2,951,082. Magnesium turnings, 4.86 g (0.2 g-atom) was placed in a 500 ml reaction flask fitted with a mercury sealed stirrer, reflux condenser and a dropping funnel. Tetrahydrofuran, 50 ml and calcium hydride, 500 mg, were added. Ethyl bromide, 2.18 g and a crystal of iodine then were added. A vigorous reaction set in that evolved sufficient heat to induce refluxing. After 5 minutes, a solution of 3-dimethylaminopropyl chloride (dried over calcium hydride) in 50 ml of tetrahydrofuran was added to the refluxing solution at such a rate that gentle refluxing was maintained. The addition required 25 minutes.

The reaction mixture was stirred at reflux for an additional 30 minutes when nearly all of the magnesium had dissolved and determination of magnesium in an aliquot of the solution showed that an 82% yield of Grignard reagent had been obtained. The reaction mixture was cooled in an ice bath and stirred while 24.67 g (0.1 mol) of 2-chlorothiaxanthone was added over a period of 10 minutes. The reaction was stirred at room temperature for 30 minutes then allowed to stand overnight in the refrigerator. The tetrahydrofuran was evaporated at 50°C under reduced pressure. Benzene, 150 ml, was added to the residue.

The mixture was hydrolyzed in the cold by the dropwise addition of 50 ml of water. The benzene layer was separated by decantation and the gelatinous precipitate washed with two 100 ml portions of benzene.

The precipitate was then mixed with diatomaceous earth, collected on a filter, and washed with water and extracted with two 100 ml portions of boiling

benzene. The aqueous filtrate was extracted with 50 ml of benzene, the combined benzene extracts washed with water and evaporated to dryness under reduced pressure. The crystalline residue, MP 140° to 147°C, weighed 30.8 g. Recrystallization from a mixture of benzene and hexane gave 27.6 g (83%) of 2-chloro-10-(3-dimethylaminopropyl)-10-hydroxythiaxanthene, MP 152° to 154°C. Analytically pure material from another experiment melted at 153° to 154°C.

2-Chloro-10-(3-dimethylaminopropyl)-10-hydroxythiaxanthene, 3.34 g (0.01 mol) obtained as described was dissolved in 15 ml of dry, alcohol-free chloroform. Acetyl chloride, 2.36 g (0.03 mol) was added and the clear yellow solution was refluxed for one hour in a system protected by a drying tube. The solvent then was evaporated on the steam bath under reduced pressure and the residue dissolved in absolute alcohol. The hydrochloride of 2-chloro-10-(3-dimethylaminopropylidene)-thiaxanthene was precipitated by the cautious addition of absolute ether. After drying at 70°C the yield of white crystalline 2-chloro10-(3-dimethylaminopropylidene)-thiaxanthene hydrochloride, MP 189 to 190°C (to a cloudy melt), was 3.20 g (90%). This material is a mixture of geometric isomers.

Trans-2-chloro-9-(ω-dimethylamino-propylidene)-thioxanthene [MP 98°C, MP of the hydrochloride 225°C (corr.)], is a valuable medicinal agent, being used as a tranquilizer and antiemetic agent, whereas the corresponding cis isomer (MP 44°C, MP of the hydrochloride 209°C) is not useful for these indications, as described in US Patent 3,115,502, which describes procedures for conversion of the cis to the trans form.

References

Merck Index 2166
Kleeman and Engel p. 200
PDR p. 1503
OCDS Vol. 1 p. 389 (1977)
DOT 9 (6) 229 (1973)
I.N.p. 225
REM p. 1087
Sprague, J.M. and Engelhardt, E.L.; US Patent 2,951,082; August 30, 1960; assigned to Merck and Co., Inc.
Schlapfer, R. and Spiegelberg, H.; US Patent 3,115,502; December 24, 1963;assigned to Hoffmann-LaRoche Inc.

CHLORQUINALDOL

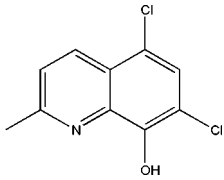
Therapeutic Function: Antibacterial

Chemical Name: 5,7-Dichloro-2-methyl-8-quinolinol

Common Name: Hydroxydichloroquinaldine; Chloroquinaidol

Chemical Abstracts Registry No.: 72-80-0

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Sterosan	Geigy	US	1954
Gynotherax	Bouchard	France	1967
Afungyl	EGYT	Hungary	-
Chinosicc	Schering	W. Germany	-
Chinotiol	Bouty	Italy	-
Gyno-Sterosan	Geigy	W. Germany	-
Intensol	Anasco	W. Germany	-
Lonjee	Sampo	Japan	-
Phyletten	Muller Rorer	W. Germany	-
Quesil	EGYT	Hungary	-
Rub-All T	Toyama	Japan	-
Saprosan	C.I.F.	Rumania	-
Serviderm	Servipharm	Switz.	-
Siogeno	Geigy	W. Germany	-
Siogene	Geigy	France	-
Siosteran	Fujisawa	Japan	-
Steroxin	Geigy	UK	-

Raw Materials

8-Hydroxyquinaldine
Chlorine

Manufacturing Process

11.1 parts of 8-hydroxy-quinaldine are dissolved in 140 parts of formic acid. Chlorine is introduced into this solution under cooling, until the increase in weight corresponds to the required quantity of chlorine and a test of the chlorination mixtures gives no more dyestuff formation with diazo-benzene in an acetic acid solution.

When the chlorination is complete, the reaction mixture is poured into 1,000 parts of water and treated with a dilute sodium bisulfite solution, until no more reaction may be observed with starch potassium iodide paper. Thereby the 5,7-dichloro-8-hydroxy-quinaldine separates out in form of a weakly yellowish colored precipitate. The same is filtered off and thoroughly washed with water.

After drying, 15 parts of 5,7-dichloro-8-hydroxy-quinaldine melting at 111°C to 112°C are obtained. When recrystallized from alcohol, the product is obtained in voluminous, slightly yellowish needles having the melting point of 111.5°C to 112°C.

References

Merck Index 2168
Kleeman and Engel p. 201
I.N. p. 225
Senn, E.; US Patent 2,411,670; November 26, 1946; assigned to J.R. Geigy AG

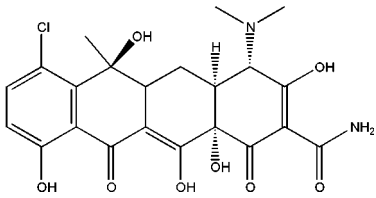
CHLORTETRACYCLINE

Therapeutic Function: Antibacterial

Chemical Name: 7-Chloro-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: -

Structural Formula:



Chemical Abstracts Registry No.: 57-62-5

Trade Name	Manufacturer	Country	Year Introduced
Aureomycin	Lederle	US	1948
Aureomycine	Specia	France	1951
Aureum	Farmigea	Italy	-
Aufofac	American Cyanamid (AHP)	US	-
B-Aureo	Biokema	Switz.	-
Chevita C-10	Chevita	W. Germany	-
Chlortet	Langley	Australia	-
Chrysomycin	Dispersa	Switz.	-
Ciorteta	Pierrel	Italy	-

Trade Name	Manufacturer	Country	Year Introduced
Colircusi Aureomicina	Cusi	Spain	-
CTC Soluble	Diamond Shamrock	US	-
Vi-Mvcin	Vineland Chemical	US	-

Raw Materials

Sucrose
Corn steep liquor
S. aureofaciens bacterium

Manufacturing Process

The following process description is taken from US Patent 2,987,449. An appropriate S. aureofaciens strain such as mutant S1308 (ATCC No. 12,748) is grown aerobically in a suitable inoculum medium. A typical medium used to grow the primary inoculum is prepared according to the following formula: sucrose, 20.0 g; corn steep liquor, 16.5 ml, ammonium sulfate, 2.0 g; calcium carbonate, 7.0 g; and water to 1,000 ml.

A 100 ml aliquot of this medium is placed in a 500 mi Erlenmeyer flask and sterilized by autoclaving for 20 minutes under 15 psi pressure. Spores of mutant strain S. aureofaciens S1308 (ATCC No. 12,748) are washed from an agar slant into the flask with sterile distilled water to form a suspension containing approximately 10^8 spores per milliliter. A 1.0 ml portion of this suspension is used to inoculate the fermentation media in the example which follows. A fermentation medium consisting of the following ingredients was prepared.

	Grams
$(NH_4)_2SO_4$	5.0
$CaCO_3$	9.0
NH_4Cl	1.5
$MgCl_2 \cdot 6H_2O$	2.0
$FeSO_4 \cdot 7H_2O$	0.06
$MnSO_4 \cdot 4H_2O$	0.05
$CoCl_2 \cdot 6H_2O$	0.005
$ZnSO_4 \cdot 7H_2O$	0.1
Corn steep liquor	25.0
Cornstarch	55.0
Water to	1,000 ml

25 ml aliquots of this fermentation medium were placed in each of two 250 ml Erlenmeyer flasks and 0.5 ml of lard oil was added to each flask. Then 0.002 mg/ml of riboflavin was added to one flask, the other flask being retained as a control. The flasks were sterilized in an autoclave for 20 minutes under 15 psi pressure, then cooled to room temperature (25°±5°C). At this point, a 1.0 ml portion of inoculum of mutant strain S. aureofaciens S1308 (ATCC No. 12,748) was added to each of the two flasks. The flasks were incubated at

25°C for 120 hours on a rotary shaker operating at 180 rpm. Upon completion of the fermentation period the mashes were assayed for 7-chlorotetracycline content.

The increase in production due to the addition of riboflavin was very noticeable in the above example. A similar effect was reported for cupric sulfate pentahydrate addition according to US Patent 3,050,446.

References

Merck Index 2170
Kleeman and Engel p. 203
PDR p. 1007
OCDS Vol. 1 p. 212 (1977)
I.N. p. 226
REM p. 1208
Duggar, B.M.; US Patent 2,482,055; September 13, 1949; assigned to American Cyanamid Company
Niedercorn, J.G.; US Patent 2,609,329; September 2, 1952; assigned to American Cyanamid Company
Winterbottom, R., Mendelsohn, H., Muller, S.A., and McCormick, J.R.D.; US Patent 2,899,422; August 11, 1959; assigned to American Cyanamid Company
Miller, P.A., Goodman, J.J., Sjolander, N.O. and McCormick, J.R.D.; US Patent 2,987,449; June 6, 1961; assigned to American Cyanamid Company
Goodman, J.J.; US Patent 3,050,446; August 21, 1962; assigned to American Cyanamid Company

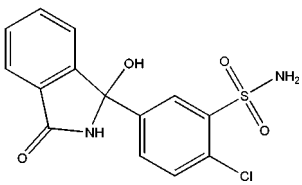
CHLORTHALIDONE

Therapeutic Function: Diuretic, Antihypertensive

Chemical Name: 2-Chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl) benzenesulfonamide

Common Name: Chlortalidone

Structural Formula:



Chemical Abstracts Registry No.: 77-36-1

Trade Name	Manufacturer	Country	Year Introduced
Hygroton	Geigy	US	1960
Hygroton	Ciba Geigy	France	1960
Hygroton	Ciba Geigy	Switz.	1960
Hygroton	Ciba Geigy	W. Germany	1960
Hygroton	Ciba Geigy	UK	1960
Igroton	Geigy	Italy	1961
Thalitone	Boehringer Ingelheim	US	1982
Aquadon	Ikapharm	Israel	-
Hybasedock	Sawai	Japan	-
Hydoban	Medica	Finland	-
Hydro-Long	Sanorama	W. Germany	-
Hygroton	Pliva	Yugoslavia	-
Hygroton	Geigy	Japan	-
Hypertol	Farmos	Finland	-
Igrolina	Benedetti	Italy	-
Novothalidone	Novopharm	Canada	-
Regretron	U.S.V.	US	-
Renon	Medal	Italy	-
Servidone	Servipharm	Switz.	-
Urid	Protea	Australia	-
Uridon	I.C.N.	Canada	-
Urolin	Sidus	Italy	-
Zambesil	Spemsa	Italy	-

Raw Materials

4-Chloro-3-amino-benzophenone-2'-carboxylic acid
Sodium nitrate
Hydrogen chloride
Sulfur dioxide
Thionyl chloride
Ammonia

Manufacturing Process

15 parts of aqueous 46% sodium nitrite solution are gradually added to a mixture of 27.5 parts of 4-chloro-3-amino-benzophenone-2'-carboxylic acid, 200 parts of glacial acetic acid and 20 parts of 37% hydrochloric acid at 0° to 10°C. The solution of the diazonium salt is poured into an ice-cooled mixture of 200 parts of 30% sulfur dioxide solution in glacial acetic acid and 3 parts of crystallized cupric chloride in 15 parts of water. Nitrogen is developed and, after a short time, the 4-chloro-2'-carboxy-benzophenone-3-sulfochloride crystallizes out. After 1 hour it is filtered off and washed with water. MP 178° to 182°C.

35.9 parts of 4-chloro-2'-carboxy-benzophenone-3-sulfochloride and 50 parts of thionyl chloride are heated first for 3 hours at 30° to 35°C and then for 1 hour at 45°C. The excess thionyl chloride is distilled off in the vacuum, the dichloride, 3-chloro-3-(3'-chlorosulfonyl-4'-chlorophenyl)phthalide, which remains as a crystallized mass is dissolved in 150 parts of chloroform and a mixture of 200 parts of 25% aqueous ammonia solution and 200 parts of ethanol is added dropwise at about 10°C while stirring and cooling. After stirring for 1 hour at 40°C, the solvent is distilled off in the vacuum and diluted hydro chloric acid is added to the residue whereupon the 1-oxo-3-(3'-sulfamyl-4'-chloro-phenyl)3-hydroxy-isoindoline which is tautomeric to the 4-chloro-2'-carbamyl-benzophenone-3-sulfonamide, separates out. On recrystallizing from diluted ethanol, the isoindoline derivative melts at 215°C on decomposition.

Instead of reacting the dichloride in aqueous solution with ammonia, it can also be reacted at -50° to -40°C with a great excess of liquid ammonia. After removal of the ammonia, the crude product obtained is recrystallized as described above.

References

Merck Index 2171
Kleeman and Engel p. 202
PDR pp. 509, 676, 682, 830, 993, 1326, 1606, 1786, 1813, 1820, 1999
OCDS Vol. 1 p. 322 (1977)
DOT 16 (1) 32 (1980)
I.N. p. 226
REM p. 938
Graf, W., Schmid, E. and Stoll, W.G.; US Patent 3,055,904; September 25, 1962; assigned to Geigy Chemical Corporation

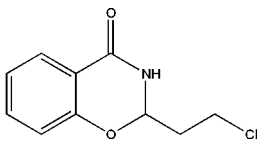
CHLORTHENOXAZINE

Therapeutic Function: Antipyretic, Analgesic

Chemical Name: 2-(2-Chloroethyl)-2,3-dihydro-4H-1,3-benzoxazin-4-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 132-89-8

Trade Name	Manufacturer	Country	Year Introduced
Reugaril	Farber	Italy	1966
Apirogen	Dessy	Italy	-
Betix	Saba	Italy	-
Fiobrol	Geigy	W. Germany	-
Ossazin	Scalari	Italy	-
Ossazone	Brocchieri	Italy	-
Ossipirina	Radiumpharma	Italy	-
Oxal	Saita	Italy	-
Reulin	Isola-Ibi	Italy	-
Reumital	Farge	Italy	-
Valtorin	Boehringer Ingelheim	-	-

Raw Materials

Acrolein
Hydrogen chloride
Salicylamide

Manufacturing Process

A mixture of 4 liters chloroform and 1,050 cc ethanol was saturated with dry hydrogen chloride gas at -5°C to +5°C in a vessel having a net volume of 15 liters and provided with a stirring device, reflux cooler, gas feed line, thermometer and dropping funnel. 455 g acrolein which had been precooled to 0°C were added dropwise to the solution over a period of 1 to 2 hours while maintaining the temperature below +5°C and vigorously stirring. 1,070 g salicylamide and 1,080 g glacial acetic acid were added to the resulting solution of beta-chloropropionaldehyde acetal, thereby forming a suspension which was heated to 60°C while stirring. A clear solution was formed which was maintained at 60°C for an additional hour. The solution was allowed to cool to about 40°C and was then washed with water by passing a strong stream of water under the surface of the chloroform and continuously withdrawing the upper phase. When the water had reached a pH of 3-4, the precipitated reaction product was separated by vacuum filtration. The chloroform phase of the filtrate was evaporated under a weak vacuum and the residue was combined with the precipitate first obtained. The combined products were stirred with 2 liters of a 5% sodium hydroxide solution. The raw reaction product was then washed with water, dried and recrystallized from ethanol. The product had the melting point of 146°C to 147°C (decomposition). The yield was 1,260 g, corresponding to 76% of the theoretical yield.

References

Merck Index 2172
Kleeman and Engel p. 203
I.N. p. 226
Ohnacker, G. and Scheffler, H.; US Patent 2,943,087; June 28, 1960; assigned to Dr. Karl Thomae G.m.b.H. (Germany)

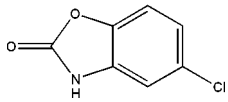
CHLORZOXAZONE

Therapeutic Function: Muscle relaxant

Chemical Name: 5-Chloro-2(3H)-benzoxazolone

Common Name: 5-Chloro-2-hydroxybenzoxazole

Structural Formula:



Chemical Abstracts Registry No.: 95-25-0

Trade Name	Manufacturer	Country	Year Introduced
Paraflex	McNeil	US	1958
Benzoflex	Benzon	Denmark	-
Biomioran	Bioindustria	Italy	-
Chroxin	Kanyo	Japan	-
Chlozoxine	Sanko	Japan	-
Deltapyrin	Kodama	Japan	-
Escoflex	Streuli	Switz.	-
Framenco	Fuso	Japan	-
Kiricoron	Sampo	Japan	-
Mesin	Yamanouchi	Japan	-
Myoflex	Pliva	Yugoslavia	-
Myoflexin	Chinoin	Hungary	-
Oxyren	Astra	-	-
Paraflex	Cilag	W. Germany	-
Pathorysin	Kowa	Japan	-
Remoflex	Belupo Ltd.	Yugoslavia	-
Solaxin	Eisai	Japan	-
Sorazin	Toho	Japan	-
Trancrol	Mohan	Japan	-

Raw Materials

2-Amino-5-chlorobenzoxazole
Hydrogen chloride
Sodium hydroxide

Manufacturing Process

A solution of 16.9 g (0.1 mol) of 2-amino-5-chlorobenzoxazole in 200 ml of 1 N HCl is refluxed until precipitation is complete. The resulting solid is collected

by filtration, dissolved in 200 ml of 1 N NaOH and the solution extracted with 50 ml of ether. Acidification of the alkaline solution gives a precipitate which is purified by crystallization from acetone to give 2-hydroxy-5-chlorobenzoxazole melting at 191° to 191.5°C.

References

Merck Index 2174
Kleeman and Engel p. 204
PDR pp. 830, 993, 1093, 1441, 1606, 1999
OCDS Vol. 1 p. 323 (1977)
I.N. p. 227
REM p. 926
Marsh, D.F.; US Patent 2,895,877; July 21, 1959; assigned to McNeil Laboratories, Inc.

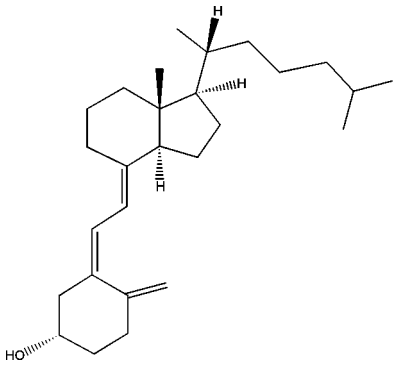
CHOLECALCIFEROL

Therapeutic Function: Vitamin, Antirachitic

Chemical Name: 9,10-Secocholesta-5,7,10(19)-trien-3-ol, (3β,5Z,7E)

Common Name: Cholecalciferol; Colecalciferol; Dehydrocholesterolum activatum; Oleovitamin D_3; Vitamin D; Vitamin D_3

Structural Formula:



Chemical Abstracts Registry No.: 67-97-0

Trade Name	Manufacturer	Country	Year Introduced
Vitamin D	Country Life	-	-
Vitamin D	Nature's Way	-	-
Vitamin D	Solgar	-	-

Trade Name	Manufacturer	Country	Year Introduced
Vitamin D	Vitamin Power	-	-
Vitamin D	Carlson Laboratories	-	-
Vitamin D	Solaray	-	-
Vitamin D_3	Solgar	Netherlands	-

Raw Materials

7-Dehydrocholesteryl acetate
Acetic acid
n-Hexane

Manufacturing Process

5 g of 7-dehydrocholesteryl acetate (prepared by W.R. Ness, R. S. Kostic and Mosetting, J. Am. Chem. Soc. 78, 436, 1956) were dissolved in 500 ml of n-hexane. This solution was irradiated with ultraviolet ray by recyclicly passing it through a quartz apparatus surrounding 450 w high pressure mercury vapor lamps for 80 minutes. After irradiation and then the distillating off of n-hexane the solution was added with 50 ml of ethanol and the ethanolic solution was left to stand overnight at the temperature of -20°C. The formed crystals were filtered off from ethanolic solution and filtrate was heated at the temperature 78°C for 4 hours. After cooling of filtrate, the cooled filtrate was added with 4 ml of ethanolic solution containing 0.7 g of potassium hydroxide to effect a reaction at the temperature of 20°C and under nitrogen for 60 minutes. The reaction product was added with 0.7 ml glacial acetic acid and then ethanol was distilled off under reduced pressure from the reaction product. The obtained residue was extracted with 50 ml of n-hexane and extract was washed with water and n-hexane was distilled off from extract to obtain 2.5 g of yellow oily matter containing vitamin D_3. The content of vitamin D_3 in yellow oily matter was 40.2% by weight.

References

Toyoda M. et al.; US Patent No. 3,661,939; May 9, 1972; Assigned to Nisshin Flour Milling Co., Ltd., Tokyo, Japan
Hunziker H., Mullner F.X.; Helv. Chim. Acta 41, 70, 1958

CHOLESTYRAMINE

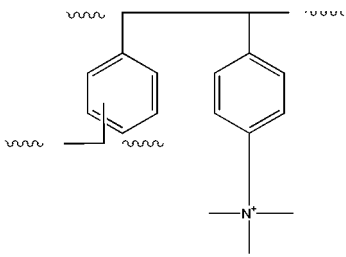
Therapeutic Function: Anticholesteremic

Chemical Name: Cholestyramine

Common Name: Cholestyramine (Resin); Colestyramine; Divistyramine; Filicol; Resin-colestiramina

Chemical Abstracts Registry No.: 11041-12-6

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
LoCholest	Warner-Chilcott	USA	-
Prevalite	Upsher-Smith Laboratories, Inc.	USA	-
Questran	Bristol-Myers Squibb	USA	-

Manufacturing Process

For reducing cholesterol blood levels were used the polymeric compounds which can to bind bile acids such as 1) "Acryloid CQ" and "Acrysol CQ", a linear acrylic type quaternary ammonium salt having a molecular weight of the order of about 2,000,000, made by Rohm and Haas Company, Philadelphia. This polymers, structurally a straight carbon skeleton with ester side chains, the esters being from quaternary ammonium substituted alcohols, are soluble in water, and the water solution has a viscosity of 2500 to 5000 centipoises in 5% aqueous solution at room temperature. Equivalent weight of the polymers based on the ammonium groups, are about 350-360; 2) "Acrysol CA", a soluble tertiary amine salt available from Rohm and Haas Company. Equivalent weight of the polymer is of the order 325; 3) Linear polyethyleneimine with a molecular weight is about 30,000 and equivalent weight of the order of about 43. This polymer is available from the Borden and Yaas Cj, New York; 4) "Separan CR70", made bt the Dow Chemical Co., Midland, Michigan. This material is a copolymer acrylamide and vinyl benzyl trimethylammonium chloride in weight ratio of about 30:70, having equivalent weight of about 302 and a average molecular weight about 100,000; 5) Chlormethylated polystyrene which was modified with by tertiary amines such as trimethylamine and dimethylaminoethanol. The examined polymeric compounds are used as per os.

References

Wolf F.J. et al., US Patent No. 3,308,020; 07.05.1967; Assigned: Merck and Co., Inc.

Todd R.S. et al.; US Patent No. 4,172,120; Oct. 23, 1979; Assigned: Reckitt and Colman Products Limited (London, GB2)

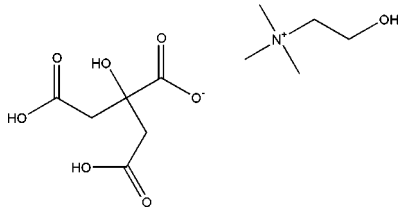
CHOLINE DIHYDROGEN CITRATE

Therapeutic Function: Lipotropic

Chemical Name: (2-Hydroxyethyl)trimethylammonium citrate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 77-91-8

Trade Name	Manufacturer	Country	Year Introduced
Chothyn	Flint	US	1945
Citrocholine	United	US	1949

Raw Materials

Trimethyl amine
Ethylene oxide
Citric acid

Manufacturing Process

30 lb of trimethylamine were added to 70.4 lb of methyl alcohol to which 9.2 lb of water had previously been added. To the resulting solution in a closed vessel 23 lb of ethylene oxide gas were introduced and the resulting mixture then maintained at a temperature of 16 C to 30 C and agitated for 6 hours. During the reaction the pressure in the reaction vessel varied from about 17.5 psi at the start of the reaction to 0 psi at the end of the reaction. The resulting solution was then added with agitation to a refluxing solution of 40 liters of isopropyl alcohol containing 95 lb of citric acid dissolved therein. This mixture was then cooled to 0°C and held at that temperature overnight. The white crystalline choline dihydrogen citrate which formed was separated from the solvent mixture by filtration and dried in vacuo. 117 lb of anhydrous, crystalline choline dihydrogen citrate having a purity of 99.6% were obtained. This was a yield of 78% based on the amount of trimethylamine employed.

References

Merck Index 2187
I .N. p. 227

REM p. 1026
Klein, H.C., DiSalvo, W.A. and Kapp, R.; US Patent 2,870,198; January 20, 1959; assigned to Nopco Chemical Co.

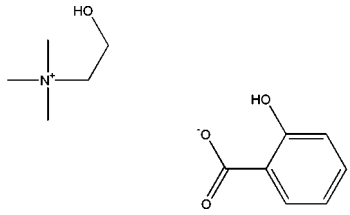
CHOLINE SALICYLATE

Therapeutic Function: Analgesic; Antipyretic

Chemical Name: 2-Hydroxy-N,N,N-trimethyl-ethanaminium salt with 2-hydroxy benzoic acid

Common Name: Choline salicylic acid salt

Structural Formula:



Chemical Abstracts Registry No.: 2016-36-6

Trade Name	Manufacturer	Country	Year Introduced
Arthropan	Purdue Frederick	US	1959
Actasal	Purdue Frederick	US	1959
Atilen	Spofa	Czechoslovakia	-
Audax	Napp	UK	-
Audax	Ethimed	S. Africa	-
Audax	Mundipharma	W. Germany	-
Bonjela	Lloyds	UK	-
Mundisal	Mundipharma	Switz.	-
Mundisal	Erco	Denmark	-
Otho	Purdue Frederick	US	-
Sachol	Polfa	Poland	-
Rheumavincin	Owege	W. Germany	-
Salicol	Sais	Italy	-
Satibon	Grelan	Japan	-
Syrap	Carrion	France	-
Teejel	Napp	UK	-
Tegunor	Mundipharma	W. Germany	-
Trilisate	Purdue Frederick	US	-

Raw Materials

Choline chloride
Sodium salicylate

Manufacturing Process

A method of preparation is to react an acid salt of choline (such as choline chloride or choline bromide) with an alkaline salt of salicylic acid (such as sodium salicylate, potassium salicylate, or magnesium salicylate) in an alcoholic media.

References

Merck Index 2189
Kleeman and Engel p. 205
I.N. p. 228
Broh-Kahn, E.H. and Sasmor, E.J.; US Patent 3,069,321; December 18, 1962; assigned to Laboratories for Pharmaceutical Development, Inc.

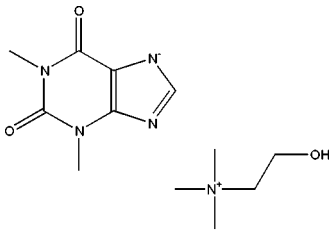
CHOLINE THEOPHYLLINATE

Therapeutic Function: Smooth muscle relaxant

Chemical Name: Theophylline cholinate

Common Name: Oxotriphylline; Oxytrimethylline

Structural Formula:



Chemical Abstracts Registry No.: 4499-40-5

Trade Name	Manufacturer	Country	Year Introduced
Sabidal S.R.	Zyma	UK	1983
Brondaxin	Ferrosan	Denmark	-
Cholecyl	Substancia	Spain	-
Choledyl	Nepera	US	-
Cholegyl	Substantia	Netherlands	-

Trade Name	Manufacturer	Country	Year Introduced
Chophyllin	Ferraton	Denmark	-
Euspirax	Ascher	W. Germany	-
Glomax	Midlands Int. Chem.	UK	-
Isoperin	Spofa	Yugoslavia	-
Monofillina	Manetti-Roberts	Italy	-
Novotriphyl	Novopharm	Canada	-
Rouphylline	Rougier	Canada	-
Sclerofillina	Medici Domus	Italy	-
Teocolina	Nessa	Spain	-
Teofilcolina	Salfa	Italy	-
Teovent	Ferrosan	Denmark	-

Raw Materials

Theophylline
Choline bicarbonate

Manufacturing Process

18 parts by weight of theophylline are added to 37.8 parts by weight of aqueous choline bicarbonate (47% assay) and the mixture stirred and heated at 80°C to 90°C until the evolution of carbon dioxide has ceased and complete solution effected. Water is separated from the reaction mixture by distillation under a vacuum sufficient to keep the still temperature between 50°C and 55 C. After about 95 parts by weight of water have been separated, about 80 parts by weight of isopropyl alcohol are added and the mixture subjected to further distillation under a vacuum sufficient to keep the mixture boiling at about 40°C. The distillation removes some of the water as an azeotrope with the isopropyl alcohol. During the removal of the water-isopropyl alcohol azeotrope a crystalline precipitate forms. The mixture is further cooled slowly to 5°C and the crystalline precipitate filtered off. The choline theophyllinate crystals are then washed with isopropyl alcohol and dried under vacuum at about 70°C. A second crop of the product may be obtained from the mother liquor by further reduction in volume and cooling. A yield of 90.5% of theory of choline theophyllinate is obtained completely free of inorganic salts.

References

Merck Index 2190
I.N. p. 228
REM p. 872
Ladenburg, K., Duesel, B.F. and Fand, T.I.; US Patent 2,776,287; January 1, 1957; assigned to Nepera Chemical Co., Inc.

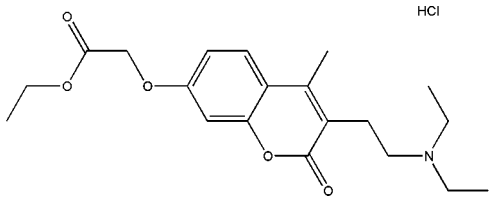
CHROMONAR HYDROCHLORIDE

Therapeutic Function: Coronary vasodilator

Chemical Name: [[3-[2-(Diethylamino)ethyl]-4-methyl-2-oxo-2H-1-benzopyran-7-yl]oxy]acetic acid ethyl ester hydrochloride

Common Name: Carbocromene

Structural Formula:



Chemical Abstracts Registry No.: 655-35-6; 804-10-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Intensain	Hoechst	Switz.	1963
Intensain	Cassella	W. Germany	1963
Intensain	Diamant	France	1966
Intensain	Pierrel	Italy	1971
Antiagor	I.S.M.	Italy	-
Beta-Intensain	Cassella	W. Germany	-
Cardiocap	Fidia	Italy	-
Cromene	Scharper	Italy	-
Intensain	Takeda	Japan	-
Intensacrom	Albert Pharma	Spain	-
Sedo-Intensain	Diamant	France	-
Intenkordin	Polfa	Poland	-

Raw Materials

Resorcinol
2-(2-Diethylaminoethyl)acetic acid ethyl ester
Bromoacetic acid ethyl ester

Manufacturing Process

18.7 g of 3β-diethylaminoethyl-4-methyl-7-hydroxy-coumarin chlorhydrate are dissolved in 200 cc methyl ethyl ketone and 18 g anhydrous potassium carbonate are added. The mixture is stirred for 1 hour at 70°C and then 12 g bromoacetic acid ethyl ester are allowed to drop in. The reaction mixture is stirred under reflux for 9 hours and then it is filtered off with suction in the heat. The filtrate is concentrated in the vacuum to dryness and the resultant

residue is dissolved in ether. The etheric solution is washed with diluted caustic soda solution for several times and, subsequently, dried with Glauber's salt. By introduction of hydrochloric acid gas into the etheric solution the reaction product is precipitated in the form of chlorhydrate. Yield: 15 g of 3β-diethylaminoethyl-4-methylcoumarin-7-ethyl oxyacetate chlorhydrate having a melting point of 154° to 156°C (= 63% of the theory).

The starting material is produced by reacting resorcinol with 2-(2-diethylaminoethyl)acetic acid ethyl ester.

References

Merck Index 2217
Kleeman and Engel p. 150
OCDS Vol. 1 p. 331 (1977)
I.N. p. 185
Ritter, H., Hanau, K., Beyerle, R. and Nitz, R.-E.; US Patent 3,282,938; November 1, 1966; assigned to Cassella Fabrwerke Mainkur AG, Germany

CHYMOPAPAIN

Therapeutic Function: Proteolytic enzyme

Chemical Name: See structure

Common Name:

Structural Formula: Chymopapain is a sulfhydryl enzyme similar to papain. Has components of molecular weight about 35,000

Chemical Abstracts Registry No.: 9001-09-06

Trade Name	Manufacturer	Country	Year Introduced
Chymodiactin	Smith	US	1982
Chemolase	Ortho-Tex	US	-
Discase	Travenol	US	-

Raw Materials

Papaya latex
Hydrochloric acid

Manufacturing Process

The undried latex of papaya is mixed with about three times its weight of hundredth normal hydrochloric acid. To this mixture is then added dilute hydrochloric acid (about normal) until a pH of substantially 2 has been

attained. The acidified latex is next allowed to stand over night or longer in a cold place (0°C to 10°C). The material still in solution is then separated out, by any convenient means, such as filtration through paper. From the soluble portion, a small amount of inert protein is precipitated, by half saturation with sodium chloride at about 10°C. The desired enzyme is next precipitated as a nearly pure protein by raising the concentration of salt to full saturation, while the pH is kept at a level of substantially 2, by the addition of normal alkali, if necessary. The precipitate of protein is removed by any suitable means, and may be kept as a thick paste out of contact with the air, and in the cold, The keeping properties at higher temperatures are enhanced by addition of enough alkali to the protein to bring its pH to 4.5-6.0.

This protein may be further purified, if desired, and eventually may be crystallized, by redissolving the paste in saturated sodium chloride solution by adjusting the pH to 4.5-6.0, and reprecipitating the enzyme protein by the gradual addition of acid in the cold, until a pH of approximately 2.0 is obtained; or, the purification may be accomplished by dissolving the protein in acid at a pH of 2, and then precipitating the enzyme, by increasing the concentration of salt.

When the activity and other properties of the several times recrystallized new enzyme protein are compared with those of the uncrystallized precipitate obtained in the first stages of the process, it is found that even in the first stages, the enzyme is present in sufficiently pure form for most purposes.

References

Merck Index 2244
PDR p. 1732
DOT 19 (7) 413 (1983) and (8) 454 (1983)
I.N. p. 229
REM p. 1036
Jansen, E.F. and Balls, A.K.; US Patent 2,313,875; March 16, 1943; assigned to Government of the USA.
Stern, I.J.; US Patent 3,558,433; January 26, 1971; assigned to Baxter Laboratories, Inc.

CICLONICATE

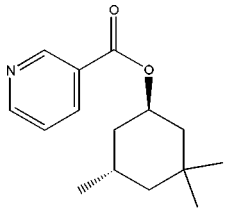
Therapeutic Function: Vasodilator

Chemical Name: 3-Pyridinecarboxylic acid 3,3,5-trimethylcyclohexyl ester

Common Name: Cyclonicate

Chemical Abstracts Registry No.: 53449-58-4

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Bled	Poli	Italy	1978
Bled	Poli	Switz.	1981
Cortofludan	Knoll	W. Germany	-
Elastan 200	Byk Liprandi	Argentina	-

Raw Materials

trans-3,3,5-Trimethylcyclohexanol
Niacin chloride hydrochloride
Sodium hydroxide

Manufacturing Process

To a solution of 142 g (1 mol) of trans-3,3,5-trimethylcyclohexanol in 400 cc of anhydrous benzene heated to 70 C is added gradually 178 g (1 mol) of niacin chloride hydrochloride. Heating is carried out under reflux conditions for 3 hours, the solution is cooled, the ester hydrochloride is filtered off and then recrystallized in an ethanol-ethyl ether mixture to obtain 227 g (80% yield) of product melting at 155°C to 157°C.

By treating the hydrochloride with an aqueous solution of NaOH at 0°C, the free base is obtained in the form of a viscous white liquid which boils at 115°C under 0.05 mm.

References

Merck Index 2249
DOT 19 (1) 12 (1983)
I.N. p.231
British Patent 1,409,990; October 15, 1975; assigned to Poli Industria Chimica S.p.A. (Italy)

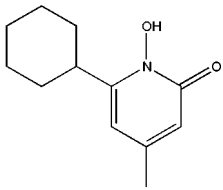
CICLOPIROX

Therapeutic Function: Antifungal

Chemical Name: 2(1H)-Pyridinone, 6-cyclohexyl-1-hydroxy-4-methyl-

Common Name: Cicloprox

Structural Formula:



Chemical Abstracts Registry No.: 29342-05-0

Trade Name	Manufacturer	Country	Year Introduced
Fungirox Esmalte	UCI-Farma	-	-
Loprox Laca	Aventis Pharma, S. A. de C. V.	-	-
Mycoster 8%	Sinbio	-	-
Mycoster 8%	Pierre Fabre	-	-
Nagel Batrafen	Aventis Pharma D	-	-
Penlac Nail Laquer	Dermik Laboratories Inc.	-	-

Raw Materials

Hexahydrobenzoyl chloride
β,β-Dimethylacrylic acid methyl ester
Hydroxylamine hydrochloride
Sodium hydroxide

Manufacturing Process

A mixture of 5-oxo-3-methyl-5-cyclohexylpentene-2 acid 1-methyl ester and 5-oxo-3-methyl-5-cyclohexylpentene-3 acid 1-methyl ester was obtained by condensation of hexahydrobenzoyl chloride with β,β-dimethylacrylic acid methyl ester. 11.2 g of this mixture and a solution of 4.6 g of sodium acetate and 4 g of hydroxylamine hydrochloride were shaken for 20 hours at 25°C with a mixture of 8 ml of water and 15 ml methanol. Subsequently, a solution of 4 g of sodium hydroxide in 8 ml of water was then added, while cooling, shaken for 1 hour at room temperature. The mixture was extracted by means of benzene and the aqueous phase was acidified to reach a pH of 6. 3.5 g of 1-hydroxy-4-methyl-6-cyclohexyl-2-pyridone were obtained; melting point 144°C.

For preparation of cyclopirox from 1-hydroxy-4-methyl-6-cyclohexyl-2-pyridone was added 2-aminoethanol (1:1).

References

Merck Index, Monograph number: 2325, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Greene L.A.; US Patent No. 5,846,984; Dec. 8, 1998; Assigned to The Trustees of Columbia University in the City of New York (New York, NY)
Lohaus G. et al.; US Patent No. 3,883,545; May 13, 1975; Assigned to Hoechst Aktiengesellschaft, Frankfurt am Main, Germany

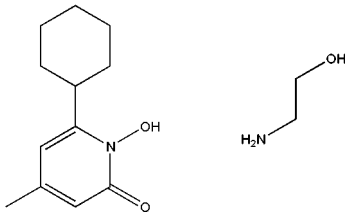
CICLOPIROXOLAMINE

Therapeutic Function: Antifungal

Chemical Name: 6-Cyclohexyl-1-hydroxy-4-methyl-2(1H)-pyridone ethanolamine salt

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 41621-49-2

Trade Name	Manufacturer	Country	Year Introduced
Batrafen	Cassella-Riedel	W. Germany	1980
Batrafen	Hoechst	Japan	1981
Loprox	Hoechst	Canada	1983
Loprox	Hoechst	US	1983

Raw Materials

4-Methyl-6-cyclohexyl-2-pyrone
Hydroxylamine hydrochloride
Ethanolamine

Manufacturing Process

Ciclopirox may be produced as follows: 2 g of 4-methyl-6-cyclohexyl-2-pyrone were heated with 1 g of hydroxylamine hydrochloride and 5 g of 2-

aminopyridine to 80 C for 8 hours.

The reaction mixture was then dissolved in methylene chloride, the amine was removed by shaking with dilute hydrochloric acid, the reaction product was extracted from the organic phase by means of dilute sodium hydroxide solution and the alkaline solution was acidified with acetic acid to a pH value of 6. The 1-hydroxy-4-cnethyl-6-cyclohexyl-2-pyridone precipitated in crystalline form. It was filtered off with suction, washed with water and dried. The yield was 1.05 g (49% of theory); melting point 143 C.

Reaction of ciclopirox with ethanolamine gives the desired product.

References

Merck Index 2250
DFU 4 (11) 795 (1979)
Kleeman and Engel p. 206
PDR p. 940
OCDS Vol. 2 p. 282 (1980)
DOT 17 (9) 364 (1981)
I.N. p. 231
REM p. 1230
Lohaus, G. and Dittmar, W.; US Patents 3,972,888; August 3, 1976; and 3,883,545; May 13, 1975; both assigned to Hoechst A.G.

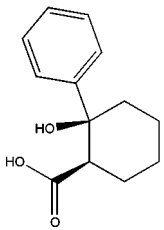
CICLOXILIC ACID

Therapeutic Function: Choleretic

Chemical Name: cis-2-Hydroxy-2-phenylcyclohexanecarboxylic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 57808-63-6

Trade Name	Manufacturer	Country	Year Introduced
Plecton	Guidotti	Italy	1975
Sintiabil	Sintyal	Argentina	-

Raw Materials

2-Hydroxymethyl cyclohexanone
Bromobenzene
Potassium permanganate
Magnesium

Manufacturing Process

25 g of 2-hydroxy-methyl-cyclohexanone, diluted in 20 cc of ether, were dropped into a vessel containing an ether suspension of phenyl-magnesium-bromide (prepared from 19.6 g of magnesium and 128 g of bromobenzene in 300 cc of ether according to usual techniques by stirring and external ice-cooling). The mixture was stirred for some time, then the magnesium compound was decomposed by pouring it carefully into water and ice; the magnesium hydroxide was dissolved in 50 cc of a saturated solution of ammonium chloride, the ether portion was separated and the aqueous portion extracted with further ether.

Collected and dried ether extracts were evaporated and the residue vacuum distilled yielded 15 g of a thick oil of boiling point at 0.1 to 0.2 mm Hg 127°C to 135°C.

This product crystallized by dissolving in ether and reprecipitation with petroleum ether yielded 7 g of 1-phenyl-2-hydroxy-ethylene-cyclohexan-1-ol, melting point (Kofler) 81°C to 83°C.

The thus obtained product was dried and finely powdered, and then suspended in 1.4 liters of an aqueous solution of 14 g of $KMnO_4$ and 7 g of N_2CO_3, and the suspension was thoroughly stirred for one day.

After filtering off the MnO_2, thus formed, a small amount of Na_2SO_3 was added until the violet coloration disappeared; MnO_2 was filtered again and the alkaline solution was acidified with concentrated HCl.

After one day standing in a refrigerator, the product was filtered and washed with water, thus yielding 5 g of 2-phenyl-2-hydroxy-cyclohexane-carboxylic acid, melting point (Kofler) 143°C to 145°C.

References

Kleeman and Engel p. 207
DOT 15 (4) 185 (1979)
I.N. p. 18
Turbanti, L.; US Patent 3,700,775; October 24, 1972

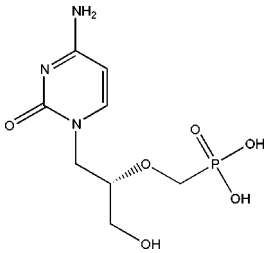
CIDOFOVIR

Therapeutic Function: Antiviral

Chemical Name: Phosphonic acid, ((2-(4-amino-2-oxo-1(2H)-pyrimidinyl)-1-(hydroxymethyl)ethoxy)methyl)-, (1S)-

Common Name: Cidofovir

Structural Formula:



Chemical Abstracts Registry No.: 113852-37-2

Trade Name	Manufacturer	Country	Year Introduced
Cidofovir	Pharmacia and Upjohn	-	-
Forvade	Gilead Sciences Inc.	-	-
Vistide	Pharmacia and Upjohn	-	-
Vistide	Gilead Sciences Inc.	-	-

Raw Materials

N-Benzoyl uracil
2-Trityloxy-oxirane
Toluene-(4-sulfomethyl)phosphonic acid diethyl ester
Hydrogen chloride
Trimethylsilyl bromide
Ammonium hydroxide

Manufacturing Process

By the alkylation of N-benzoyl uracil with the chiral 2-trityloxy-oxirane was obtained glycoside-like derivative N-[1-(2-hydroxy-3-trityloxy-propyl)-2-oxo-1,2-dihydroxypyrimidin-4-yl]-N-methylbenzamide as a single isomer. From N-[1-(2-hydroxy-3-trityloxy-propyl)-2-oxo-1,2-dihydroxypyrimidin-4-yl]-N-methylbenzamide and toluene-(4-sulfomethyl)phosphonic acid diethyl ester was prepared [2-[(benzoylmethylamino)-2-oxo-2H-pyrimidin-1-yl]-1-trityloxymethylethoxymethyl]phosphonic acid diethyl ester. As a result of

treatment of the product with hydrogen chloride was synthesized [2-[(benzoylmethylamino)-2-oxo-2H-pyrimidin-1-yl]-1-hydroxymethylethoxy-methyl]phosphonic acid diethyl ester. Sequential reaction with trimethylsilyl bromide and ammonium hydroxide cleaves the phosphite ethyl groups and saponifies the benzamide function to afford (1S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine (Cidofovir).

References

Brodfuehrer H. et al., Tetrahedron Lett., 1994, 35, 3243

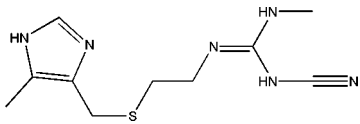
CIMETIDINE

Therapeutic Function: Antiulcer

Chemical Name: N-Cyano-N'-methyl, N''-[2-[[(5-methyl-1H-imidazol-4-yl)methyl]thio]ethyl]guanidine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 51481-61-9

Trade Name	Manufacturer	Country	Year Introduced
Tagamet	SKF	UK	1977
Tagamet	SKF	US	1977
Tagamet	SKF	France	1977
Tagamet	SKF	W. Germany	1977
Tagamet	SKF	Switz.	1977
Euroceptor	Zambon	Italy	1978
Tagamet	Fujisawa	Japan	1982
Cimetag	Cehasol	Austria	1983
Acibilin	Exa	Argentina	-
Aciloc	Orion	Finland	-
Altramet	Lek	Yugoslavia	-
Belomet	Belupo Ltd.	Yugoslavia	-
Biomag	Pulitzer	Italy	-

Trade Name	Manufacturer	Country	Year Introduced
Brumetidina	Bruschettini	Italy	-
Cimetum	Sintyal	Argentina	-
Cinamet	Isis	Yugoslavia	-
Cinulcus	Wassermann	Spain	-
Citius	Prodes	Spain	-
Civent	Medica	Finland	-
Fremet	Antibioticos	Spain	-
Gastromet	Sigurta	Italy	-
Itacem	Italchemie	Italy	-
Mansal	Vita	Spain	-
Peptol	Horner	Canada	-
Stomakon	Andromaco	Brazil	-
Tametin	Giuliani	Italy	-
Tratul	Ricar	Argentina	-
Ulcedin	Agips	Italy	-
Ulcedine	I.C.N.-Usafarma	Brazil	-
Ulcerfen	Finadiet	Argentina	-
Ulcestop	Gibipharma	Italy	-
Ulcimet	Farmasa	Brazil	-
Ulcodina	Locatelli	Italy	-
Ulcomet	Italfarmaco	Italy	-
Ulhys	Farnex	Italy	-

Raw Materials

2-Chloroacetic acid ethyl ester
Cysteamine
Dimethyl sulfate
Ammonia sodium
Methylamine
Potassium hydroxide
Carbon disulfide
Formamide
Cyanamide

Manufacturing Process

In an initial step, 2-chloroacetic acid ethyl ester is reacted with formamide to give 5-methylimidazole-4-carboxylic acid ethyl ester. Then sodium in ammonia is used to convert that to 4-hydroxymethyl-5-methylimidazole-hydrochloride. Cysteamine HCl ($HSCH_2CH_2NH_2 \cdot HCl$) is then reacted to give 4-(2-aminomethyl)-thiomethyl-5-methyl-imidazole dihydrochloride. Then N-cyanamido-5,5-dimethyl-dithio-carbonate (from cyanamid, KOH, CS_2 and $((CH_3)_2SO_4)$ is reacted to give a further intermediate which is finally reacted with methylamine to give cimetidine.

The preparation of the pyridyl analogs of the imidazolyl compounds of the type of cimetidine are discussed in the patent cited below.

Further references are given by Kleeman and Engel in the reference below.

References

Merck Index 2254
DFU 1 (1) 13 (1976)
Kleeman and Engel p. 208
PDR p. 1725
OCDS Vol. 2 p. 353 (1980)
DOT 13 (5) 187 (1977) and 16 (11) 393 (1980)
I .N p. 232
REM p.797
Durant, G.J., Emmett, J.C. and Ganellin, C.R.; US Patent 3,876,647; April 8, 1975; assigned to Smith Kline and French Laboratories Limited

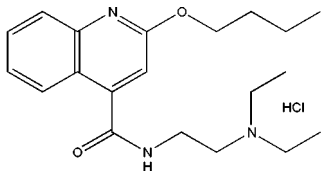
CINCHOCAINE HYDROCHLORIDE

Therapeutic Function: Local anesthetic

Chemical Name: 4-Quinolinecarboxamide, 2-butoxy-N-(2-(diethylamino)ethyl)-, hydrochloride

Common Name: Cincaini chloridum; Cinchocaine hydrochloride; Cinchocainium chloride; Cinkain; Sovcain(um); Zinchokainhydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 85-79-0

Trade Name	Manufacturer	Country	Year Introduced
Cincain	Ophtha	-	-
Dibucaine hydrochloride	Nacalai Tesque	-	-
Dibucaine hydrochloride	Sigma-Aldrich	-	-
DoloPosterine N	Dr. Kade Pharmazeutische Fabrik	-	-

Raw Materials

α-Chloro-γ-quinoline-carboxylic acid chloride

Diethylethylenediamine
Sodium
Butanol

Manufacturing Process

A benzene solution of 2.2 parts of α-chloro-γ-quinoline-carboxylic acid chloride is gradually mixed, while cooling, with 2.3 parts of unsymmetrical diethylethylenediamine. When the reaction is at an end the solution is washed with water and the new base extracted by means of hydrochloric acid. The base is precipitated by means of sodium carbonate and extracted with benzene. The solvent is distilled and the base recrystallized from petroleum ether. The α-chloro-γ-quinoline-carboxylic acid diethyl-amino-ethylene amide forms colorless lamina crystals of melting point 74°C. With acids the base forms neutral salts soluble in water.

A solution of 2.5 parts of sodium in n-butylalcohol is boiled with 30 parts of α-chloro-γ-quinoline-carboxylic acid diethyl-amino-ethylene-amide in a reflux apparatus, and when the reaction is over the excess of butylalcohol is distilled. The remaining base is taken up with ether; the solution is washed with water and dried. The solvent is then distilled. The α-n-butoxy-γ-quinoline-carboxylic acid diethyl-amino-ethylene-amide forms as colorless crystals, after recrystallization from petroleum ether melting point of it 64°C.

In practice it is usually used as hydrochloride.

References

Miescher K.; US Patent No. 1,825,623; Sep. 29, 1931; Assigned: Ferm society of chemical industry in Basle, of Basel, Switzerland

CINEPAZET MALEATE

Therapeutic Function: Antianginal

Chemical Name: 4-[1-Oxo-3-(3,4,5-trimethoxyphenyl)-2-propenyl)-1-piperazineacetic acid ethyl ester (Z)-2-butenedioate (1:1)

Common Name: Ethyl cinepazate maleate

Chemical Abstracts Registry No.: 50679-07-7; 23887-41-4 (Base)

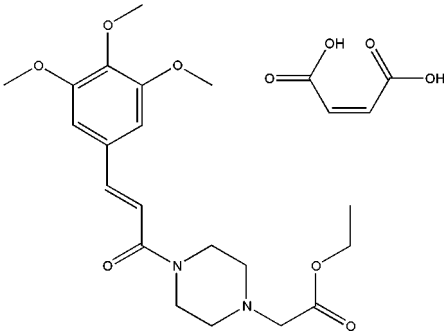
Trade Name	Manufacturer	Country	Year Introduced
Vascoril	Delalande	France	1971
Vascoril	Delalande	Italy	1974

Raw Materials

1-Piperazine ethyl acetate

Sodium bicarbonate
3,4,5-Trimethoxy cinnamoyl chloride
Maleic acid

Structural Formula:



Manufacturing Process

A solution of 1-piperazino ethyl acetate (0.2 mol) in benzene (300 ml) is treated with 3,4,5-trimethoxy cinnamoyl chloride (0.2 mol) in the presence of sodium bicarbonate (0.3 mol). After contacting for one hour at room temperature, the mixture is refluxed for a further hour. The benzene solution is then treated with an aqueous solution of sodium bicarbonate. After evaporation of the solvent, a solid product is obtained which is recrystallized from isopropyl ether. Melting point = 96°C. This base, when treated with hydrochloric acid, gives a hydrochloride having a melting point of 200°C with decomposition. By the action of maleic acid the acid maleate is obtained, having a melting point of 130°C.

References

Merck Index 2266
Kleeman and Engel p. 210
OCDS Vol. 3 p. 157 (1984)
DOT 10 (12) 336 (1974)
I.N. p. 233
Fauran, C., Huguet, G., Raynaud,G., Pourrias, B. and Turin, M.; US Patent 3,590,034; June 29, 1971; assigned to Delalande S.A. (France)

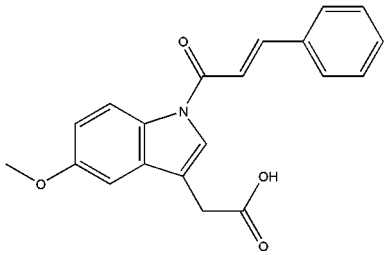
CINMETACIN

Therapeutic Function: Antiinflammatory

Chemical Name: 1H-Indole-3-acetic acid, 5-methoxy-2-methyl-1-(1-oxo-3-phenyl-2-propenyl)-

Common Name: Cinmetacin; Tsinmetatsin

Structural Formula:



Chemical Abstracts Registry No.: 20168-99-4

Trade Name	Manufacturer	Country	Year Introduced
Cindomet	Chiesi	-	-
Indolacin	Sumitomo	-	-
Indolacin	Jian An Pharmaceutical Ltd.	-	-
Indolacin	Yinduolaxin Changrong Jiaonang	-	-
Cinmetacin	Yick-Vic Chemicals and Pharmaceuticals (HK) Ltd.	-	-
Cinmetacin	North China Pharmaceutical Group Corp. (NCPC)	-	-

Raw Materials

Cinnamoyl chloride
Triethylamine
Acetonylmalonic acid
p-Methoxyphenylhydrazine hydrochloride
Hydrogen chloride

Manufacturing Process

6.0 g of cinnamoyl chloride was dropwise added to a mixture of 8.7 g of p-methoxyphenylhydrazine hydrochloride, 10.1 g of triethylamine and 200 ml of toluene under cooling at -5° to 0°C. The reaction mixture was stirred at 20°-25°C for 1 h. The separated precipitates were filtered off and dry gaseous hydrogen chloride was introduced into the filtrate. As a result a large amount of crystals of N^1-cinnamoyl-N^1-(p-methoxyphenyl)hydrazine hydrochloride were produced. These crystals were collected by filtration and washed with 20 ml of ether and dried to yield N^1-cinnamoyl-N^1-(p-methoxyphenyl)hydrazine hydrochloride of melting point 183°-185°C.

A mixture of N^1-cinnamoyl-N^1-(p-methoxyphenyl)hydrazine hydrochloride and

acetonylmalonic acid was heated in acetic acid at heating with stirring. Thereafter, the reaction mixture was allowed to cool, and was poured into cold water, and then crystals were produced. They were collected by filtration, and dried to give crude product. The recrystallization from acetone-water gave fine white needle crystals of 1-cinnamoyl-2-methyl-5-methoxy-3-indolylacetic acid, melting point 164°-165°C.

References

Yamamoto H. et al.; US Patent No. 3,576,800; April 27, 1971; Assigned: Sumitomo Chemical Company, Ltd., Osaka, Japan

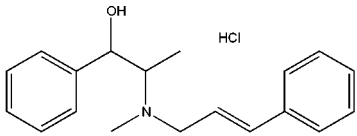
CINNAMEDRINE HYDROCHLORIDE

Therapeutic Function: Smooth muscle relaxant

Chemical Name: Benzenemethanol, α-(1-(methyl(3-phenyl-2-propenyl) amino)ethyl)-, hydrochloride

Common Name: Cinnamedrine hydrochloride; Cinnamylephedrine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 90-86-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Midol Tab	Sterling Winthrop	-	-
Midol - Caplet	Bayer Inc., Consumer Care Division	-	-

Raw Materials

1-Phenyl-2-methylaminopropanol-1
Hydrochloric acid
Cinnamylbromide
Ammonia

Manufacturing Process

8.0 g of 1-phenyl-2-methylaminopropanol-1 are dissolved in 30 ml of warm benzene and the solution is mixed with 5.0 g of cinnamylbromide. It is

allowed to stand for 2 h at room temperature; the whole is then filtered with suction to eliminate the phenylmethylaminopropanol hydrobromide formed and the filtrate is shaken out with dilute hydrochloric acid, while adding such a quantity of water that the thick oil drops which separate are dissolved. The aqueous extract is filtered until it is clear, rendered alkaline by means of ammonia, shaken with ether, the ether is distilled off, the residue is recrystalized, so 1-phenyl-2-methyl-cinnamylaminopropanol-1 was obtained.

In practice it is usually used as hydrochloride.

References

Stolz F., Flaecher F.; US Patent No. 1,959,392; May 22, 1934; Assigned: Winthrop Chemica Company, Inc., New York, N.Y., a corporation of New York

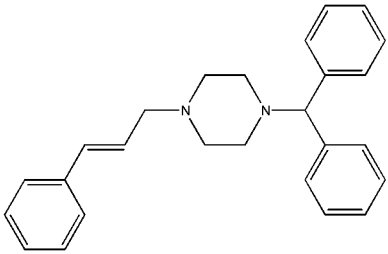
CINNARIZINE

Therapeutic Function: Antihistaminic

Chemical Name: 1-(Diphenylmethyl)-4-(3-phenyl-2-propenyl)piperazine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 298-57-7

Trade Name	Manufacturer	Country	Year Introduced
Stugeron	Janssen	UK	1961
Stutgeron	Janssen	W. Germany	1961
Midronal	Delalande	France	1962
Sturgeron	Janssen	Italy	1970
Aplactan	Janssen	Belgium	1970
Stugeron	Cilag Chemie	Switz.	1980
Amynoral	Delalande	France	-

Trade Name	Manufacturer	Country	Year Introduced
Annarizine	Sioe	Japan	-
Antigeron	Farmasa	Brazil	-
Aplactan	Eisai	Japan	-
Aplexal	Taiyo	Japan	-
Apomiterl	Teizo	Japan	-
Apotomin	Kowa	Japan	-
Apsatan	Wakamoto	Japan	-
Artate	Nippon Chemiphar	Japan	-
Carecin	Zensei	Japan	-
Cerebolan	Tobishi	Japan	-
Cerepar	Merckle	W. Germany	-
Cero-Aterin	Chassot	Switz.	-
Cinaperazine	Kinki	Japan	-
Cinazin	Siegfried	Switz.	-
Cinazyn	Italchimici	Italy	-
Cinnabene	Merckle	W. Germany	-
Cinnacet	Schwarzhaupt	W. Germany	-
Cinnageron	Streuli	Switz.	-
Cinnarizine	Green Cross	Japan	-
Cinnipirine	A.C.F.	Netherlands	-
Coldrin	JandJ	US	-
Corathiem	Ohta	Japan	-
Cysten	Tsuruhara	Japan	-
Denapol	Teikoku	Japan	-
Dismaren	Gerardo Ramon	Argentina	-
Ederal	Esteve	Spain	-
Eglen	Tatsumi	Japan	-
Folcodal	Syncro	Argentina	-
Giganten	Tropon	W. Germany	-
Glanil	Leo	Sweden	-
Hilactan	Kyoritsu	Japan	-
Hirdsyn	Fuso	Japan	-
Izaberizin	Tohu	Japan	-
Katoseran	Hishiyama	Japan	-
Midronal	Delalande	France	-
Milactan	Miwa	Japan	-
Myodel	Delalande	France	-
Olamin	Siegfried	Switz.	-
Pericephal	Hofmann	Austria	-
Plegitux	Carrion	France	-

Trade Name	Manufacturer	Country	Year Introduced
Processine	Sankyo	Japan	-
Purazine	Lennon	S. Africa	-
Razlin	S.S. Pharm	Japan	-
Ribrain	Endopharm	W. Germany	-
Roin	Maruishi	Japan	-
Salarizine	Iwaki	Japan	-
Sapratol	Takeda	Japan	-
Sedatromin	Takata	Japan	-
Sefal	Nobel	Turkey	-
Sigmal	Fuji Zoki	Japan	-
Siptazin	Isei	Japan	-
Spaderizine	Kotobuki	Japan	-
Stunarone	Abic	Israel	-
Toliman	Corvi	Italy	-
Tolesmin	Sato	Japan	-
Torizin	Towa	Japan	-

Raw Materials

Cinnamoyl chloride
Benzhydryl piperazine
Lithium aluminum hydride

Manufacturing Process

This compound can be prepared by the reaction of cinnamoyl chloride with benzhydryl piperazine. The reaction is carried out in dry benzene under reflux. The benzene is then evaporated, the residue taken up in chloroform, washed with dilute HCl and then made alkaline.

The chloroform layer is washed with a dilute aqueous sodium hydroxide solution, thereafter with water, and is finally dried over potassium carbonate. The residue, which is obtained after evaporation of the chloroform, is dissolved by heating in a mixture of 25% of toluene and 75% of heptane. On cooling this solution to about 20°C the product precipitates. That compound is reduced with $LiAlH_4$, to give cinnarizine.

References

Merck Index 2281
DFU 3 (8) 572 (1978)
Kleeman and Engel p. 272
OCDS Vol. 1 p. 58 (1977)
DOT 16 (10) 360 (1974) and 18 (1) 27 (1982)
I.N. p. 234
Janssen, P.A.J.; US Patent 2,882,271; April 14, 1959; assigned to Laboratoria Pharmaceutica Dr. C. Janssen, Belgium

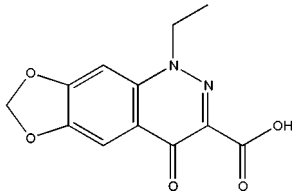
CINOXACIN

Therapeutic Function: Antibacterial

Chemical Name: 1-Ethyl-6,7-methylenedioxy-4(1H)-oxocinnoline-3-carboxylic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 28657-80-9

Trade Name	Manufacturer	Country	Year Introduced
Cinobac	Lilly	UK	1979
Cinobac	Lilly	Switz.	1979
Cinobactin	Lilly	W. Germany	1980
Cinobac	Lilly	US	1981
Cinobact	Shionogi	Japan	1983
Cinobactin	Lilly	Sweden	1983

Raw Materials

1-Ethyl-6,7-methylenedioxy-4(1H)-oxocinnoline-3-carbonitrile
Hydrogen chloride

Manufacturing Process

About 23 g (0.095 mol) of 1-ethyl-6,7-methylenedioxy-4(1H)-oxocinnoline-3-carbonitrile were added to a mixture of 200 ml of concentrated hydrochloric acid and 200 ml of acetic acid. The resultant reaction mixture was heated under reflux for 18 hours, The excess acids were removed under vacuum, and the residue was taken up in 150 ml of a 5% sodium bicarbonate solution. The resultant solution was treated with 5 g of charcoal and filtered. The filtrate was made acidic by the addition of hydrochloric acid and the resulting precipitate was removed by filtration. 23 g, representing a yield of 91.6% of 1-ethyl-6,7-methylenedioxy-4(1H)-oxocinnoline-3-carboxylic acid as light tan crystals which melted at 261°C to 262°C with decomposition were recovered.

References

Merck Index 2284
DFU 3 (1) 22 (1978)

Kleeman and Engel p. 213
PDR p. 836
OCDS Vol. 2 p. 388 (1980)
DOT 11 (10) 402 (1975) and 16 (2) 45 (1980)
I.N. p. 235
REM p. 1216
White, W.A.; US Patent 3,669,965; June 13, 1972; assigned to Eli Lilly and Company

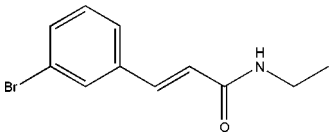
CINROMIDE

Therapeutic Function: Anticonvulsant, Antiepileptic

Chemical Name: (E)-3-(3-Bromophenyl)-N-ethyl-2-propenamide

Common Name: Cinromide; Vumide

Structural Formula:



Chemical Abstracts Registry No.: 58473-74-8

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

Raw Materials

trans-3-Bromocinnamoyl chloride
Sulfuric acid
Sodium methylate
Ethylamine
Sodium hydroxide
Molecular sieves

Manufacturing Process

3-Bromo-N-ethylcinnamamide:

I). A solution of trans-3-bromocinnamoyl chloride (12.3 g) in anhydrous toluene (150 ml) was added slowly with stirring to a solution of ethylamine (10 g) in dry ether (100 ml) at room temperature. The reaction mixture was heated at reflux for 1 hour, and the solvent and excess amine were then removed under reduced pressure. The residue was triturated with water, filtered, and recrystallized from ethanol-water to give trans-3-bromo-N-ethylcinnamamide, m.p. 89-90°C, as a white crystalline material. NMR and IR spectra as well as elemental analysis were consistent with the assigned

structure.

II). trans-m-Bromocinnamic acid (14.8 g), ethanol (173 ml) and concentrated sulfuric acid (0.4 ml) were combined and heated at reflux for 15 hours. About 150 ml of the ethanol was distilled off, and the remaining solution was poured into ice/water (140 ml). The cold mixture was made strongly alkaline with 40% sodium hydroxide and extracted with methylene chloride (4x60 ml). The combined methylene chloride extract was dried over anhydrous potassium carbonate. The potassium carbonate was removed by filtration and the solvent stripped off under reduced pressure. trans-ethyl-3-Bromocinnamate, was obtained as a partially solidified oil. (IR spectrum was consistent with this compound).

trans-Ethyl-3-bromocinnamate (8.4 g), ethylamine (6.7 g), methanol (18 ml) and 4A molecular sieves (1 g) were combined and heated at reflux for ½ hour. The mixture was cooled to about 45°C and sodium methylate (0.6 g) added. The mixture was then heated at reflux 1½ hour and then cooled. It was acidified with concentrated hydrochloric acid (12 ml). The sieves were removed by filtration. Ice water was added to the filtrate to precipitate trans 3-bromo-N-ethylcinnamamide, m.p. 89-90°C (after recrystallization from ethanol/water).

References

Grivsky Eugene M.; US Patent No. 4,041,071; August 9, 1977; Assignee to Burroughs Wellcome Co. (Research Triangle Park, NC)

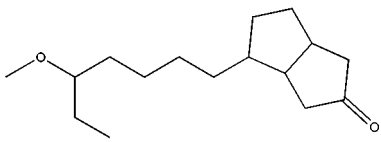
CIOTERONEL

Therapeutic Function: Antiandrogen

Chemical Name: Hexahydro-4-(5-methoxyheptyl)-2(1H)-pentalenone

Common Name: Cioteronel; Cyoctol

Structural Formula:



Chemical Abstracts Registry No.: 89672-11-7

Trade Name	Manufacturer	Country	Year Introduced
Cyoctol	Squibb	-	-
Ethocyn	Chantal Pharmaceutical Corporation	-	-

Raw Materials

Magnesium	1-Chloro-5-methoxyheptane
3-Chlorocyclopentene	Dichloroacetyl chloride
Triethylamine	Diazomethane
Potassium hydroxide	N-Methyl-N-nitroso-p-toluene sulfonamide
Acetic acid	Zinc

Manufacturing Process

3-(5-Methoxyhept-1-yl)cyclopentene:

A three-neck, round-bottomed flask containing magnesium metal turnings (7.2 g, 0.299 moles), is equipped with a Friedrich condenser and kept under a nitrogen atmosphere. Tetrahydrofuran (300 ml) is added and the contents are allowed to stir. A solution of 1-chloro-5-methoxyheptane (48.1 g, 0.292 moles) is added in small portions and refluxed. The mixture is allowed to stir for 3 hours. The resultant dark yellow solution is cooled to -25°C, and the condenser is removed and replaced with a dry ice addition funnel. A solution of 3-chlorocyclopentene (29.9 g, 0.292 moles) is added over a period of one hour. The viscous solution is poured into two liters of saturated ammonium chloride, extracted with ether, and dried over anhydrous sodium sulfate. Distillation yields 3-(5-methoxyhept-1-yl)cyclopentene (51.5 g, 0.262 moles) as clear, colorless oil boiling at about 90°C/0.3 mm and 54°C/0.1 mm.

6,6-Dichloro-2-(5-methoxyhept-1-yl)bicyclo[3.2.0]heptan-7-one:

A 1,000 ml three-neck, round-bottomed flask, containing 3-(5-methoxyhept-1-yl)cyclopentene (15.0 g, 0.076 moles) in 300 ml of hexane, is equipped with a reflux condenser. Freshly distilled dichloroacetyl chloride (35.1 g, 0.240 moles) is added and the solution stirred and heated to reflux. Triethylamine (25.2 g, 0.249 moles) in 200 ml hexane, is added dropwise to the refluxing solution and the solution allowed to stir for 4 hours. The solvent is removed and the residue distilled and chromatographically purified with silica gel, leaving the 6,6-dichloro-2-(5-methoxyhept-1-yl)bicyclo[3.2.0]heptan-7-one (17 g).

6,6-Dichloro-2-(5-methoxyhept-1-yl)bicyclo[3.3.0]octan-7-one:

6,6-Dichloro-2-(5-methoxyhept-1-yl)bicyclo[3.2.0]heptan-7-one (5 g), is dissolved in 100 ml of ether and transferred to a 500 ml, round-bottomed flask. An excess of diazomethane is generated in situ by reacting N-methyl-N-nitroso-p-toluene sulfonamide (60 g) with potassium hydroxide in ethanol. The diazomethane is allowed to react for 50 min, after which time acetic acid is added to destroy any remaining diazomethane. The solution is extracted with ether and dried over anhydrous sodium sulfate and yields the crude 6,6-dichloro-2-(5-methoxyhept-1-yl)bicyclo[3.3.0]octan-7-one as an orange oil.

2-(5-Methoxyhept-1-yl)bicyclo[3.3.0]octan-7-one:

6,6-Dichloro-2-(5-methoxyhept-1-yl)bicyclo[3.3.0]octan-7-one (45.9 g) is added to a 100 ml, round-bottomed flask fitted with a condenser. Powdered zinc metal (92 g) and glacial acetic acid (312 ml) are added to the flask and

the solution allowed to reflux for an hour. The solution is filtered to remove the zinc and zinc chloride, formed in the reaction. The product is washed with an aqueous sodium bicarbonate solution and extracted three times with ether. The ether extracts are combined and dried over anhydrous sodium sulfate. The resulting yellow oil is chromatographed on silica gel and eluted with 4:1 hexane:ether. The fractions are combined, and gave 2-(5-methoxyhept-1-yl)bicyclo[3.3.0]octan-7-one as a clear, colorless oil.

References

Kasha Walter J., Burnison; Chantal S.; US Patent No. 4,689,345; August 25, 1987; Assigned to CBD Corporation (Los Angeles, CA)

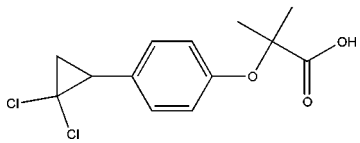
CIPROFIBRATE

Therapeutic Function: Antihyperlipidemic

Chemical Name: 2-[4-[2',2'-Dichlorocyclopropyl)phenoxy]-2-methylpropionic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 52214-83-3

Trade Name	Manufacturer	Country	Year Introduced
Lipanor	Winthrop	France	1983

Raw Materials

p-(2,2-Dichlorocyclopropyl)phenol
Acetone
Sodium hydroxide
Chloroform

Manufacturing Process

A mixture of 8 g (0.0356 mol) of p-(2,2-dichlorocyclopropyl)phenol, 11.2 g (0.28 mol) of sodium hydroxide pellets, 11 g of chloroform and 350 ml of acetone was prepared at 0°C. The cooling bath was removed, the mixture stirred for a minute and then heated on a steam bath to reflux temperature. The reaction mixture was stirred at reflux for three hours and then concentrated in vacuo. The residual gum was partitioned between dilute

hydrochloric acid and ether, and the ether layer was separated, dried and concentrated in vacuo. The residual oil (14 g) was partitioned between dilute aqueous sodium bicarbonate and ether. The sodium bicarbonate solution was acidified with concentrated hydrochloric acid and extracted with ether. The ether solution was dried over anhydrous sodium sulfate and concentrated. The residue (9.5 g of yellow oil) was crystallized twice from hexane to give 6.0 g of 2-[p-(2,2-dichlorocyclopropyl)phenoxy]-2-methyl propionic acid in the form of a pale cream-colored solid, MP 114°C to 116°C.

References

Merck Index 2286
DFU 2 (5) 297 (1977)
OCDS Vol. 3 p. 44 (1984)
I.N. p. 235
Phillips, D.K.; US Patent 3,948,973; April 6, 1976; assigned to Sterling Drug, Inc.

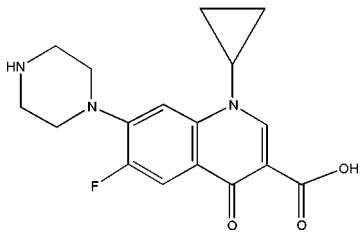
CIPROFLOXACIN

Therapeutic Function: Antibiotic

Chemical Name: 1-Cyclopropyl-6-fluoro-4-oxo-7-(1-piperazinyl)-1,4-dihydro-3-quinolinecarboxylic acid

Common Name: Ciprofloxacin

Structural Formula:



Chemical Abstracts Registry No.: 85721-33-1

Trade Name	Manufacturer	Country	Year Introduced
Alcipro	Alkem Laboratories Ltd.	India	-
Aquacipro	Aquarius Enterprises	India	-
Cipro	Bayer Pharma	-	-
Ciprobay	Bayer Pharma	Germany	-

Trade Name	Manufacturer	Country	Year Introduced
Ciprofloxacin	Natur Produkt Europe B.V.	Netherlands	-
Ciprofloxacin	Balkanpharma-Dupnitza AD	Bulgaria	-
Ciflocin	Deva Holding	Turkey	-
Cifloxinal	Pro. Med. CS Praha a.s.	Czech Republic	-
Citeral	Alkaloid	Macedonia	-
Ificipro	Unique	India	-
Lyproquin	Lyka Labs	India	-
Microflox	Micronova Pharmaceuticals	India	-
Quintor	Torrent	India	-
Vero-Ciprofloxacin	Okasa Pharma	Japan	-

Raw Materials

Cyclopropyl-6-fluoro-4-oxo-7-(1-piperazinyl)-1,4-dihydro-3-quinolinecarboxylic acid
Piperazine

Manufacturing Process

Cyclopropyl-6-fluoro-4-oxo-7-(1-piperazinyl)-1,4-dihydro-3-quinolinecarboxylic acid was synthesized by heating of a mixture of 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-quinolin-3-carboxylic acid and 30.1 g dry piperazine in 100 ml DMSO for 2 hours at 135-140°C. DMSO was evaporated in high vacuum. The residue was heated with 100 ml of water, and was dried over $CaCl_2$ in vacuum. Cyclopropyl-6-fluoro-4-oxo-7-(1-piperazinyl)-1,4-dihydro-3-quinolinecarboxylic acid obtained has a temperature of decomposition 255-257°C.

References

Grohe K. et al.; EP 0078362; 29.10.82; Assigned to BAYER AG European Patent Application 49,355 and German Patent Application 3,142,854

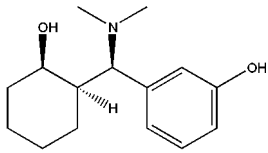
CIRAMADOL

Therapeutic Function: Analgesic

Chemical Name: [1R-[1α-(R*),2α]]-3-[(Dimethylamino)(2-hydroxycyclohexyl)methyl]phenol

Common Name: Ciradol; Ciramadol

Structural Formula:



Chemical Abstracts Registry No.: 63269-31-8

Trade Name	Manufacturer	Country	Year Introduced
Ciramadol	American Home Products (AHP)	-	-
Ciramadol	Wyeth	-	-

Raw Materials

m-Methoxymethoxybenzaldehyde
Potassium hydroxide
Lithium aluminum hydride
Hydrochloric acid
Cyclohexanone
Dimethylamine
Sodium hydroxide

Manufacturing Process

m-Methoxymethoxybenzaldehyde (167 g, 1.0 mole) and cyclohexanone (318 ml, 3.0 moles) were refluxed for 4 hours under nitrogen with a solution of potassium hydroxide (50 g, 0.89 moles) in water (1 liter). After cooling the oily layer was extracted with ether (twice). The ether solution was washed with water (thrice), brine, dried (sodium sulfate), and evaporated. The residue was distilled and the product obtained as a yellow oil (132 g.), boiling point of m-methoxymethoxybenzalcyclohexanone 173-176°C at 0.3 mm, λ_{max} 287 nm (ethanol, ε 13,000).

A solution of m-methoxybenzalcyclohexanone (50 g) in ether (50 ml) was cooled to -5°C in a pressure bottle and treated with 20 ml dimethylamine. The bottle was stoppered and left at room temperature during 60 hours. The above reaction was performed in duplicate (IR monitoring indicates the mixture attains an equilibrium concentration in which the β-dimethylamino ketone addition product is favored over the m-methoxybenzalcyclohexanone by a ratio of ca. 2:1). the combined total reaction mixtures were added dropwise under nitrogen to a stirred suspension of $LiAlH_4$ (20 g) in ether (1.2 liters) and the mixture was refluxed during 4 hours. The ice cooled reaction mixture was treated with 3% aqueous sodium hydroxide solution (100 ml) and filtered. The precipitated solids were washed with boiling ether and the combined filtrates evaporated to approximately 1 liter. The ether layer was extracted (twice) with an excess of dilute hydrochloric acid followed by a water extraction. The combined aqueous extracts were back extracted with ether, basified with 50% sodium hydroxide solution and extracted with ether (twice). The ether layers were washed with brine and evaporated to an oil (50 g) to give a mixture containing predominantly (96%) of two components. 32 g of the residue were chromatographed on a Woelm alumina column (900 g

neutral activity Grade III), built in benzene-hexane (1:1). Benzene-hexane fractions (1:1 and 2:1) eluted the major component trans-2-(α-dimethylamino-m-methoxybenzyl)cyclohexanol (20 g).

Cis-2-[α-dimethylamino-m-(methoxymethoxy)benzyl] cyclohexanol (10 g) in ether was treated with a slight excess of isopropanolic hydrogen chloride. The gummy solid which crystallized on trituration with boiling ether-acetone was recrystallized first from ethanol-ether and finally from methanol-acetone to give the cis-2-(α-dimethylamino-m-hydroxybenzyl)cyclohexanol, hydrochloride, melting point 263-265°C; $[\alpha]_D^{25}$ = -15.3° (methanol).

References

Yardley John P., Russel; Peter B.; US Patent No. 4,017,637; April 12, 1977; Assigned to American Home Products Corporation (New York, NY)

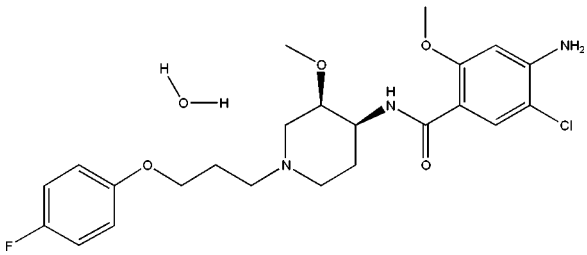
CISAPRIDE MONOHYDRATE

Therapeutic Function: Gastrointestinal drug

Chemical Name: Benzamide, 4-amino-5-chloro-N-(1-(3-(4-fluorophenoxy) propyl)-3-methoxy-4-piperidinyl)-2-methoxy-, monohydrate, cis-

Common Name: Cisapride

Structural Formula:



Chemical Abstracts Registry No.: 81098-60-4

Trade Name	Manufacturer	Country	Year Introduced
Cisapride	Janssen-Cilag	-	-
Cisapride	Manav Drugs Pvt. Ltd.	India	-
Peristal	Mustafa Nevzat	Turkey	-
Prepulsid	Janssen-Ortho Inc.	Canada	-
Propulsid	Janssen	-	-
Propulsid Quicksolv	Jansssen	-	-

Raw Materials

1-[3-(4-Fluorophenoxy)-propyl]-3-methoxy-4-piperidinone
Hydrogen
4-Amino-5-chloro-2-methoxybenzoic acid
Benzylamine
Palladium on charcoal
Nitric acid
Ethyl chloroformate

Manufacturing Process

A mixture of 1-[3-(4-fluorophenoxy)-propyl]-3-methoxy-4-piperidinone (140 mg), benzylamine (61 mg), Pd 10% on charcoal (100 mg) and a 0.02% solution of thiophene in THF was reacted under hydrogen gas for 3 hours at 50°C. The catalyst was filtered off and fresh palladium 10% on charcoal (100 mg) was added. Debenzylation of the formed intermediate took place under hydrogen atmosphere for 18 hours at 50°C. The reaction mixture was filtered and evaporated under a stream of nitrogen to yield 1-[3-(4-fluorophenoxy)-propyl]-3-methoxy-4-piperidinamine having a cis/trans ratio of about 93/7.

1-[3-(4-Fluorophenoxy)-propyl]-3-methoxy-4-piperidinamine (50 g) was dissolved in methyl isobutylketone (250 ml) and a nitric acid solution (65%, 12.8 ml) was carefully added so that the temperature of the solution did not exceed 45°C. The reaction mixture was stirred at a temperature of 30°C and seeded. When crystallisation started, the reaction mixture was cooled to 0°C and stirred for another 2 hours. The product was filtered off, washed with a small amount of toluene and dried, yielding 1-[3-(4-fluorophenoxy)-propyl]-3-methoxy-4-piperidinamine nitrate (m.p. 60°C).

1-[3-(4-Fluorophenoxy)-propyl]-3-methoxy-4-piperidinamine nitrate was dissolved in water (95 ml). The reaction mixture was stirred and toluene (95 ml) was added. A NaOH solution (50%, 10.3 ml) was slowly added and the temperature of the reaction mixture was raised to 75°C. After 30 min, the aqueous layer was discarded and the organic layer was evaporated, yielding 1-[3-(4-fluorophenoxy)-propyl]-3-methoxy-4-piperidinamine having a cis/trans ratio equal to or higher than 98/2.

To a solution of 4-amino-5-chloro-2-methoxybenzoic acid (20.2 g) in methyl isobutylketone (250 ml) and triethyl amine (15.3 ml) was slowly dropped ethyl chloroformate (9.6 ml). The reaction mixture was stirred for 30 min at room temperature. To the formed mixed anhydride was then added 1-[3-(4-fluorophenoxy)-propyl]-3-methoxy-4-piperidinamine (28.2 g) and the reaction mixture was stirred for 2 hours at room temperature. Subsequently, the reaction mixture was washed with water (80 ml) and a NaOH solution (6.5% w/v, 50 ml). The organic layer was warmed to 65°C and methanol (50 ml) and water (8.5 ml) were added. The solution was cooled slowly and stirred for 2 days during which crystallisation occurred, yielding benzamide, 4-amino-5-chloro-N-(1-(3-(4-fluorophenoxy)propyl)-3-methoxy-4-piperidinyl)-2-methoxy-, monohydrate, cis- (Cisapride) having a cis/trans ratio higher than 99/1.

References

Lu Y.-F. et al.; US Patent No. 5,585,387; 12.17.1996; Assigned: Torcan Chemical Ltd.
De Knaep A.G.M.,Moens L.J.R.; US Patent No. 6,218,542; 04.17.2001; Assigned: Jenssen Pharmaceutica

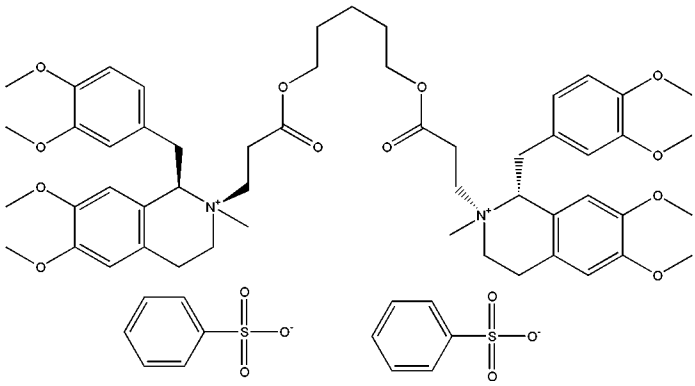
CISATRACURIUM BESYLATE

Therapeutic Function: Neuromuscular blocker

Chemical Name: Isoquinolinium, 2,2'-(1,5-pentanediylbis(oxy(3-oxo-3,1-propanediyl)))bis(1-((3,4-dimethoxyphenyl)methyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-, (1R,1'R,2R,2'R)-, dibenzenesulfonate

Common Name: Cistracurium besylate

Structural Formula:



Chemical Abstracts Registry No.: 96946-42-8

Trade Name	Manufacturer	Country	Year Introduced
Nimbex	GlaxoWellcome	-	-
Nimbex	GlaxoSmithKline	UK	-
Nimbex	DSM Catalytica Pharmaceuticals, Inc.	US	-

Raw Materials

Acryloyl chloride
Pentane-1,5-diol
Oxalic acid
Tetrahydropapaverine
Pyrogallol
Triethylamine

Manufacturing Process

Acryloyl chloride (0.2 mole) in dry benzene (60 ml) was added over 0.5 hour to pentane-1,5-diol (0.1 mole), triehylamine (0.2 mole) and pyrogallol (0.1 g) in dry benzene (100 ml). Further dry benzene (100 ml) was added followed by triehylamine (10 ml), and the mixture stirred at 50°C for 0.5 hour. The triehylamine hydrochloride was filtered off and the solvent removed in vacuo to leave yellow oil which was distilled in the presence of a trace of p-methoxyphenol, excluding light, to give 1,5-pentamethylene diacrylate (12.9

g, 61%, b.p. 90-95°C/0.01 mm Hg).

A solution of tetrahydropapaverine (4.43 g) and 1,5-pentamethylene diacrylate (1.30 g) in dry benzene (15 ml) was stirred under reflux for 48 hours, excluding light. The solvent was removed in vacuo and the residual pale red oil dissolved in chloroform (10 ml). Addition of ether (ca. 400 ml), followed by saturated ethereal oxalic acid solution (ca. 500 ml) gave a flocculent white precipitate, which was filtered off, washed with ether and dried. Crystallization (twice) from ethanol gave N,N'-4,10-dioxa-3,11-dioxodecylene-1,13-bis-tetrahydropapaverine dioxalate as a white powder (3.5 g, 51%, m.p. 117-121°C).

The free base N,N'-4,10-dioxa-3,11-dioxodecylene-1,13-bis-tetrahydropapaverine was obtained by basifying an aqueous solution of the dioxalate with sodium bicarbonate solution, followed by extraction with toluene and evaporation of the solvent, to give a colorless viscous oil.

Scrupulously dried base in spectroscopically pure acetonitrile was treated with benzenesulfonic acid at room temperature for 22 hours. The filtered reaction mixture was added dropwise to dry ether (ca. 450 ml). The flocculent white precipitate was filtered off, washed with dry ether, and dried in vacuo over P_2O_5 at 50°C to yield N,N'-4,10-dioxa-3,11-dioxodecylene-1,13-bis-tetrahydropapaverine dimesylate, a white powder with m.p. 104-112°C.

References

Stenlake J.B. et al., US Patent No. 4,179,507; 12.18.1979; Assigned to Burroughs Wellcome Co.
Chamberlin St.A. et al.; US Patent No. 5,684,154; 11.04.1977; Assigned to Abbot Laboratories

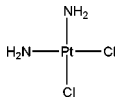
CISPLATIN

Therapeutic Function: Antitumor

Chemical Name: Platinum, diamminedichloro-, (SP-4-2)-

Common Name: Cisplatin

Structural Formula:



Chemical Abstracts Registry No.: 15663-27-1

Trade Name	Manufacturer	Country	Year Introduced
Blastolem	Lemery	Mexico	-
Cisplatin	Teva	Israel	-
Cisplatin	Laboratoires Thissen	Belgium	-
Cisplatin	Yunnan Gejiu Biochemical Pharmaceutical Factory	China	-
Cisplatin	Choongwae Pharma Corporation	Korea	-
Cisplatin	Pharmacia and Upjohn	Australia	-
Cisplatin	Serum Institute of India	India	-
Cisplatin-Ebewe	Ebewe	Austria	-
Cisplatin-Teva	Pharmachemie	Netherlands	-
Cisplatyl	Rhone-Poulenc Rorer	France	-
Citoplatin	Cipla Limited	India	-
Kemoplat	Dabur Pharmaceuticals Ltd.	India	-
Platamine	Pharmacia and Upjohn	Italy	-
Platidiam	Lachema	Czech Republic	-
Platinol	Bristol-Myers Squibb	Italy	-
Vero-Cisplatin	Okasa Pharma	Japan	-

Raw Materials

Potassium hexachlorplatinate
Potassium iodide
Hydrazine
Ammonium hydroxide

Manufacturing Process

The synthesis proceeds dy reduction of potassium hexachlorplatinate with hydrazine to give potassium tetrachloroplatinate. This is converted to potassium tetraiodoplatinate by treatment with potassium iodide and then reacted with 6 M ammonium hydroxide to give crystals of cisplatin.

References

Kauffman G.B., Cowan D.O., Inorg. Synth., 7, 239 (1969)
Kaplan M.A., Granatek A.P.; US Patent No. 4,322,391; Mar. 30, 1982; Assigned to Bristol-Myers Company, N.Y.

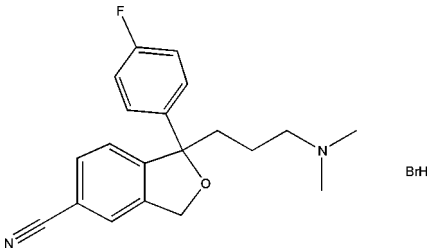
CITALOPRAM HYDROBROMIDE

Therapeutic Function: Antidepressant

Chemical Name: 5-Isobenzofurancarbonitrile, 1-(3-(dimethylamino)propyl)-1-(4-fluorophenyl)-1,3-dihydro-, monohydrobromide

Common Name: Citalopram hydrobromide; Nitalapram hydrobromide

Structural Formula:



Chemical Abstracts Registry No.: 59729-32-7

Trade Name	Manufacturer	Country	Year Introduced
Celexa	Lundbeck, Forest Laboratories Inc.	-	-
Celica	Solus	India	-
Cipramil	Lundbeck	Denmark	-
Seropram	Lundbeck	Switz.	-

Raw Materials

5-Bromo-1-(4-fluorophenyl)-1-(3-dimethylaminopropyl)-1,3-dihydroisobenzofuran
Magnesium
Butyl lithium
tert-Butyl methyl ether
Isopropylmagnesium chloride
Thionyl chloride
Sulfamide
Dry ice

Manufacturing Process

5-Carboxy-1-(4-fluorophenyl)-1-(3-dimethylaminopropyl)-1,3-dihydroisobenzofuranwas synthesized by three methods:

1. A solution of 1-(4-fluorophenyl)-1-(3-dimethylaminopropyl)-1,3-dihydro-isobenzofuran-5-yl magnesium bromide in dry THF (90 mL) (prepared by ordinary methods from 5-bromo-1-(4-fluorophenyl)-1-(3-

dimethylaminopropyl)-1,3-dihydro-isobenzofuran (9 g, 0.024 mole) and magnesium (0.73 g, 0.03 mole)) was added to dry solid CO_2 (50 g). After addition, the mixture was left at room temperature for 16 hours. The volatile materials were removed in vacuo and the residue was taken up in water (100 mL). pH was adjusted to 5.5 by adding HCl (aqueous, 4 N). The aqueous phase was extracted with toluene (100 mL). The toluene was removed in vacuo and the 5-carboxy-1-(4-fluorophenyl)-1-(3-dimethylaminopropyl)-1,3-dihydroisobenzofuran was obtained as oil. Yield 6 g.

2. To a solution of 5-bromo-1-(4-fluorophenyl)-1-(3-dimethylaminopropyl)-1,3-dihydroisobenzofuran (9 g, 0.024 mole) in tertbutyl methyl ether (150 mL) was added n-BuLi (1.6 M in hexanes, 40 mL) at -78 to -65°C. The temperature of the solution was allowed to raise to -30°C over a period of 2 hours. The reaction mixture was added to dry solid CO_2 (50 g). After addition, the mixture was left at room temperature for 16 hours. The volatile materials were removed in vacuo and the residue was taken up in water (100 mL). pH was adjusted to 5.5 by adding HCl (aqueous, 4 N). The aqueous phase was extracted with toluene (100 mL). The toluene was removed in vacuo and the 5-carboxy-1-(4-fluorophenyl)-1-(3-dimethylaminopropyl)-1,3-dihydroisobenzofuran was obtained as an oil. Yield 7.5 g.

3. n-BuLi (20 mL, 1.6 M in hexane) was added to a solution of isopropylmagnesium chloride (8.0 mL, 2 M in diethyl ether) in THF (25 mL) at 0°C. The resulting mixture was stirred at 0°C for 1 h, then cooled to -78°C and a solution of 5-bromo-1-(4-fluorophenyl)-1-(3-dimethylaminopropyl)-1,3-dihydro-isobenzofuran (5.0 g, 13.0 mmol) in THF (25 mL) was added. The mixture was allowed to warm to -10°C during 1 h, then cooled again to -78°C and CO_2 (5.7 g, 130 mmol) was added. The mixture was allowed to warm to room temperature, and then evaporated. Ion exchange chromatography of the residue (Dowex RTM-50, acidic form) eluting with 1 M NH_3 afforded the 5-carboxy-1-(4-fluorophenyl)-1-(3-dimethylaminopropyl)-1,3-dihydroisobenzofuran as a thick oil.

5-Carboxy-1-(4-fluorophenyl)-1-(3-dimethylaminopropyl)-1,3-dihydroisobenzofuran (5 g, 0.015 mole) and sulfamide (1.65 g, 0.017 mole) were dissolved in sulfolane (15 mL). Thionyl chloride (2.25 g, 0.019 mole) was added at room temperature and the temperature of the reaction mixture was raised to 130°C for 2 hours. The reaction mixture was allowed to cool to 75°C and water (25 mL) was added. The temperature was held at 75°C for 15 min, and then the reaction mixture was cooled to room temperature. pH was ajusted to 9 with ammonium hydroxide and then n-heptane (75 mL) was added. The temperature was raised to 70°C and the hot n-heptane layer was isolated from which the 5-cyano-1-(4-fluorophenyl)-1-(3-dimethylaminopropyl)-1,3-dihydroisobenzofuran (Citalopram, free base) crystallised on cooling. Yield 3.77 g. Purity (HPLC peak area) >97%.

The hydrobromide was prepared in conventional manner and crystallized from isopropanol; melting point 148-150°C.

References

Bogese K.,Toft A.S.; US Patent No. 4,136,193; 01.23.1979; Assigned to Kefalas A/S, Denmark

Petersen H.,Ahmadian H.; US Patent No. 6,426,422; 07.30.2002; Assigned to H. Lundbeck A/S, Denmark

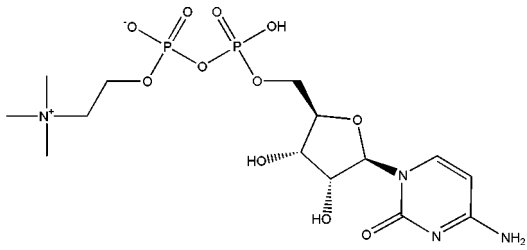
CITICOLINE

Therapeutic Function: Cerebral circulation stimulant

Chemical Name: Cytidine 5'-(trihydrogen diphosphate)mono[2-(trimethylammonio)ethyl]ester hydroxide inner salt

Common Name: Citidoline; Cytidine diphosphate choline

Structural Formula:



Chemical Abstracts Registry No.: 987-78-0

Trade Name	Manufacturer	Country	Year Introduced
Nicholin	Cyanamid	Italy	1971
Rexort	Cassenne	France	1977
Alaton	Zambon	Italy	-
Andes	Nippon Kayaku, Co.	Japan	-
Brassel	Alfa Farm.	Italy	-
CDP-Choline	Kowa	Japan	-
Cereb	Ohta	Japan	-
Ceregut	Kodama	Japan	-
Cidifos	Neopharmed	Italy	-
Colite	Nippon Chemiphar	Japan	-
Corenalin	Kaken	Japan	-
Cyscholin	Kanto	Japan	-
Daicoline	Daisan	Japan	-
Difosfocin	Magis	Italy	-
Emicholine	Dojin	Japan	-
Emilian	Beppu	Japan	-
Ensign	Yamanouchi	Japan	-
Erholen	Nichiiko	Japan	-

Trade Name	Manufacturer	Country	Year Introduced
Haibrain	Ono	Japan	-
Haocolin	Fuso	Japan	-
Hornbest	Hoei	Japan	-
Intelon	Takata	Japan	-
Meibis	Sanken	Japan	-
Neucolis	Nippon Shinyaku	Japan	-
Nicholin	Takeda	Japan	-
Niticolin	Morishita	Japan	-
Plube	Mochida	Japan	-
Recognan	Toyo Jozo	Japan	-
Rupis	Vitacain	Japan	-
Sauran	Abello	Spain	-
Sinkron	Ripari-Gero	Italy	-
Sintoclar	Pulitzer	Italy	-
Somazina	Ferrer	Spain	-
Startonyl	Cyanamid	-	-
Suncholin	Mohan	Japan	-

Raw Materials

Cytidine-5'-monophosphate
Choline
Brevibacterium ammoniagenes

Manufacturing Process

A 250 ml conical flask containing 30 ml of a reaction liquor (pH 7.0) having a composition of 7.38 mg/ml of disodium salt of CMP (cytidine-5'-monophosphate), 24 mg/ml of choline, 10 mg/ml of glucose, 100 mg/ml of acetone-dried cells of Brevibacterium ammoniagenes ATCC 6872, 11.6 mg/ml of monopotassium phosphate, 20 mg/ml of dipotassium phosphate and 2.96 mg/ml of magnesium sulfate, ($MgSO_4 \cdot 7H_2O$), was subjected to culturing at 30°C for 4 hours. Cytidine diphosphate choline was formed and accumulated at a concentration of 3.8 mg/ml in the culture liquor.

The pH of 1.2 liters of filtrate containing 3.8 mg/ml of cytidine diphosphate choline, obtained by removing solid matters from the culturing liquor, was adjusted to a pH of 8.5 with a 0.5 N KOH solution. The filtrate was passed through a column of strongly basic anion exchange resin, Dowex 1 x 2 (formic acid type). After washing the resin with water, a formic acid solution was passed through the column with gradual increase in the concentration of formic acid (until 0.04 N max.). A fraction of cytidine diphosphate choline was collected by elution according to the so-called gradient elution method and absorbed onto carbon powders. Then, elution was effected with acetone, and the eluate was concentrated and dried. 1.3 g of cytidine diphosphate choline powders were obtained.

References

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Kleeman and Engel p. 214
DOT 4 (2) 68 (1968)
I.N. p. 237
Nakayama, K. and Hagino, H.; US Patent 3,684,652; August 15, 1972; assigned to Kyowa Hakko Kogyo Co., Ltd. (Japan)
Nakamachi, H., Kamiya, K. and Nishikawa, M.; US Patent 3,687,932; August 29, 1972; assigned to Takeda Chemical Industries, Ltd. (Japan)

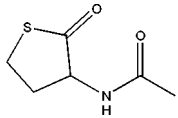
CITIOLONE

Therapeutic Function: Hepatoprotectant

Chemical Name: 2-Acetamido-4-mercaptobutyric acid γ-lactone

Common Name: Acetylhomocystein thiolactone; Acetamido thiobutyrolactone

Structural Formula:



Chemical Abstracts Registry No.: 1195-16-0

Trade Name	Manufacturer	Country	Year Introduced
Citiolase	Roussel Maestretti	France	1970
Thioxidrene	Bottu	France	1972
Citiolase	Roussel Maestretti	Italy	1976
Mucorex	Berenguer-Beneyto	Spain	-
Reducdyn	Nordmark	W. Germany	-
Sitilon	Roussel	-	-
Thioncycline	Merrell	France	-

Raw Materials

Acetyl methionine
Ammonia sodium
Hydrogen chloride

Manufacturing Process

12.73 kg of acetyl methionine are gradually introduced into a brine-cooled

pressure-tight apparatus provided with a stirrer and containing 140 liters of liquid ammonia at -50°C. The amino acid is dissolved after a short time; 6.5 kg of sodium metal are then introduced over a period of from 4 to 5 hours at a temperature of from -40°C to 60°C. Eventually, a persistent blue coloration of the ammoniacal solution indicates the end of the reaction. The ammonia is distilled off and the residue is taken up in 70 liters of methanol. In order to remove ammonia which has been formed from sodium amide, 30 to 40 liters of methanol are distilled off and the residue is made up with methanol to 80 liters. The strongly alkaline solution is neutralized with 22 liters of concentrated aqueous hydrochloric acid. The solution is filtered off from the precipitated sodium chloride and evaporated to dryness in vacuo. The closing of the thiolactone ring takes place as a result of the evaporation of the solution to dryness in the acid pH range and the N-acetyl homocystein originally present is converted into N-acetyl homocystein thiolactone. In order to isolate this compound, the residue is recrystallized from 25% aqueous alcohol.

9 kg of N-acetyl homocystein thiolactone are obtained, this corresponding to a yield of 85% of the theoretical.

References

Merck Index 2291
Kleeman and Engel p. 215
DOT 7 (1) 14 (1971)
I.N. p. 237
British Patent 955,231; April 15, 1964; assigned to Deutsche Gold-und Silber-Scheideanstalt Vormals Roessler (Germany)

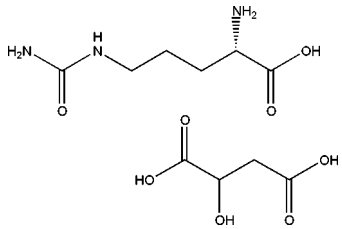
CITRULLINE MALATE

Therapeutic Function: Stimulant, Detoxicant

Chemical Name: L-Ornithine, N5-(aminocarbonyl)-, mono(+-)-hydroxybutanedioate

Common Name: Citrulline malate

Structural Formula:



Chemical Abstracts Registry No.: 70796-17-7; 372-75-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
StaminO2	ErgoPharm	-	-
Citrulline malate	Sinochem Qingdao	-	-
Dynergum	Sanobia	-	-
Dynergum	Laboratoires Biocodex Biodiphar N.V.	-	-
Stimol	Biocodex	-	-
Stimufor	Vifor SA	-	-

Raw Materials

L-Arginine hydrochloride
Copper oxide
Sodium hydroxide
Hydrogen sulfide

Manufacturing Process

Citrulline is obtained as a result of a reaction of L-arginine hydrochloride with sodium hydroxide, copper oxide and hydrogen sulfide.

In practice it is usually used as malate salt.

References

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

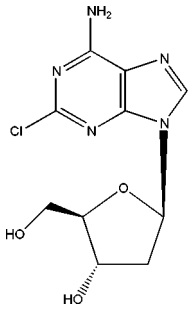
CLADRIBINE

Therapeutic Function: Cytostatic

Chemical Name: Adenosine, 2-chloro-2'-deoxy-

Common Name: 2-Chlorodeoxyadenosine; Cladaribine; Cladribine

Structural Formula:



Chemical Abstracts Registry No.: 4291-63-8; 24757-90-2

Trade Name	Manufacturer	Country	Year Introduced
Cladribine	Janssen-Cilag	-	-
Leukeran	GlaxoSmithKline	-	-
Leustatin	Ortho Biotech. Inc.	-	-

Raw Materials

Guanosine
Pyridine
N,N-Dimethylaniline
n-Pentyl nitrite
Phenyl chlorothionoformate
4-Dimethylaminopyridine
Tri-n-butyltin hydride
Acetic anhydride
Tetraethylammonium chloride
Phosphorous oxychloride
Triphenylmethyl chloride
1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane
Azobisisobutyronitrile

Manufacturing Process

Preparation of 2',3',5'-O-triacetyl guanosine

A mixture of guanosine (355 g, 1.25 M), acetic anhydride (0.750 L), pyridine (0.375 L) and dimethylformamide (1 L) is stirred at room temperature for 2 hours and then heated at 75°C for 4 hours. After the heating, the mixture is cooled to room temperature and stirred overnight. Most of the solvent is then removed by vacuum distillation at 45°C to yield a white precipitate. The solid is isolated by filtration and washed with isopropanol. The solid is suspended in isopropanol, and heated to reflux whereupon most of the solid dissolves. The isopropanol is then allowed to cool to room temperature, and filtered to yield a white solid that is dried overnight in a vacuum oven at 60°C to yield the title compound (358 g, 69.8%).

Preparation of 9-(2',3',5'-O-triacetyl-β-D-ribofuranosyl)-2-amino-6-chloropurine

A mixture of 2',3',5'-O-triacetyl guanosine (480 g, 1.17 M), N,N-dimethylaniline (150 mL), tetraethylammonium chloride (386.4 g) and acetonitrile (0.70 L) is prepared, and then phosphorous oxychloride (400 mL) is added slowly (dropwise) over 3 hours at room temperature under a N_2 atmosphere. After the addition, the mixture is heated at 100°C for 14 minutes, and then cooled to room temperature. Most of the solvent is removed in vacuo to yield a red oil. The oil is treated with methylene chloride (2 L), and then poured into ice water (1.5 L). The organic layer is separated and the aqueous layer extracted with CH_2Cl_2 (3x500 mL). The separated organic layer and the organic extracts are combined, washed with a saturated sodium bicarbonate solution until a pH of 6 to 7 is reached, and then washed with ice-water (2 times 1 L). The organic layer is dried over sodium sulfate, and the solvent removed in vacuo to yield a thick oil. The oil is treated with isopropanol (200 mL), stirred at 45°C for 1 hour, allowed to cool to room temperature, and left overnight whereupon a precipitate is formed. The precipitate is isolated by filtering and then the precipitate is washed with cold isopropanol to yield the title compound (235 g, 47%).

Preparation of 9-(2',3',5'-O-triacetyl-β-D-ribofuranosyl)-2,6-dichloropurine

n-Pentyl nitrite (98 g, 838 mM) is added over one hour at room temperature under nitrogen to a mixture of the above purine compound (350 g, 819 mM), triphenylmethyl chloride (500 g, 1.79 M) and potassium carbonate (65 g) in CH_2Cl_2 (3 L). The resulting mixture is heated at reflux for 20 minutes, cooled to room temperature and filtered. The filtrate is concentrated in vacuo, and the resulting residue is purified by column chromatography on silica gel (2.5 kg, ethyl acetate/hexane 1:4-3:7) to yield the title compound as a pale yellow solid (272 g, 74%).

Preparation of 2-chloroadenosine

A mixture of 9-(2',3',5'-O-triacetyl-β-D-ribofuranosyl)-2,6-dichloropurine (271 g, 0.606 M), concentrated ammonium hydroxide (4 L) and tetrahydrofuran (0.5 L) is stirred at room temperature under nitrogen for 4 days. The solvent volume is reduced in vacuo and the resulting residue is triturated with absolute ethanol. The title compound is precipitated out of the ethanolic solvent to yield a light brown solid, (159 g, 87%).

Preparation of 2-chloro-(3',5'-O-tetraisopropyldisiloxyl)adenosine

A mixture of 2-chloroadenosine (13 g, 43 mM), 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (15 g, 47.6 mM) and pyridine (150 mL) is stirred at room temperature under nitrogen for 3 hours. The solvent volume is reduced in vacuo and the resulting residue is dissolved in CH_2Cl_2 (250 mL), washed with a saturated copper sulfate solution (2x150 mL) and dried with sodium sulfate. The organic layer is concentrated in vacuo and purified by column chromatography on silica gel (200 g) with ethyl acetate/hexane (1:1) to yield the title compound as a white powder (14.7 g, 63%, MP 198-200°C). NMR, IR and elemental analysis are confirmed the structure of the title compound.

Preparation of 2-chloro-2'-O-phenoxythiocarbonyl-(3',5'-O-tetraisopropyl-disiloxyl)adenosine

Phenyl chlorothionoformate (4.66 g, 27 mM) is added to a mixture of 2-chloro-(3',5'-O-tetraisopropyldisiloxyl)adenosine (14 g, 25.8 mM), 4-dimethylaminopyridine (DMAP) (6.88 g, 56.4 mM) and acetonitrile (400 mL) at room temperature under nitrogen, and stirred overnight. The solvent is removed in vacuo and the residue is purified by column chromatography on silica gel (200 g) with ethyl acetate/hexane (4:6) to yield the title compound as a pale yellow powder (9.8 g, 56%, MP 153-155°C). NMR, IR and elemental analysis are confirmed the structure of the title compound.

Preparation of 2-chloro-2'-deoxy-(3',5'-O-tetraisopropyldisiloxyl)adenosine

A mixture of the compound of 2-chloro-2'-O-phenoxythiocarbonyl-(3',5'-O-tetraisopropyldisiloxyl)adenosine (5.8 g, 8.54 mM), tri-n-butyltin hydride (3 mL, 11 mM) and azobisisobutyronitrile (320 mg) in benzene (100 mL) is heated to reflux for 3 hours under nitrogen. After cooling, the solvent is removed in vacuo and the residue is purified by column chromatography on silica gel (200 g) with ethyl acetate/hexane (4.5:5.5) to yield the title compound as a white powder (3.78 g, 84%, MP 171°-173°C). NMR, IR and

elemental analysis are confirmed the structure of the title compound.

Preparation of 2-chloro-2'-deoxy-adenosine

A mixture of 2-chloro-2'-deoxy-(3',5'-O-tetraisopropyldisiloxyl)adenosine (2.5 g, 4.74 mM), and tetra-n-butylammonium fluoride (1.1 M, 8.6 mL, 9.46 mM) in tetrahydrofuran (10 mL) is stirred at room temperature under nitrogen for 2 hours. The solvent volume is reduced in vacuo and the resulting residue is treated with water (200 mL) and extracted with ether (3x20 mL). The aqueous layer is purified by preparative HPLC (C-18 reverse phase column, methanol/water 15:85 to 20:80) to yield the title compound (600 mg, 44%); MP >230°C.

References

Chen R.; US Patent No. 5,208,327; May 4, 1993; Assigned to Ortho Pharmaceutical Corporation, Raritan, N.J.

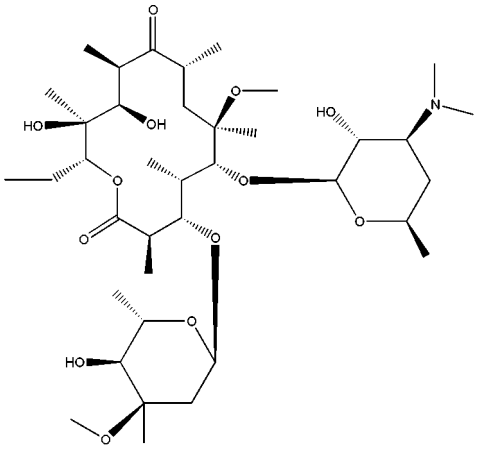
CLARITHROMYCIN

Therapeutic Function: Antibiotic

Chemical Name: Erythromycin, 6-O-methyl-

Common Name: Clarithromycin

Structural Formula:



Chemical Abstracts Registry No.: 81103-11-9

Trade Name	Manufacturer	Country	Year Introduced
Biaxin	Neo Quimica	-	-
Biaxin	EMS/Sigma	-	-
Binoclar	Novartis Limited	Bangladesh	-
Claricin	Brown and Burk Pharmaceuticals Ltd.	India	-
Clarith	Taisho Pharmaceutical Co., Ltd.	-	-
Clarithromycin	Alembic Ltd.	India	-
Fromilid	Krka	Slovenia	-
Klabax	Ranbaxy	India	-
Klacid	Abbott	France	-
Klaricid	Cipla Limited	India	-
Klaricid	Abbott	-	-
Klaricid	Dainabot Co., Ltd.	-	-
Klacid SR	Abbott	UK	-
Klerimed	Medochemie Ltd.	Cyprus	-

Raw Materials

O,N-Dibenzyloxycarbonyl-des-N-methylerythromycin A
Triethylamine
Formaldehyde
Methyl iodide
Sodium hydride
Palladium

Manufacturing Process

In a mixture of 50 ml of dry dimethylsulfoxide and 100 ml of dry tetrahydrofuran were dissolved 30 g of O,N-dibenzyloxycarbonyl-des-N-methylerythromycin A and 18 ml of methyl iodide. The solution was stirred under cooling at -12-10°C in a nitrogen stream and 2.4 g of 55-65% sodium hydride oily dispersion were added thereto in small portions. The mixture was stirred for a further one hour. After completion of the reaction, 50 ml of triethylamine were poured into the reaction mixture with stirring under ice-cooling, and the precipitates were filtered off. The obtained solid product was washed thoroughly with ethyl acetate, and the washings and the mother liquor were combined. The combined liquor was washed with a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was evaporated in vacuo and the crude product was applied onto a silica gel dry column (E. Merck Darmstadt; silica gel 60 for column chromatography, 70-230 mesh). The mixture was eluted with of ethyl acetate/n-hexane (1:1).

15 ml each of fraction was collected and analyzed by silica gel thin layer chromatography, developing in a mixture of ethyl acetate and n-hexane (1:1). The fractions having R_f value 0.16 were combined (c.f., Rf value of starting compound 0.07) and the solvent was evaporated in vacuo, affording 12.2 g of

a colorless froth.

In a mixture of 1.32 g of sodium acetate, 0.8 ml of sodium acetate, 40 ml of water and 200 ml of ethanol were dissolved 10 g of the colorless froth obtained, and 1.0 g of palladium black was added to the above solution. Catalytic reduction was performed for 5 hours at room temperature under atmospheric pressure in a gentle hydrogen stream. 32 ml of 37% aqueous formaldehyde solution were poured into the reaction mixture and the catalytic reduction was continued for a further 7 hours. After completion of the reaction, the catalyst was filtered off and the filtrate was concentrated under reduced pressure approximately to a quarter volume. To the concentrate were added 100 ml of water, and the mixture was adjusted to about pH 10 with an aqueous sodium carbonate solution. The mixture was extracted thoroughly with chloroform and the extract was washed with water and dried. After evaporation of the solvent in vacuo, the residue was recrystallized from a mixture of chloroform and diethyl ether, giving 6 g of crystals.

The crystals were stirred for 5 hours in 500 ml of diethyl ether and filtered off. The filtrate was concentrated to dryness and the residual substance was recrystallized from a mixture of chloroform and diethyl ether, giving 4.5 g of 6-O-methylerythromycin A (Clarithromycin) in the form of colorless needles; m.p. 217-220°C (with decomposition).

References

Dominguez A. et al.; US Patent No. 6,642,364; Nov. 4, 2003; Assigned to Ercros Industrial, S.A. (Barcelona, ES)
Watanabe Y., et al.; US Patent No. 4,331,803, May 25, 1982; Assigned to Taisho Pharmaceutical Co., Ltd. (JP)

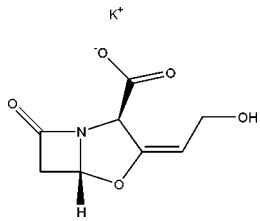
CLAVULANATE POTASSIUM

Therapeutic Function: Beta-lactamase inhibitor

Chemical Name: 4-Oxa-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3-(2-hydroxyethylidene)-7-oxo-, monopotassium salt, (2R-(2α,3Z,5α))-

Common Name: Clavulanate potassium; Potassium clavulanate

Structural Formula:



Chemical Abstracts Registry No.: 61177-45-5

Trade Name	Manufacturer	Country	Year Introduced
Clavulanate potassium	Lek	-	-
Potassium clavulanate	Paganfarma	-	-
Potassium clavulanate	Yick-Vic Chemicals and Pharmaceuticals (HK) Ltd.	-	-

Raw Materials

Streptomyces clavuligerus
Glucose
Oxoid Malt Extract
Peptone
Potassium hydrocarbonate
Yeatex
Oxoid agar No. 3
Glycerol
Water
Sodium hydroxide

Manufacturing Process

Clavulanic acid may be obtained by aerobic cultivation of Streptomyces clavuligerus in conventional nutrient media at, for example, about 25°-30°C under roughly neutral conditions.

Cultivation of Streptomyces clavuligeru:

Streptomyces clavuligerus was cultivated at 26°C on agar slopes containing 1% Yeatex (yeast extract) ("Yeatex" is a Registered Trade mark), 1% glucose and 2% Oxoid agar No. 3, pH 6.8. A sterile loop was used to transfer mycelium and spores from the slope into 100 ml of a liquid medium in a 500 ml Ehrlenmeyer flask. The liquid medium had the following composition: Oxoid Malt Extract 10g/L, Oxoid Bacteriological Peptone 10g/L, Glycerol 20 g/L, Tap water 1 L.

The medium was adjusted to pH 7.0 with sodium hydroxide solution and 100 ml volumes dispensed into flasks which were closed with foam plugs prior to autoclaving at 15 lb/sq.in. for 20 min. An inoculated seed flask was shaken for 3 days at 26°C on a rotary shaker with a 2 inch throw and a speed of 240 r.p.m.

Production stage flasks containing the liquid medium described above were inoculated with 5% vegetative inoculum and grown under the same conditions as the seed flask.

Clavulanic acid may be extracted from the culture medium. Normally the cells of the Streptomyces clavuligerus are first removed from culture medium by filtration or centrifugation. Then clavulanic acid is extracted into an organic solvent, for example, n-butanol or ethyl acetate, or n-butyl acetate, or methyl isobutyl ketone. Then n-butanol fraction are treated with new aqueous phase using potassium hydrogen carbonate and then this aqueous phase is washed with n-butanol. This aqueous extract, after separation of the phases, is concentrated under reduced pressure. Freeze-drying at -20°C may also be

employed to provide a solid crude preparation of the potassium Z-(2R,5R)-3-(β-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3,2,0]heptane-2-carboxylate (clavulanate potassium).

References

Cole M. et al.; GB Patent No. 1,508,977; April 26, 1978; Assigned: Beecham Group Limited, a British Company of Beecham House, Great West Road, Brentford, Middlesex, England

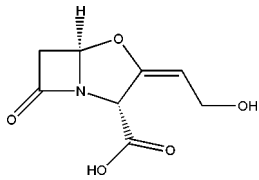
CLAVULANIC ACID

Therapeutic Function: Antibacterial

Chemical Name: 3-(2-Hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0] heptane-2-carboxylic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 58001-44-8

Trade Name	Manufacturer	Country	Year Introduced
Augmentin	Beecham	UK	1981
Augmentin	Beecham	Switz.	1982
Augmentan	Beecham	W. Germany	1982
Synulox	Beecham	-	-

Raw Materials

Dextrin
Soybean flour
Bacterium Streptomyces Clavuligerus

Manufacturing Process

100 ml of sterile water was added to a sporing culture which had been grown on Bennetts agar in a Roux bottle for 10 days at 26°C. A mycelium/spore

suspension was produced and used to inoculate 75 liters of steam sterilized medium of the following composition in tap water.

Dextrin	2% W/V
Arkasoy '50'*	1% W/V
10% Pluronic L81 in soybean oil	0.03% V/V

*Arkasoy is soybean flour supplied by British Arkady Co., Old Trafford, Manchester, UK

The pH of the medium was adjusted to 7.0

The medium was contained in a 100 liter stainless steel baffled fermenter, agitated by a 7.5 inch vaned disc impeller at 140 rpm. Sterile air was supplied at 75 liters per minute and the tank incubated for 72 hours at 26°C.

The contents of the seed fermenter were used to inoculate 1,500 liters of steam sterilized medium of the following composition in tap water.

Arkasoy '50'	1.5% W/V
Glycerol	1.0% W/V
KH_2PO_4	0.1% W/V

10% Pluronic L81 in soybean oil 0.2% V/V

The pH of the medium was adjusted to 7.0

The medium was contained in a 2,000 liter stainless steel fully baffled fermenter agitated by two 19 inch vaned disc impellers at 106 rpm.

Sterile air was supplied at 1,200 liters per minute. Antifoam was added in 25 ml amounts as required. (10% Pluronic L81 in soybean oil). The fermentation was controlled at 26°C until a maximum yield of clavulanic acid was obtained between 3-5 days when 200-300 μg/ml of clavulanic acid were produced.

References

Merck Index 2311
DFU 2 (6) 372 (1977)
PDR p. 659
DOT 19 (3) 169 (1983)
I.N. p. 18
REM p. 1200
Cole, M., Howarth, T.T. and Reading, C.; US Patent 4,110,165; August 29, 1978; assigned to Beecham Group, Ltd. (UK)

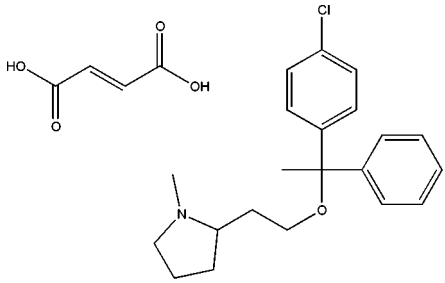
CLEMASTINE FUMARATE

Therapeutic Function: Antihistaminic

Chemical Name: 2-[2-[1-(4-Chlorophenyl)-1-phenylethoxy]ethyl]-1-methylpyrrolidine hydrogen fumarate

Common Name: Meclastin

Structural Formula:



Chemical Abstracts Registry No.: 14976-57-9; 15686-51-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Tavegyl	Sandoz	France	1967
Tavegyl	Sandoz	Switz.	1967
Tavegil	Sandoz	W. Germany	1967
Tavegyl	Sandoz	Italy	1968
Tavegyl	Sankyo	Japan	1970
Tavegil	Sandoz	UK	1971
Tavist	Dorsey	US	1978
Agasten	Sandoz	-	-
Alagyl	Sawai	Japan	-
Aloginan	Tobishi	Japan	-
Alphamin	S.S. Pharm	Japan	-
Anhistan	Nippon Zoki	Japan	-
Antriptin	Nippon Yakuhin	Japan	-
Arrest	Taisho	Japan	-
Batomu	Zensei	Japan	-
Benanzyl	Isei	Japan	-
Chlonaryl	Ohta	Japan	-
Clemanil	Kyoritsu	Japan	-
Fuluminol	Tatsumi	Japan	-
Fumalestine	Hishiyama	Japan	-
Fumaresutin	Hishiyama	Japan	-
Inbestan	Maruko	Japan	-
Kinotomin	Toa Eiyo	Japan	-
Lacretin	Toyo Tanabe	Japan	-

Trade Name	Manufacturer	Country	Year Introduced
Lecasol	Kaken	Japan	-
Maikohis	Nichiiko	Japan	-
Mallermin-F	Taiyo Yakuko	Japan	-
Marsthine	Towa	Japan	-
Masletine	Shioe	Japan	-
Piloral	Nippon Kayaku, Co.	Japan	-
Raseltin	Maruishi	Japan	-
Reconin	Toyama	Japan	-
Romien	Fuji Zoki	Japan	-
Telgin G	Taiyo	Japan	-
Trabest	Hoei	Japan	-
Xolamin	Sanko	Japan	-

Raw Materials

Sodium amide
Fumaric acid
α-Methyl-p-chlorobenzhydrol
N-Methylpyrrolidyl-(2)-ethyl chloride

Manufacturing Process

9.9 g of α-methyl-p-chlorobenzhydrol are added to a suspension of 2.3 g of powdered sodamide in 30 cc of benzene. Subsequently 7.4 g of N-methylpyrrolidyl-(2)-ethyl chloride are added and the solution is heated to the boil at reflux for 20 hours. Then shaking is first effected with water and then 4 times each time with 25 cc of 2 N hydrochloric acid. The acid extracts are made alkaline with potassium hydroxide solution while cooling strongly, and the precipitated oil is extracted with ether. After drying of the ethereal solution over potassium carbonate, the solvent is evaporated and the residue is fractionally distilled in a high vacuum, whereby N-methyl-2-[2'-(α-methyl-p-chlorobenzhydryloxy)-ethyl]-pyrrolidine boils over at 154°C/0.02 mm Hg. The base is converted to the fumarate by reaction with fumaric acid.

References

Merck Index 2314
Kleeman 81 Engel p. 216
PDR p. 1597
OCDS Vol. 2 p. 32 (1980)
I.N. p. 239
REM p. 1127
British Patent 942,152; November 20, 1963; assigned to Sandoz Ltd.

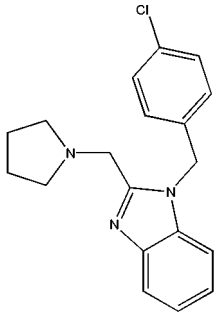
CLEMIZOLE

Therapeutic Function: Antihistaminic

Chemical Name: 1-[(4-Chlorophenyl)methyl]-2-(1-pyrrolidinylmethyl)]-1H-benzimidazole

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 442-52-4; 1163-36-6 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Allercur	Roerig	US	1960
Reactrol	Purdue Frederick	US	1961
Allercur	Schering	Switz.	-
Allerpant	Panther-Osfa	Italy	-
Deliproct	S.E.P.S.S.	France	-
Penargyl	Morgan	Italy	-
Ultralan	S.E.P.S.S.	France	-
Ultraproct	S.E.P.S.S.	France	-

Raw Materials

o-Nitrochlorobenzene
Chloroacetyl chloride
Pyrrolidine
p-Chlorobenzylamine
Hydrogen

Manufacturing Process

From 13.1 g of N-p-chlorobenzyl-2-nitroaniline (MP 110°C, obtained in the form of orange-red needles, from o-nitrochlorobenzene and p-chlorobenzylamine by reaction for 3 hours at 150°C) by reduction with Raney-nickel and hydrogen, in which reaction the substance may be suspended in methanol or dissolved in methanol-ethyl acetate at normal pressure and at about 40°C with combination of the theoretical quantity of hydrogen, 12.2 g are obtained of o-amino-N-p-chlorobenzylaniline, which after recrystallization from aqueous methanol has a MP of 90°C.

8 g of o-amino-N-p-chlorobenzylaniline and 2.8 g of pyridine are dissolved in dry ether and reacted with an ethereal solution of 3.9 g of chloracetyl chloride with cooling in a mixture of ice and common salt. 8 g of N-p-chlorobenzyl-N'-chloracetyl-o-phenylene diamine are obtained which can be worked up in the form of the crude product and, in the slightly colored form, has a MP of 130°C.

7.6 g of this compound are boiled with 3.9 g of pyrrolidine in 70 cc of toluene for some hours under reflux. After extraction by shaking with water and treatment with hydrochloric acid the hydrochloride is produced of N-p-chlorobenzyl-N'-pyrrolidylacetyl-o-phenylene diamine together with some 1-p-chlorobenzyl-2-N-pyrrolidylmethyl-benzimidazole. The former, after recrystallization from butanol, melts with foaming at 205°C, the latter, after recrystallization from butanol melts at 239°C to 241°C, and is in the form of white microscopic rods. Boiling in nitrobenzene converts the former compound into the latter.

References

Merck Index 2315
Kleeman and Engel p.217
OCDS Vol. 1 p. 324 (1977)
I.N. p. 239
Schenck, M. and Heinz, W.; US Patent 2,689,853; September 21, 1954; assigned to Schering A.G. (Germany)

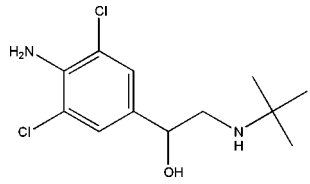
CLENBUTEROL

Therapeutic Function: Anti-asthmatic

Chemical Name: 4-Amino-3,5-dichloro-[[(1,1-dimethylethyl)amino]methyl] benzenemethanol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 37148-27-9

Trade Name	Manufacturer	Country	Year Introduced
Spiropent	Thomae	W. Germany	1977
Monores	Valeas	Italy	1981

Raw Materials

1-(4'-Aminophenyl)-2-t-butylaminoethanol-(1) HCl
Chlorine hydrogen chloride

Manufacturing Process

127 g of 1-(4'-aminophenyl)-2-t-butylaminoethanol-(1) hydrochloride were dissolved in a mixture of 250 cc of glacial acetic acid and 50 cc of water, and chlorine added while stirring the solution and maintaining the temperature of the reaction mixture below 30°C by cooling with ice water. After all of the chlorine had been added, the reaction mixture was stirred for thirty minutes more, then diluted with 200 cc of water, and made alkaline with concentrated ammonia while cooling with ice, taking care that the temperature of the reaction mixture did not rise above 40°C. The alkaline mixture was extracted three times with 200 cc portions of chloroform, and the chloroform extract solutions were combined, dried with sodium sulfate and evaporated. The residue, the free base 1-(4'-amino-3',5'-dichlorophenyl)-2-t-butylaminoethanol-(1), was dissolved in absolute ethanol, gaseous hydrogen chloride was passed through the solution, and the precipitate formed thereby was collected. It was identified to be 1-(4'-amino-3',5'-dichlorophenyl)-2-t-butylaminoethanol-(1) hydrochloride, melting point 174.0°C to 175.5°C (decamp.).

References

Merck Index 2316
DFU 1 (5) 221 (1976)
Kleeman and Engel p. 218
DOT 14 (2) 59 (1978) and 17 (8) 339 (1981)
I.N. p.240
Keck, J., Kruger, G., Machleidt, H., Noll, K., Engelhardt, G. and Eckenfels, A.; US Patent 3,536,712; October 27, 1970: assigned to Boehringer Ingelheim G.m.b.H. (Germany)

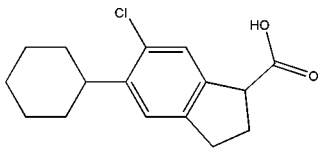
CLIDANAC

Therapeutic Function: Antiinflammatory, Antipyretic

Chemical Name: 6-Chloro-5-cyclohexyl-2,3-dihydro-1H-indene-1-carboxylic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 34148-01-1

Trade Name	Manufacturer	Country	Year Introduced
Indanal	Takeda	Japan	1981
Britai	Bristol Banyu	Japan	1981

Raw Materials

N-Chlorosuccinimide
5-Cyclohexyl-1-indancarboxylic acid

Manufacturing Process

N-chlorosuccinimide (8.2 g.0.0614 mol) was added to a stirred, cooled (ice-water) solution of (±)-5-cyclohexyl-1-indancarboxylic acid (10.0 g, 0.0409 mol) in dimethylformamide (82 ml). The solution was stirred for fifteen minutes at 0°C. thirty minutes at 25°C. nine hours at 50°C, followed by eight hours at 25°C. The solution was diluted with cold water (400 ml) and stirred until the precipitated product turned granular (fifteen minutes). The crude product was collected, washed with cold water, and dried. Crystallization from Skellysolve B with charcoal treatment gave colorless crystals (6.65 g, 58%), MP 149°C to 150°C. The product was recrystallized twice from Skellysolve B to give (±)-6-chloro-5-cyclohexyl-1-indancarboxylic acid as colorless crystals, MP 150.5°C to 152.5°C.

References

Merck Index 2319
DFU 4 (3) 229 (1979)
DOT 17 (8) 319 (1981)
I.N. p. 240
Juby, P.F., DeWitt, R.A.P. and Hudyma,T.W.; US Patent 3,565,943; February 23, 1971; assigned to Bristol-Myers Co.

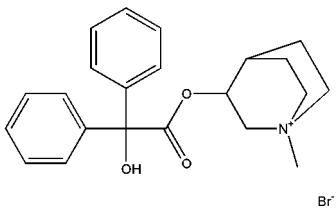
CLIDINIUM BROMIDE

Therapeutic Function: Anticholinergic

Chemical Name: 3-[(Hydroxydiphenylacetyl)oxy]-1-methyl-1-azoniabicyclo [2.2.2]octane bromide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 3485-62-9

Trade Name	Manufacturer	Country	Year Introduced
Librax	Roche	US	1961
Quarzan	Roche	US	1976
Dolibrax	Roche	France	-

Raw Materials

1-Azabicyclo[2.2 2]-3-octanol
Sodium
Diphenylchloroacetyl chloride
Methyl bromide

Manufacturing Process

5.12 g of 1-azabicyclo[2.2.2]-3-octanol were refluxed with a suspension of 0.92 g of finely divided sodium in 50 cc of toluene, until most of the sodium had reacted (about 4 hours). The thus obtained suspension of the white amorphous alcoholate was cooled with ice, and reacted with 10.16 g of diphenylchloroacetyl chloride, which was added in form of a solution in approximately 40 cc of toluene. The mixture was stirred for 1 hour at room temperature. Small amounts of unreacted sodium were destroyed with isopropanol, and 120 cc of 1 N hydrochloric acid were then added, The mixture was refluxed for 1/2 hour, in order to convert the first formed product, diphenylchloroacetic acid ester of 1-azabicyclo[2.2.2]-3-octanol, into the corresponding benzilic acid ester.

The toluene phase was separated and discarded. The aqueous phase, together with a precipitated water- and toluene-insoluble oil, was made alkaline and extracted repeatedly with chloroform. The chloroform solution was concentrated in vacuo. The residue was recrystallized from a mixture of acetone and ether (alternatively, from chloroform and ether), and formed needles melting at 164° to 165°C. It was identified as 3-benziloyloxy-1-azabicyclo[2.2.2]octane.

3-Benziloyloxy-1-azabicyclo[2.2.2]octane methobromide was prepared by adding 20 cc of a 30% solution of methyl bromide in ether to a solution of 2.5 g of 3-benziloyloxy-1-azabicyclo[2.2.2]octane in 20 cc of chloroform. After standing for 3 hours at room temperature and 15 hours at +5°C, a crystalline precipitate had formed. This was filtered off and recrystallized from a mixture of methanol, acetone, and ether; prisms melting at 240° to 241°C.

References

Merck Index 2320
Kleeman and Engel p. 219
PDR pp. 1510, 1606, 1999
I.N. p. 240
REM p. 914
Sternbach, L.H.; US Patent 2,648,667; August 11, 1953; assigned to Hoffmann-LaRoche, Inc.

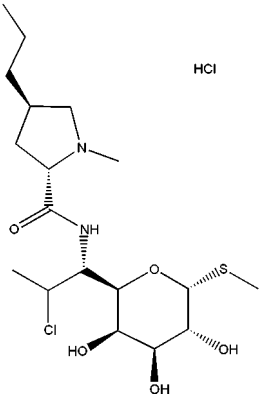
CLINDAMYCIN HYDROCHLORIDE

Therapeutic Function: Antibacterial

Chemical Name: 7(S)-Chloro-7-deoxylincomycin hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 21462-39-5; 18323-44-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Dalacin-C	Diethelm	Switz.	1968
Sobelin	Upjohn	W. Germany	1968
Cleocin	Upjohn	US	1970
Dalacin-C	Upjohn	UK	1970
Dalacin	Sumitomo	Japan	1971
Dalacin C	Upjohn	Italy	1975
Dalacin	Alter	Spain	-

Raw Materials

Lincomycin hydrochloride
Triphenylphosphine
Acetonitrile
Hydrogen chloride

Manufacturing Process

The following procedure is described in US Patent 3,475,407. A solution of 50 g of lincomycin hydrochloride, 120 g of triphenylphosphine, and 500 ml of acetonitrile in a 3 liter flask equipped with a stirrer was cooled in an ice bath and 500 ml of carbon tetrachloride was added in one portion. The reaction mixture was then stirred for 18 hours without addition of ice to the cooling

bath. The reaction was evaporated to dryness under vacuum on a 50° to 60°C water bath, yielding a clear, pale yellow viscous oil. An equal volume of water was added and the mixture shaken until all of the oil was dissolved. The resulting suspension of white solid (Ph_3PO) was filtered through a sintered glass mat and discarded. The filtrate was adjusted to pH 11 by addition of 6 N aqueous sodium hydroxide. A solid precipitated.

The resulting slurry was extracted with four 300 ml portions of chloroform. The aqueous phase was discarded. The combined chloroform extract was washed once with 100 ml of saturated aqueous sodium chloride solution and the sodium chloride phase was discarded. The chloroform phase was evaporated to dryness under vacuum on a 50° to 60°C water bath and an equal volume of methanol was added to the residue and the resulting solution heated at reflux for 1 hour. The methanol solution was evaporated to dryness under vacuum on a 50° to 60°C water bath. The residue was a clear pale yellow viscous oil. An equal volume of water and 10 ml of 37% aqueous HCl was added and the resultant was shaken until the oil dissolved and a white solid (more Ph_3PO) remained in suspension. The suspension was filtered through a sintered glass mat at pH 1 to 2 and the solid discarded.

The filtrate was extracted twice with 100 ml of carbon tetrachloride. The carbon tetrachloride phase was discarded. The aqueous phase was adjusted to pH 11 by addition of 6 N aqueous sodium hydroxide and extracted four times with 300 ml portions of chloroform. The combined chloroform extract was washed three times with 100 ml of saturated aqueous sodium chloride solution and the sodium chloride phase was discarded. The chloroform extract was dried over anhydrous magnesium sulfate, filtered and the filtrate evaporated to dryness under vacuum on a 50° to 60 °C water bath. The residue was a clear, colorless glass weighing 45 g analyzing about 95% 7(S)-chloro-7-deoxylincomycin. To the crude product there was added 100 ml of ethanol with warming until a clear solution was obtained. Then 150 ml ethyl acetate was added and the resultant filtered through a glass mat and the filtrate adjusted to pH 1 by the addition of saturated ethanolic HCl. Crystallization soon occurred. The resultant was allowed to stand at 0°C for 18 hours and then filtered through a sintered glass mat. The solid was dried under vacuum at 60°C for 18 hours yielding 35 g, a 67% yield of 7(S)-chloro-7-deoxylincomycin hydrochloride as an ethanol solvate.

References

Merck Index 2321
Kleeman and Engel p. 220
PDR p. 1827
DOT 5 (1) 32 (1969) and 7 (5) 188 (1972)
I.N. p. 240
REM p. 1209
Birkenmeyer, R.D.; US Patent 3,475,407; October 28, 1969; assigned to The Upjohn Company
Kagan, F. and Magerlein, B.J.; US Patent 3,509,127; April 28, 1970; assigned to The Upjohn Company

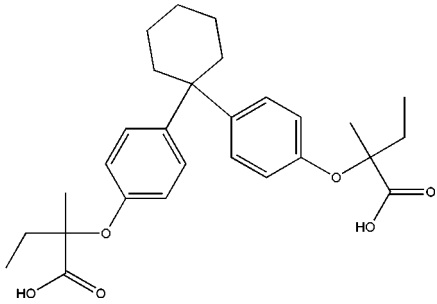
CLINOFIBRATE

Therapeutic Function: Antihyperlipoproteinemic

Chemical Name: 2,2'-[Cyclohexylidene-bis(4,1-phenyleneoxy)]bis[2-methylbutanoic acid]

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 30299-08-2

Trade Name	Manufacturer	Country	Year Introduced
Lipocrin	Sumitomo	Japan	1981
Lipocyclin	Sumitomo	Japan	-

Raw Materials

Bis-(phenyleneoxy)cyclohexane
Methylethyl ketone

Manufacturing Process

Into a mixture of 6.0 g of a bishydroxyphenyl derivative, and 44.0 g of methyl ethyl ketone was added 16.2 g of crushed potassium hydroxide or sodium hydroxide. Chloroform was added dropwise into the above mixture with stirring at 20°C to 80°C, and the resultant mixture was heated for 20 hours under reflux to complete the reaction. Thereafter the reaction mixture was concentrated to give a residue. Into the residue was added water. After cooling, the resultant mixture was treated with activated charcoal and acidified by diluted hydrochloric acid or sulfuric acid to give an oily substance. The oily substance was extracted by ether and the ether solution was contacted with aqueous diluted Na_2CO_3 solution. The separated aqueous layer was washed with ether, acidified and again extracted with ether. The obtained ester layer was dried over anhydrous sodium sulfate and concentrated to give 1.0 g of a crude product which was purified by recrystallization or chromatography, to give crystals MP 143°C to 146°C (decomp.).

References

Merck Index 2322
DFU 3 (12) 905 (1978)
DOT 18 (5) 221 (1982)
I.N.p.241
Nakamura, Y., Agatsuma, K., Tanaka, Y. and Aono, S.; US Patent 3,716,583; February 13, 1973; assigned to Sumitomo Chemical Co., Ltd. (Japan)

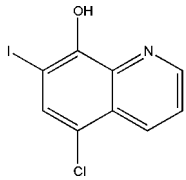
CLIOQUINOL

Therapeutic Function: Antibacterial

Chemical Name: 8-Quinolinol, 5-chloro-7-iodo-

Common Name: Chinoform(um); Chlorjodhydroxycginolinum; Chloroiodoquine; Chlorojodochin; Cliochinolum; Clioquinol; Iodochlorhydroxyquin; Iodochloroxychinoline; Quiniodochlor

Structural Formula:



Chemical Abstracts Registry No.: 130-26-7

Trade Name	Manufacturer	Country	Year Introduced
Clioquinol	CIBA-GEIGY Corp.	-	-
Clioquinol	Napp Chemicals Inc.	-	-
Clioquinol	Polychemical Laboratories Inc.	-	-
Clioquinol	Geneva Generics Inc.	-	-
Clioquinol	C and M Pharmaceutical Inc.	-	-
Clioquinol	UAD Laboratories Inc	-	-
Budoform	Dolder	-	-
Entero-Vioform	Ciba	-	-
Vioform	Ciba	-	-
Vioformio	Ciba-Geigy	-	-
Enterex	Mepha	-	-
Stanquinate	Smith Stanistreet	-	-

Trade Name	Manufacturer	Country	Year Introduced
Enterol	Vita	-	-
Iodochlorhydroxy quinolin	CFM Oskar Tropitzsch	-	-
Clioquinol	Tianjin Mid-Chem Co., Ltd.	-	-

Raw Materials

Chlor-5-oxy-8-chinoline
Potassium iodide
Sodium thiosulfate
Potassium hydroxide
Chloride of lime
Hydrochloric acid

Manufacturing Process

Chlor-5-oxy-8-chinoline (18 kg) was mixed with potassium hydroxide (6.0 kg), water (400 kg) and heated. To this solution 50 L saturated aqueous solution of potassium iodide (16.6 kg) was added, mixed and continued to heat. Solution was filtered at room temperature. Then to this yellow solution the solution of chloride of lime and 50 kg 5% solution of were added then all this was mixed and allowed to stand for 24 h.

After eliminating of free iodine by addition of sodium thiosulfate the obtained precipitate was washed with water. To residue 1% solution of acidum hydrochloricum (50.0 kg) and rapidly was heated to 50°C. Then it was washed with water and dried, so 5-chloro-7-iodo-quinolinol-8 was obtained, melting point 170°-175°C.

References

DR Patent No. 117,767; September 12, 1899; Assigned: Basler Chemische Fabrik in Basel

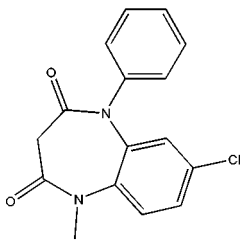
CLOBAZAM

Therapeutic Function: Tranquilizer

Chemical Name: 7-Chloro-1-methyl-5-phenyl-1H-1,5-benzodiazepine-2,4(3H,5H)-dione

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 22316-47-8

Trade Name	Manufacturer	Country	Year Introduced
Urbanyl	Diamant	France	1975
Frisium	Albert Pharma	Italy	1977
Frisium	Hoechst	W. Germany	1978
Urbanul	Hoechst	Switz.	1979
Frisium	Hoechst	UK	1979
Castilium	Hoechst	-	-
Clarmyl	Roussel-Iberica	Spain	-
Clopax	Prodes	Spain	-
Karidium	Hoechst	-	-
Noiafren	Hoechst	-	-
Sentil	Hoechst	-	-
Urbadan	Roussel	-	-
Urbanil	Sarsa	Brazil	-
Urbanol	Roussel	-	-

Raw Materials

N-Phenyl-N-(2-amino-5-chlorophenyl)malonic acid ethyl ester amide
Sodium
Ethanol
Methyl iodide

Manufacturing Process

1.65 g of N-phenyl-N-(2-amino-5-chlorophenyl)-malonic acid ethyl ester amide of MP 108° to 109°C are added to a sodium ethoxide solution, prepared from 20 ml of absolute alcohol and 150 mg of sodium. The solution is allowed to rest for 5 hours at room temperature. Then 1 ml of methyl iodide is added and the reaction mixture is refluxed for 7 hours. After evaporation of the solution in vacuo it is mixed with water and the solution is shaken with methylene chloride. The methylene chloride phase is dried and evaporated. By treatment of the residue with ethyl acetate/charcoal are isolated 500 mg of 7-chloro-1-methyl-5-phenyl-1H-1,5-benzodiazepine-2,4-(3H,5H)-dione of MP 180° to 182°C. The yield amounts to 34% of theory.

References

Merck Index 2325
Kleeman and Engel p. 221
OCDS Vol. 2 p. 406 (1980)
DOT9 (6) 240 (1973), 11 (1) 39 (1975) and 16 (1) 9 (1980)
I.N. p. 241
REM p. 1083
Hauptmann, K.H., Weber, K.-H., Zeile, K., Danneberg, P. and Giesemann, R.; South African Patent 68/0803; February 7, 1968; assigned to Boehringer Ingelheim GmbH, Germany

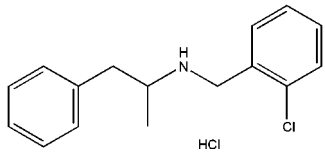
CLOBENZOREX HYDROCHLORIDE

Therapeutic Function: Anorexic

Chemical Name: Benzeneethanamine, N-((2-chlorophenyl)methyl)-α-methyl-, (+)-, hydrochloride

Common Name: Clobenzorex hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 5843-53-8; 13364-32-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Asenlix	Aventis	-	-
Dinintel	Roussel Diamant	-	-
Finedal	Llorente	-	-
Rexigen	Bago	-	-

Raw Materials

2-Chlorobenzaldehyde
Sodium borohydride
Sodium hydroxide
D-1-Phenyl-2-amino-propane
Hydrochloric acid

Manufacturing Process

A solution of 21.0 g (0.15 mol) of 2-chlorobenzaldehyde in 100 ml of ethanol (95%) was added to a solution of 20.5 g (0.152 mol) of D-1-phenyl-2-amino-propane in 100 ml of ethanol (95%). After standing for 15 h at room temperature, the ethanol was driven off, and the oily residue was then distilled to yield 36.2 g (94%) of D-N-(2-chlorobenzylidene)-2-amino-1-phenylpropane, boiling point 142°-146°C/0.1 mm Hg.

To the solution of 36.0 g (0.14 mol) of D-N-(2-chlorobenzylidene)-2-amino-1-phenylpropane in 200 ml of dry methanol were added, in portions, 5.3 g (0.14 mol) of sodium borohydride. The mixture was stirred for 1 h at room temperature, and refluxed for 1 h water (100 ml) was then added and the methanol was removed in vacuo. After acidifying carefully with dilute hydrochloric acid, the solution was made alkaline by dilute sodium hydroxide, and extracted with ether. 33.0 g (90%) of D-N-(1-phenyl-2-propyl)-2-chlorobenzylamine, boiling point 132°-134°C/0.1 mm Hg, were obtained by distillation.

References

GB Patent No. 1,123,565; Nov. 23, 1965; Assigned: Societe Industrielle Pour la Fabrication, des Antibiotiques (S.I.F.A.), Paris, France

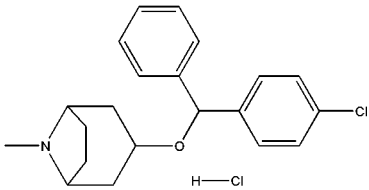
CLOBENZTROPINE HYDROCHLORIDE

Therapeutic Function: Antihistaminic

Chemical Name: 3-((p-Chloro-α-phenylbenzyl)oxy)tropane hydrochloride

Common Name: Chlorobenztropine hydrochloride; Clobenztropine hydrochloride; Teprin

Structural Formula:



Chemical Abstracts Registry No.: 5627-46-3 (Base); 14008-79-8

Trade Name	Manufacturer	Country	Year Introduced
Clobenztropine hydrochloride	Onbio Inc.	-	-

Raw Materials

3-Tropanol
Potassium carbonate
Potassium hydroxide
4-Chlorobenzhydryl chloride
Hydrochloric acid
Isopropanoic acid hydrogen chloride

Manufacturing Process

A solution of 28.2 g (0.2 mol) of 3-tropanol is prepared in 50 ml of xylol, and to this solution is added 23.8 g (0.1 mol) of 4-chlorobenzhydryl chloride. The resultant solution is heated for 7 h at 145°-155°C, following which the mixture is cooled and filtered. The clear filtrate thus obtained is washed with 50 ml of 5% aqueous potassium carbonate solution and then with three successive 25 ml portion of water. The xylol solution is then extracted with three successive 50 ml portions of 2 N hydrochloric acid. The xylol layer is discarded and the acid extracts are combined and rendered strongly basic by the addition of 22.5% aqueous potassium hydroxide, resulting in the formation of an oily base which separates and which is then extracted with

benzol, from which the benzol is evaporated to yield crude 3-(4'-chlorobenzhydryloxy)tropane as a brown oil.

2.0 g of 3-(4'-chlorobenzhydryloxy)tropane is treated with 10 ml of 4.5 N isopropanoic acid hydrogen chloride solution, and the pasty mixture which results is diluted with approximately 30 ml of absolute ether. A solid product is formed which is separated by filtration and then washed with absolute ether. The product is then purified by dissolving it in hot isopropanol, followed by clarification with activated charcoal. Upon cooling the filtrate, the 3-(4'-chlorophenylbenzyloxy)tropane separates as a crystalline powder, melting point 215°-217°C.

In practice it is usually used as hydrochloride.

References

Nield C.H., Bosch W.F.X.; US Patent No. 2,782,200; Feb. 19, 1957; Assigned: Schenley Laboratories, Inc., New York, N.Y., a corporation of Delaware

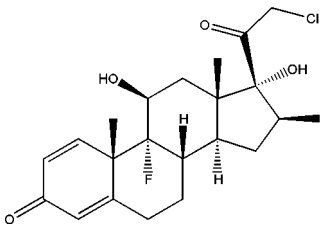
CLOBETASOL

Therapeutic Function: Corticosteroid, Antiinflammatory

Chemical Name: 21-Chloro-9-fluoro-11β,17-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 25122-41-2; 25122-46-7 (Propionate)

Trade Name	Manufacturer	Country	Year Introduced
Dermovate	Glaxo	UK	1973
Dermoxin	Glaxo	W. Germany	1976
Clobesol	Glaxo	Italy	1977
Dermoval	Glaxo	France	1978
Dermovate	Glaxo	Japan	1979
Dermadex	Glaxo	-	-

Raw Materials

Betamethasone-21-methanesulfonate
Lithium chloride
Propionic anhydride

Manufacturing Process

A solution of betamethasone 21-methanesulfonate (4 g) in dimethylformamide (25 ml) was treated with lithium chloride (4 g) and the mixture heated on the steam bath for 30 minutes. Dilution with water gave the crude product which was recrystallized to afford the title compound, MP 226°C.

Clobetasol is usually converted to the propionate as the useful form by reaction with propionic anhydride.

References

Merck Index 2330
Kleeman and Engel p. 222
DOT 9 (8) 339 (1973)
I.N. p. 242
Elks, J., Phillipps, G.H. and May, P.J.; US Patent 3,721,687; March 20, 1973; assigned to Glaxo Laboratories Limited, England

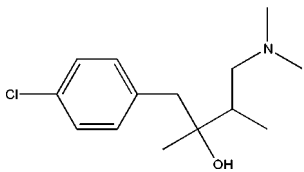
CLOBUTINOL

Therapeutic Function: Antitussive

Chemical Name: 4-Chloro-α-[2-(dimethylamino)-1-methylethyl]-a-methyl benzeneethanol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 14860-49-2; 1215-83-4 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Silomat	Boehringer Ingelheim	Switz.	1960
Silomat	Thomae	W. Germany	1960

Trade Name	Manufacturer	Country	Year Introduced
Camaldin	Boehringer Ingelheim	Italy	1962
Silomat	Badrial	France	1969
Silomat	Morishita	Japan	1975
Biotertussin	Bioter	-	-
Lomisat	Boehringer Ingelheim	-	-
Pertoxil	Violani-Farmavigor	Italy	-

Raw Materials

3-Methyl-4-dimethylamino-butanone-(2)
Magnesium
p-Chlorobenzyl chloride
Hydrogen chloride

Manufacturing Process

A solution of 0.2 mol (33 g) of 3-methyl-4-dimethylamino-butanone-(2) [produced according to Mannich, Arch. Pharm., vol. 265, page 589 (1927)] in 50 cc absolute ether was added dropwise, while stirring and cooling with ice, to a Grignard solution of 0.4 mol p-chlorobenzylmagnesium-chloride which was produced from 64.5 g p-chlorobenzyl-chloride and 9.8 g magnesium in 200 cc absolute ether. The reaction product was heated for an additional one-half hour under reflux to bring the reaction to completion, and thereafter the reaction mixture was decomposed into an ether phase and an aqueous phase with about 50 cc concentrated hydrochloric acid and about 200 g ice. The ether phase was discarded and the aqueous phase was adjusted to an alkaline pH with ammonia and then thoroughly extracted with ether. After concentrating the united, dried ether extract solutions, the oily residue was fractionally distilled. The reaction product was obtained in the form of a colorless oil having a boiling point of 179° to 181°C. The yield was 48.5 g corresponding to 95% of theory.

The hydrochloride addition salt of the above reaction product was prepared in customary fashion, that is, by reaction with hydrochloric acid, followed by fractional crystallization from a mixture of alcohol and ether. The two possible racemic forms were obtained thereby. The difficultly soluble racemate had a melting point of 169° to 170°C and the more readily soluble racemate had a boiling point of 145° to 148°C.

References

Merck Index 2332
Kleeman and Engel p. 224
OCDS Vol. 2 p. 121 (1980)
I.N.p. 242
Berg, A.; US Patent 3,121,087; February 11, 1964; assigned to Dr. Karl Thomae GmbH, Germany

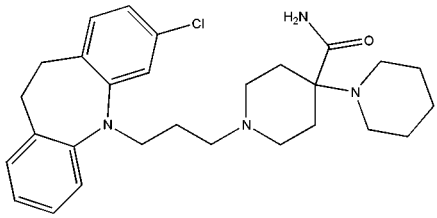
CLOCAPRAMINE

Therapeutic Function: Neuroleptic

Chemical Name: 1'-[3-(3-Chloro-10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)propyl][1,4-bipiperidine]-4]carboxamide

Common Name: Clocarpramine

Structural Formula:



Chemical Abstracts Registry No.: 47739-98-4

Trade Name	Manufacturer	Country	Year Introduced
Clofekton	Yoshitomi	Japan	1974

Raw Materials

3-Chloro-5-(3-chloropropyl)-10,11-dihydro-5H-dibenz[b,f]azepine
4-Carbamoyl-4-piperidinopiperidine

Manufacturing Process

A mixture of 5.0 g of 3-chloro-5-(3-chloropropyl)-10,11-dihydro-5H-dibenz[b,f]azepine, 5.0 g of 4-carbamoyl-4-piperidinopiperidine and 50 ml of dimethylformamide is heated at 100°C for 10 hours. The solvent is distilled off. After the addition of a 2% sodium carbonate solution to the flask, the content is scratched to yield a semisolid, which is dissolved in 50 ml of isopropanol. A solution of 5 g of maleic acid in 50 ml of isopropanol is added, and the precipitate is collected by filtration and recrystallized from isopropanol to give 5.6 g of crystalline 3-chloro-5-[3-(4-carbamoyl-4-piperidinopiperidino) propyl]-10,11-dihydro-5H-dibenz[b,f]azepine di(hydrogen maleate) with 1/2 molecule of water of crystallization melting at 181°C to 183°C.

References

Merck Index 2334
Kleeman and Engel p. 224
OCDS Vol. 2 p. 416 (1980)
DOT 10 (5) 161 (1974)
I.N. p. 243
Nakanishi, M. and Tashiro, C.; US Patent 3,668,210; June 6, 1972; assigned to Yoshitomi Pharmaceutical Industries, Ltd. (Japan)

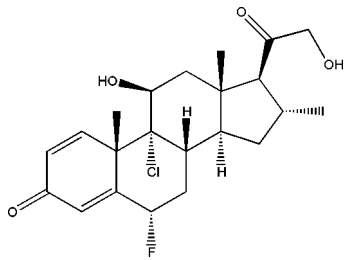
CLOCORTOLONE

Therapeutic Function: Glucocorticoid

Chemical Name: 9-Chloro-6α-11β21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione

Common Name: Clocortolone

Structural Formula:



Chemical Abstracts Registry No.: 4828-27-7

Trade Name	Manufacturer	Country	Year Introduced
Clocortolone	Schering AG	-	-
Clocortolone	Germapharm	-	-
CLODERM	DFB Pharmaceuticals, Inc.	-	-

Raw Materials

6α-Fluoro-16α-methyl-21-hydroxy-1,4,9(11)-pregnatriene-3,20-dione
Nitroethane
Perchloric acid
t-Butyl hypochlorite
Sodium sulfite

Manufacturing Process

6α-Fluoro-16α-methyl-21-hydroxy-1,4,9(11)-pregnatriene-3,20-dione is suspended in nitroethane at heating. To this suspension 1 N perchloric acid is added and then t-butyl hypochlorite is added dropwise. The reaction mixture is agitated at heating, then cooled to room temperature, mixed with methanol, stirred and then poured with water containing ice. The mixture is then stirred, thus precipitated product is filtered, washed neutral with water, dried; The crude product is treated with hot methanol, and recrystallized from ethanol, thus 9α-chloro-6α-fluoro-11β,21-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione was obtained.

References

Kaspar E. et al.; US Patent No. 3,729,495; April 24, 1973; Schering A.G., Berlin, Germany

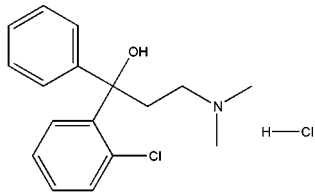
CLOFEDANOL HYDROCHLORIDE

Therapeutic Function: Antitussive

Chemical Name: Benzenemethanol, 2-chloro-α-(2-(dimethylamino)ethyl)-α-phenyl-, hydrochloride

Common Name: Chlophedianol hydrochloride; Clofendanol hydrochloride; Tigonal

Structural Formula:



Chemical Abstracts Registry No.: 511-13-7

Trade Name	Manufacturer	Country	Year Introduced
Abehol	Pliva	-	-
Alivin	Grossmann	-	-
Antitussin	Sopharma	-	-
Antitussin	Yick-Vic Chemicals and Pharmaceuticals (HK) Ltd	-	-
Chlophedianol hydrochloride	Shanghai Lancheng Corporation	-	-
Coldrin	Janssen Cilag	-	-
Coldrin	Nippon Shinyaku	-	-
Detigon linctus	Bayer (India) Limited	-	-
Tussigon	King Pharmaceuticals, Inc.	-	-
Tussistop	Atral	-	-

Raw Materials

Sodium amide
o-Chlorobenzophenone

Cobalt Raney
Formaldehyde
Nickel Raney
Acetonitrile
Hydrogen

Manufacturing Process

To a suspension of 330.0 g of sodamide (moistened with toluene) in 1500 ml of absolute ether, a solution of 1080.0 g of o-chlorobenzophenone and 350.0 g of acetonitrile in 3500 ml of absolute ether was gradually added dropwise, with stirring, such that the reaction temperature adjusted itself to 28°-30°C. The reaction mixture was stirred for 12 to 15 h at room temperature and was then added carefully to some ice water. The resulting solution was extracted 3 times with ether. The ether solution was washed with water, dried over Na_2SO_4, filtered, and finally concentrated. When 1 L of petroleum ether was added, 1240.0 g (96% of theoretical) of β-phenyl-β-o-chlorophenyl-hydroacrylonitrile (melting point 90°-92°C) precipitated.

500.0 g of the β-phenyl-β-o-chlorophenyl-hydroacrylonitrile were dissolved in 3 L of methanol and hydrogenated in the presence of 50.0 g of Raney cobalt at a temperature of 60°-70°C and a pressure of 80-85 ATM. Two moles of hydrogen were absorbed, and after separation of the methanolic solution from the catalyst, 450.0 g of 1-o-chlorophenyl-1-phenyl-3-aminopropanol-1 of melting point 117°C were obtained.

Catalytic methylation of 1-o-chlorophenyl-1-phenyl-3-aminopropanol-1 (hydrogenation in the presence of 2.2 mol of formaldehyde in aqueous methanol with Raney nickel catalyst) yielded 450.0 g of l-o-chlorophenyl-1-phenyl-3 dimethylaminopropanol-1 of melting point 120°C.

In practice it is usually used as hydrochloride.

References

Lorenz R. et al.; US Patent No. 3,031,377; April 24, 1962; Assigned: Farbenfabriken Bayer Aktiengesellschaft, a corporation of Germany

CLOFEXAMIDE

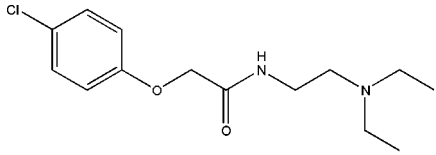
Therapeutic Function: Antidepressant, Analgesic, Antiinflammatory, Local anesthetic

Chemical Name: Acetamide, 2-(4-chlorophenoxy)-N-(2-(diethylamino)ethyl)-

Common Name: Clofexamide; Amichlophen

Chemical Abstracts Registry No.: 1223-36-5

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Clofexamide	CNRS	-	-

Raw Materials

N,N-Diethylethylenediamine
Chloride of p-chlorophenoxyacetic acid
Soda lye

Manufacturing Process

In 1 L of water there is dissolved 116.0 g (1 mole) of N,N-diethylethylenediamine and, under vigorous stirring at a temperature maintained below 50°C, there is added 205.0 g (1 mole) of the chloride of p-chlorphenoxyacetic acid. The solution becomes rapidly homogeneous; the formation of the basic amide hydrochloride is rapidly completed by further stirring the reaction mixture for 2 h at about 20°C. Then an excess of soda lye is added and the basic amide formed is extracted by ether. The ethereal solution is dried on anhydrous sodium sulfate and ether is distilled after that the residue is dried. So 2-(p-chlorophenoxy)-N-(2-(diethylamino)ethyl) acetamide is obtained.

References

GB Patent No. 942,761; November 27, 1963; Assigned: Centre National De La Recherche Scientifique, Paris, France

CLOFEZONE

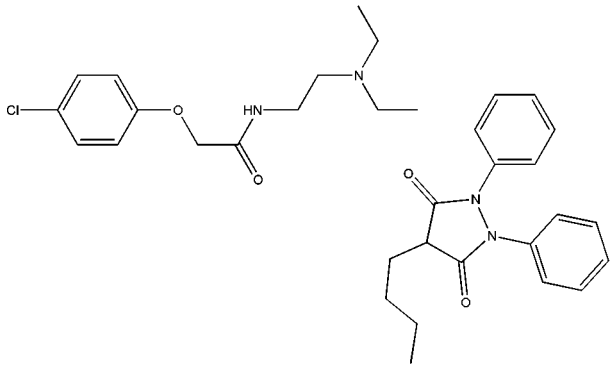
Therapeutic Function: Analgesic, Antiinflammatory

Chemical Name: Equimolar mixture of clofexamide which is 2-(p-chlorophenoxy)-N-[2-(diethylamino)ethyl]acetamide with phenylbutazone

Common Name: -

Chemical Abstracts Registry No.: 17449-96-6; 60104-29-2 (Dihydrate)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Perclusone	Anphar-Rolland	France	1967
Perclusone	Heinrich Mack	W. Germany	1974
Panas	Grelan	Japan	1976
Perclusone	Pierrel	Italy	1976
Perclusone	Abic	Israel	-
Perclustop	Uquifa	Spain	-

Raw Materials

Phenylbutazone
p-Chlorophenoxyacetic acid diethylamino ethylamide (Clofexamid)

Manufacturing Process

935 g of phenylbutazone are dissolved, with heating to a lukewarm state, in 2.7 liters of acetone containing 20% water, and the mixture is filtered if necessary. 853.5 g of p-chlorophenoxyacetic acid diethylamino ethylamide are dissolved in 300 cc of acetone containing 20% water, and the solution is poured into the phenylbutazone solution. There is slight heating, and the solution clarifies. The salt crystallizes rapidly. Drying is effected on a Buchner funnel and the mixture is washed in 450 cc of acetone containing 20% of water. The 1,702 g of product obtained is recrystallized in 2,450 cc of acetone containing 20% of water and, after drying in an oven at 37°C, 1,585 g (86%) of product are obtained. The product is in the form of a white crystalline powder having a melting point of from 87° to 89°C in the Maquenne block.

References

Kleeman and Engel p. 227
I.N.p. 245
Rumpf, P. and Thuillier, J.E.; US Patent 3,491,190; January 20, 1970

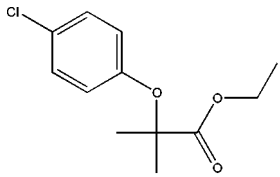
CLOFIBRATE

Therapeutic Function: Antihyperlipidemic

Chemical Name: 2-(4-Chlorophenoxy)-2-methylpropanoic acid ethyl ester

Common Name: Ethyl p-chlorophenoxyisobutyrate

Structural Formula:



Chemical Abstracts Registry No.: 637-07-0

Trade Name	Manufacturer	Country	Year Introduced
Atromid-S	I.C.I.	UK	1963
Skleromexe	Merckle	W. Germany	1964
Atromid-S	Ayerst	US	1967
Atromidin	I.C. Pharma	Italy	1969
Liposid	Ohta	Japan	1970
Amotril	Sumitomo	Japan	-
Apoterin A	Seiko	Japan	-
Arterioflexin	Arcana	Austria	-
Arterioflexin	Protea	Australia	-
Artes	Farmos	Finland	-
Artevil	N.C.S.N.	Italy	-
Ateculon	Nippon Chemiphar	Japan	-
Ateles	Tokyo Hosei	Japan	-
Atemarol	Kowa	Japan	-
Ateriosan	Finadiet	Argentina	-
Aterosol	Ferrosol	Denmark	-
Athebrate	Karenyaku	Japan	-
Atherolate	Fuji Zoki	Japan	-
Atheromide	Ono	Japan	-
Atherolip	Solac	France	-
Atheropront	Mack	W. Germany	-
Atmol	Taisho	Japan	-
Atosterine	Kanto	Japan	-
Atrofort	Dif-Dogu	Turkey	-

Trade Name	Manufacturer	Country	Year Introduced
Atrolen	Firma	Italy	-
Atromidin	I.C. Pharma	Italy	-
Atrovis	Novis	Israel	-
Auparton	Samya	Japan	-
Binograc	Zeria	Japan	-
Bioscleran	Pfleger	W. Germany	-
Bresit	Toyo Jozo	Japan	-
Cartagyl	Sopar	Belgium	-
Cholenal	Yamanouchi	Japan	-
Cholestol	Toho	Japan	-
Cholesrun	Hokuriku	Japan	-
Citiflus	C.T.	Italy	-
Claresan	Sarbach	France	-
Claripex	I.C.N.-Usafarma	Brazil	-
Clarol	Toyama	Japan	-
Climinon	Meiji	Japan	-
Cloberat	Negroni	Italy	-
Clobrat	Weifa	Norway	-
Clobrate	Chugai	Japan	-
Clobren	Morishita	Japan	-
Clof	Siegfried	Switz.	-
Clofbate	Mohan	Japan	-
Clofibral	Farmochimica	Italy	-
Clofinit	Gentili	Italy	-
Clofipront	Mack	W. Germany	-
Clofirem	Roland-Marie	France	-
Deliva	Nippon Kayaku, Co.	Japan	-
Geromid	Zoja	Italy	-
Healthstyle	Sawai	Japan	-
Hyclorate	Funai	Japan	-
Hypocerol	Fuso	Japan	-
Ipolipid	Isnardi	Italy	-
Klofiran	Remeda	Finland	-
Levatrom	Abic	Israel	-
Lipavil	Farmades	Italy	-
Lipavlon	Avlon	France	-
Lipidicon	Aristochimica	Italy	-
Liprinal	Bristol	UK	-
Liprinal	Banyu	Japan	-

Trade Name	Manufacturer	Country	Year Introduced
Miscleron	Chinoin	Hungary	-
Normolipol	Delagrange	France	-
Novofibrate	Novopharm	Canada	-
Recolip	Benzon	Denmark	-
Sclerovasal	I.T.I.	Italy	-
Scrobin	Nikken	Japan	-
Sklero-Tablinen	Sanorania	W. Germany	-
Ticlobran	Siegfried	Switz.	-
Xyduril	Dorsh	W. Germany	-
Yoclo	Shinshin	Japan	-

Raw Materials

p-Chlorophenoxyisobutyric acid
Ethanol

Manufacturing Process

The ethyl p-chlorophenoxyisobutyrate may be obtained by heating a mixture of 206 parts of dry p-chlorophenoxyisobutyric acid, 1,000 parts of ethanol and 40 parts of concentrated sulfuric acid under reflux during 5 hours. The alcohol is then distilled off and the residue is diluted with water and extracted with chloroform. The chloroform extract is washed with sodium hydrogen carbonate solution, dried over sodium sulfate and the chloroform removed by distillation. The residue is distilled under reduced pressure and there is obtained ethyl p-chlorophenoxyisobutyrate, BP 148° to 150°C/20 mm.

The p-chlorophenoxyisobutyric acid used as starting material may be obtained as follows. A mixture of 200 parts of p-chlorophenol, 1,000 parts of acetone and 360 parts of sodium hydroxide pellets is heated under reflux and 240 parts of chloroform are gradually added at such a rate that the mixture continues to reflux without further application of heat.

When addition is complete the mixture is heated under reflux during 5 hours and then the acetone is removed by distillation. The residue is dissolved in water, acidified with hydrochloric acid and the mixture extracted with chloroform. The chloroform extract is stirred with sodium hydrogen carbonate solution and the aqueous layer is separated. The alkaline extract is acidified with hydrochloric acid and filtered. The solid product is drained free from oil on a filter pump, then washed with petroleum ether (BP 40° to 60°C), and dried at 50°C. The solid residue, MP 114° to 116°C, may be crystallized from methanol (with the addition of charcoal) to give p-chlorophenoxyisobutyric acid, MP 118° to 119°C.

References

Merck Index 2340
Kleeman and Engel p. 227

PDR p. 613
OCDS Vol. 1 p. 119 (1977) and 2 pp. 79, 101, 432 (1980)
DOT 11 (4) 141 (1975)
I.N. p. 245
REM p. 863
Jones, W.G.M., Thorp, J.M. and Waring, W.S.; US Patent 3,262,850; July 26, 1966; assigned to Imperial Chemical Industries Limited, England

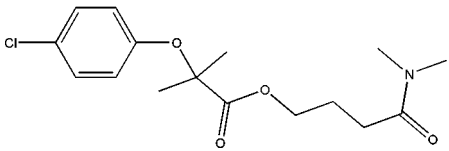
CLOFIBRIDE

Therapeutic Function: Antihyperlipidemic

Chemical Name: 3-(Dimethylaminocarbonyl)-propyl-4'-chlorophenoxyisobutyrate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 26717-47-5

Trade Name	Manufacturer	Country	Year Introduced
Lipenan	Charpentier	France	1974
Evimot	Muller Rorer	W. Germany	1978

Raw Materials

Ethyl 4'-chlorophenoxyisobutyrate
4-Hydroxy-N,N-dimethylbutyramide

Manufacturing Process

48.5 parts of ethyl 4'-chlorophenoxyisobutyrate are dissolved in 200 parts by volume of dry toluene in the presence of 262 parts of 4-hydroxy-N,N-dimethylbutyramide and 2 parts of aluminum isopropylate. The solution is heated for 8 hours, while collecting the toluene-ethanol azeotrope, in an apparatus provided with a distillation column at a controllable rate of reflux. After this it is filtered ,the solvent is evaporated in vacuo and the residue is distilled. An almost colorless, slightly yellow oil is obtained, the purity of which by chromatographic examination in the gaseous phase is of the order of 99.5%. Its boiling point is 175°C under 0.1 torr.

This oil is kept supercooled at the ambient temperature. Crystallization may be obtained by cooling or by seeding with crystals of the product. The melting point is 34°C (instantaneous on the Maquenne block).

The product can be recrystallized. For this, it is dissolved, for example, at the ambient temperature in petrol ether, ethyl ether or isopropyl ether, and this solution is cooled at about -50°C while stirring. After drying over sulfuric acid under vacuum, white needles of very great purity are thus obtained.

References

DOT 9 (5) 169 (1973)
I.N. p. 246
Nordmann, J., Mattioda, G.D. and Loiseau, G.P.M.H.; US Patent 3,792,082; February 12, 1974; assigned to Ugine Kuhlmann

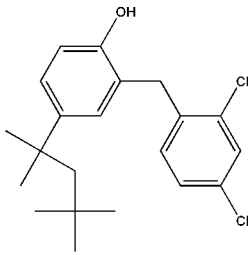
CLOFOCTOL

Therapeutic Function: Antiinfective, Bacteriostatic

Chemical Name: 2-(2,4-Dichlorobenzyl)-4-(1,1,3,3-tetramethylbutyl)phenol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 37693-01-9

Trade Name	Manufacturer	Country	Year Introduced
Octofene	Debat	France	1978

Raw Materials

p-(1,1,3,3-Tetramethylbutyl)phenol
2,4-Dichlorobenzyl chloride
Zinc chloride

Manufacturing Process

The following were introduced into a 1 liter flask provided with a reflux condenser: 206 g (1 mol) of p-(1,1,3,3-tetramethylbutyl)-phenol, 147 g (0.75 mol) of 2,4-dichlorobenzyl chloride, 27 g (0.2 mol) of pure melted zinc chloride, and 750 ml of anhydrous chloroform.

The mixture was heated to reflux for 24 hours. The chloroformic reaction mixture was washed with water, and then dried over anhydrous sodium sulfate. The chloroform was evaporated off and the oil obtained was fractionally distilled under a pressure of 0.2 mm Hg. The fraction distilling at 140°C to 160°C, being the desired product indicated above, was collected and crystallized. Yield: 94 g (32% of theory); MP 78°C (after recrystallization in petroleum ether).

References

Kleeman and Engel p. 228
DOT 15 (4) 171 (1979)
I.N. p. 246
Debat, J.; US Patent 3,830,852; August 20, 1974; assigned to Institute de Recherches Chimiques et Biologiques Appliquees (I.R.C.E.B.A.) (France)

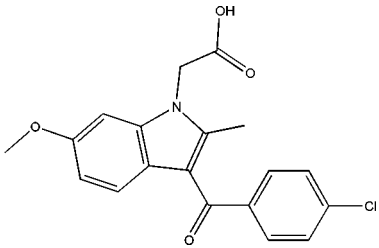
CLOMETACIN

Therapeutic Function: Analgesic, Antiinflammatory

Chemical Name: 1H-Indole-1-acetic acid, 3-(4-chlorobenzoyl)-6-methoxy-2-methyl-

Common Name: Clometacin; Mindolic acid

Structural Formula:



Chemical Abstracts Registry No.: 25803-14-9

Trade Name	Manufacturer	Country	Year Introduced
Clometacin	Roussel-Uclaf (Aventis)	-	-

Raw Materials

2-Nitro-4-methoxybenzaldehyde
Nitroethane
Palladium on charcoal
N,N-Dimethyl-p-chlorobenzamide
Sodium hydride
Potassium hydroxide
Acetic acid
Ammonium acetate
Hydrogen
Phosphorus oxychloride
Methyl monochloroacetate

Manufacturing Process

Preparation of 1-carboxymethyl-2-methyl-3-p-chlorobenzoyl-6-methoxy-indole

STEP A: 1-(2'-Nitro-4'-methoxyphenyl)-2-methyl-2-nitroethylene

15.0 g of 2-nitro-4-methoxybenzaldehyde (Boon, Soc., 1949 Suppl., p. 230) were introduced into a mixture of 75 ml of acetic acid, 9.5 ml of nitroethane and 6.5 gm of ammonium acetate and the resulting mixture was heated to reflux and held there for 2 h. After cooling the mixture to room temperature, the mixture was added to ice water and the precipitate formed was recovered by vacuum filtration. The precipitate was washed with water and twice crystallized from ethanol and treated with carbon black to obtain 9.6 gm of 1-(2'-nitro-4'-methoxyphenyl)-2-methyl-2-nitroethylene having a melting point of 111°C.

STEP B: 2-Methyl-6-rnethoxyindole

32 g of 1-(2'-nitro-4'-methoxyphenyl)-2-methyl-2-nitroethylene and 3.2 g of palladized charcoal con training 18% palladium were introduced into a mixture of 320 ml of ethyl acetate, 48 ml of ethanol and 240 ml of acetic acid and after a purge with nitrogen then with hydrogen, the mixture was agitated under a hydrogen atmosphere. The reaction temperature was allowed to rise to 50°C and was held at that temperature by cooling. 18.2 L of hydrogen were absorbed in 3 h after which the reaction mixture was purged with nitrogen and the catalyst was removed by filtration. The reaction mixture was concentrated to dryness under reduced pressure and the residue was dissolved in methylene chloride. The methylene chloride solution was washed with an aqueous solution of sodium bicarbonate, with water, was dried and concentrated to dryness under reduced pressure. The residue was crystallized from petroleum ether (boiling point 65-75°C) and the resulting product was dissolved in ether. The ether solution was filtered over alumina and 6.4 g of 2-methyl-6-methoxy-indole having a melting point of 104°C were obtained there from.

STEP C: 2-Methyl-3-p-chlorobenzoyl-6-methoxyindole

9 g of 2-methyl-6-methoxy-indole were added to a suspension of 20.6 g of N, N-dimethyl-p-chlorobenzamide and 6.4 ml of phosphorus oxychloride. The interior reaction temperature obtained was brought to 60°C and rapidly rose to 115°C, the temperature was reduced and held for 2 h at 85°C. The temperature was then reduced to 50°C and the reaction mixture was added to water and then 400 ml of ethanol were added thereto. The reaction mixture was adjusted to a pH of 10 by the addition of sodium hydroxide solution and

was stirred at room temperature overnight. The precipitate was recovered by filtration and washed with water until the wash-waters were neutral. The precipitate was impasted with 20 ml of ethanol at 20°C, vacuum filtered and dried at 60°C to obtain 16.5 g of 2-methyl-3-p-chlorobenzoyl-6-methoxyindole having a melting point of 208°C.

Step D: Methyl ester of 1-carboxymethyl-2-methyl-3-p-chlorobenzoyl-6-methoxyindole

20 ml of dimethylformamide were added to 0.32 g of a 50% suspension of sodium hydride in oil and then a solution of 2 g of 2-methyl-3-p-chlorobenzoyl-6-methoxy-indole in 20 ml of dimethylformamide was added thereto. After hydrogen evolution ceased, a solution of 1 g of methyl monochloroacetate in 5 ml of dimethylformamide was added and the reaction mixture was stirred overnight at room temperature. The mixture was evaporated to dryness and the residue was taken up in water and vacuum filtered. The crystals were washed with water and dried in vacuum at 60°C to obtain 2.5 g of product which was purified by recrystallization from hot and cold methanol to give 1.9 g of the methyl ester of 1-carboxymethyl-2-methyl-3-p-chloro-benzoyl-6-methoxy-indole having a melting point of 148-149°C as yellow crystals.

STEP E: 1-Carboxymethyl-2-methyl-3-p-chlorobenzoyl-6-methoxy-indole

2.25 g of potassium hydroxide were dissolved in 100 ml of methanol and 5 ml of water and then 7.45 g of the methylester of 1-carboxymethyl-2-methylchlorobenzoyl-6-methoxy-indole were added thereto. The mixture was heated at reflux for 1 h and then was concentrated to dryness. The residue was taken up in 70 ml of boiling water and the solution was filtered while hot. The filtrate was cooled to 20°C and acidified to a pH of 1 by the addition of 30 ml of 2 N hydrochloric acid. The precipitate was recovered by vacuum filtration and was washed with water, then methanol and finally ether and was dried at 70°C. The resulting 6.3 g of product was purified by recrystallization from ethanol to obtain 3.7 g of 1-carboxymethyl-2-methyl-3-p-chloro-benzoyl-6-methoxyindole having a melting point of 242°C.

References

Allais A., Nomine G.; US Patent No. 3,856,967; Dec. 24, 1974; Assigned: Roussel Uclaf, Paris, France

CLOMETHIAZOLE

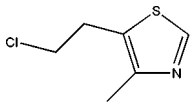
Therapeutic Function: Anticonvulsant, Hypnotic, Sedative

Chemical Name: 5-(2-Chloroethyl)-4-methylthiazole

Common Name: Chlormethiazol; Clomethiazole

Chemical Abstracts Registry No.: 533-45-9

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Clomethiazole	Hoffmann La Roche (Roche)	-	-

Raw Materials

1,3-Dichlorpentanon-4
Hydrogen chloride
Ammonium dithiocarbamate
Hydrogen peroxide

Manufacturing Process

2-Mercapto-4-methyl-5-(2-chlorethyl)-1,3-thyazol is produced as a result of reaction of 1,3-dichlorpentanon-4 with ammoniumdithiocarbamat (melting point 128°C).

To 193,5 g 2-mercapto-4-methyl-5-(2-chlorethyl)-1,3-thyazol 600.0 g 35% HCl is added and heated to 60°C, after this 30.0 g hydrogen peroxide is added. After oxidation the mixture is treated by $BaCl_2$ filtered, washed by ether and dried. So 4-methyl-5-(2-chlorethyl)-1,3-thyazol is obtained.

References

CH Patent No. 200,248; March 12, 1937; Assigned: F. Hoffmann-La Roche and Co Aktiengesellschaft, Basel (Schweiz).

CLOMETOCILLIN POTASSIUM

Therapeutic Function: Antibiotic

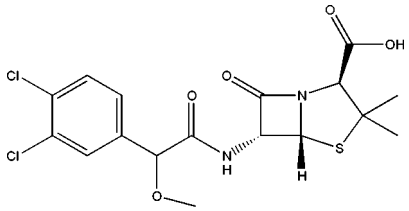
Chemical Name: (3,4-Dichloro-alpha-methoxybenzyl)penicillin potassium

Common Name: Chlomethocillin potassium; Clometocillin potassium; Penicillin 356

Chemical Abstracts Registry No.: 15433-28-0; 1926-49-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Clometocillin potassium	Ribbon	-	-
Rixapen	Menarini	-	-

Structural Formula:



Raw Materials

6-Aminopenicillanic acid
Phosphoric acid
Triethylamine
Ethylchloroformate
Potassium hydroxide
Potassium bicarbonate
α-Methoxy-3,4-dichloro-phenylacetyl chloride
α-Methoxy-4-chlorophenyl acetic acid

Manufacturing Process

2 Methods of producing of clometocillin:

1. 6-Aminopenicillanic acid (2.16 g) is dissolved in 20 ml of a one molar aqueous solution of potassium bicarbonate and 10 ml of acetone. The resultant solution is cooled in an ice-water bath and to it is added with stirring a solution of 2.7 g of alpha-methoxy-3,4-dichloro-phenylacetyl chloride in 10 ml of acetone. The pH is adjusted to 7-8 and upon completion of the addition the reaction medium is stirred for 15 min at ice bath temperature and then for 2.5 h at room temperature, maintaining the pH range between 7 and 8. The solution is extracted once with ether and then adjusted to pH 2.5 with 20% phosphoric acid. The acidic solution is extracted once with 30 ml of butyl acetate and again with 10 ml of butyl acetate. These combined butyl acetate extracts are thereafter successively washed twice with water and reextracted at pH 7 with 0.5 N aqueous potassium hydroxide solution. The aqueous layer is washed twice with ether and the remaining organic solvent is then removed by evaporation under reduced pressure. The washed aqueous layer is then lyophilized and the residue thus obtained taken up in acetone. The crystal line product is collected by filtration and dried to yield the potassium salt of 6-(α-methoxy-3,4-dichlorophenylacetamido)penicillanic acid. Upon treatment with mineral acid of an aqueous solution of the compound so prepared, there is obtained the free acid, 6-(α-methoxy-3,4-dichlorophenylacetamido)penicillanic acid.

2. A solution of 19.2 g (0.096 mole) of α-methoxy-4-chlorophenyl acetic acid in 200 ml of acetone is cooled in an ice bath to 0°C. To the cooled solution is added 10.2 g (0.1 mole) of triethylamine in 100 ml of acetone. The temperature of the reaction mixture is maintained at 10°C and a solution of 11.0 g (0.1 mole) of ethylchloroformate in 45 ml of acetone is added dropwise with agitation so as to maintain a final reaction temperature of -5°C. To this mixture is then slowly added with stirring a solution of 23.8 g (0.11 mole) of 6-aminopenicillanic acid in 40 ml of water and 15 ml of triethylamine. Upon completion of the addition, the mixture is stirred while attaining room

temperature and then stirred for an additional 1.5 h. The mixture is extracted with three portions of 300 ml, of ether and the resulting aqueous solution adjusted to pH 2.0 with 6 N sulfuric acid, maintaining a temperature of less than 10°C. At pH 2, the solution is extracted with 250 ml, of butyl acetate and then extracted twice with 75 ml each of butyl acetate. To the combined butyl acetate extracts are added 250 ml of water and the pH adjusted to 8.0 by the addition of sodium bicarbonate. The layers are separated and the aqueous layer adjusted to 2.0 by the addition of 6 N sulfuric acid at less than 10°C. This acid aqueous mixture is next extracted with 200 ml of butyl acetate and the organic extract extracted once with water and dried over sodium sulfate. To the butyl acetate solution is added with vigorous stirring a solution of potassium hydroxide in n-butanol (40 g/l) until the pH of the reaction mixture is 8.4. The mixture is then cooled until crystallization occurs. The crystals are collected by centrifugation, washed with a small amount of acetone and dried. These dried crystals are recrystallized from butanol and retried to yield 6-(α-methoxy-4-chlorophenylacetamido)penicillanic acid as the potassium salt. Treatment with acid yields the corresponding free acid 6-(α-methoxy-4-chloro-phenylacetamido)penicillanic acid.

References

Vanderhaeghe H., et al.; US Patent No. 3,007,920; Nov. 7, 1961; Assigned: Recherche et Industrie Therapeutiques, en abrege R.I.T., Genval, Belgium, a corporation of Belgium

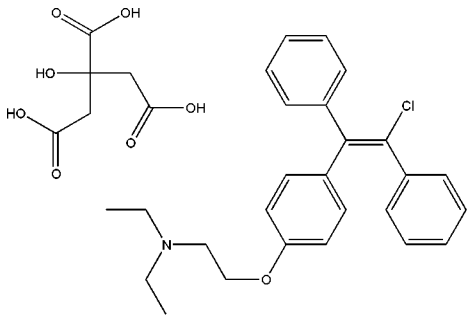
CLOMIPHENE DIHYDROGEN CITRATE

Therapeutic Function: Antiestrogen

Chemical Name: 2-[4-(2-Chloro-1,2-diphenylethenyl)phenoxy]-N,N-diethylethanamine dihydrogen citrate

Common Name: Clomifen citrate

Structural Formula:



Chemical Abstracts Registry No.: 50-41-9; 911-45-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Clomid	Lepetit	Italy	1966
Clomid	Merrell Dow	UK	1966
Clomid	Doetsch Grether	Switz.	1967
Clomid	Merrell National	US	1967
Dyneric	Merrell	W. Germany	1967
Clomid	Merrell	France	1968
Serophene	Serono	US	1982
Clomivid	Draco	Sweden	-
Clostilbegyt	EGYT	Hungary	-
Gravosan	Spofa	Czechoslovakia	-
Ikaclomine	Ika	Israel	-
Omifin	Inibsa	Spain	-
Prolifen	Chiesi	Italy	-

Raw Materials

4-(β-Diethylaminoethoxy)benzophenone
Benzyl magnesium chloride
N-Chlorosuccinimide
Hydrogen chloride
Citric acid

Manufacturing Process

A mixture of 20 g of 1-[p-(β-diethylaminoethoxy)phenyl]-1,2-diphenylethanol in 200 cc of ethanol containing an excess of hydrogen chloride was refluxed 3 hours. The solvent and excess hydrogen chloride were removed under vacuum, and the residue was dissolved in a mixture of ethyl acetate and methylene chloride. 1-[p-(β-diethylaminoethoxy)phenyl]-1,2-diphenylethylene hydrochloride was obtained, melting at 148° to 157°C. This hydrochloride salt was treated with N-chlorosuccinimide in dry chloroform under reflux. The product then obtained was converted to the free base and treated with citric acid. The dihydrogen citrate salt of 1-[p-(β-diethylaminoethoxy)phenyl]-1,2-diphenylchloroethylene was obtained, melting at 116.5° to 118°C.

The intermediate 1-[p-(β-diethylaminoethoxy)phenyl]-1,2-diphenylethanol was obtained by treating 4-(β-diethylaminoethoxy)benzophenone with benzylmagnesium chloride. It melted at 95° to 96°C.

References

Merck Index 2349
DFU 3 (11) 850 (1978)
Kleeman and Engel p. 230
PDR pp. 1225, 1699
OCDS Vol. 1 pp. 105, 148 (1977) and 2 p. 127 (1980)
I.N.p.247

REM p. 990
Allen, R .E., Palopoli, F .P., Schumann, E.L. and Van Campen, M.G. Jr.; US Patent 2,914,563; November 24, 1959; assigned to The Wm. S. Merrell Company

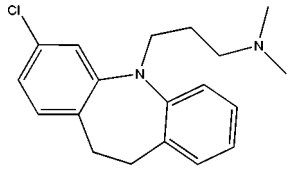
CLOMIPRAMINE

Therapeutic Function: Antidepressant

Chemical Name: 3-Chloro-10,11-dihydro-N,N-dimethyl-5H-dibenz[bf] azepine-5-propanamine

Common Name: Chlorimipramine

Structural Formula:



Chemical Abstracts Registry No.: 303-49-1; 17321-77-6 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Anafranil	Ciba Geigy	Switz.	1968
Anafranil	Ciba Geigy	W. Germany	1968
Anafranil	Fujisawa	Japan	1970
Anafranil	Ciba Geigy	Italy	1970
Anafranil	Ciba Geigy	UK	1970
Anafranil	Ciba Geigy	Australia	1983
Marunil	Unipharm	Israel	-
Hydiphen	Arzneimittelwerk Dresden	E. Germany	-

Raw Materials

3-Chloroiminodibenzyl
Sodium amide
γ-Dimethylaminopropyl chloride

Manufacturing Process

22.9 parts of 3-chloroiminodibenzyl are dissolved in 300 parts by volume of xylene, and 4 parts of sodium amide, pulverized and suspended in toluene,

are added thereto while stirring and maintaining the whole under a nitrogen atmosphere. The xylene solution immediately turns dark colored, but upon crystallization of the sodium salt therefrom it becomes again light-colored. The reaction mixture is stirred for about 2 hours at 80°C until the development of ammonia has terminated. A solution of γ-dimethylaminopropyl chloride in toluene, prepared by setting free a corresponding amount of the free base from 17.4 parts of its hydrochloride salt by addition of aqueous sodium hydroxide solution in about 10% excess, extraction with toluene and drying for 2 hours over anhydrous sodium sulfate is added to the xylene solution containing the sodium salt mentioned above and the whole is stirred under reflux for 15 hours. Precipitated sodium chloride is filtered off and the filtrate is concentrated. The residue is diluted with ether, and the hydrochloride of 3-chloro-5-(γ-dimethylaminopropyl)-iminodibenzyl is precipitated by introducing dry, gaseous hydrogen chloride. It is filtered off under suction and purified by repeated recrystallization from acetone; the pure substance melts at 191.5°C to 192°C.

References

Merck Index 2350
Kleeman and Engel p. 231
DOT 4 (4) 143 (1968) and 9 (6) 218 (1973)
I.N. p.248
Schindler, W. and Dietrich, H.; US Patent 3,515,785; June 2, 1970; assigned to Geigy Chemical Corp.

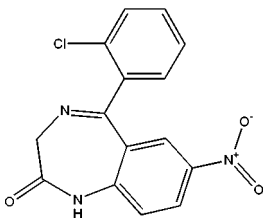
CLONAZEPAM

Therapeutic Function: Anticonvulsant

Chemical Name: 5-(o-Chlorophenyl)-1,3-dihydro-7-nitro-2H-1,4-benzodiazepin-2-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 1622-61-3

Trade Name	Manufacturer	Country	Year Introduced
Rivotril	Roche	France	1973
Rivotril	Roche	UK	1974
Clonopin	Roche	US	1975
Rivotril	Roche	Italy	1975
Rivotril	Roche	W. Germany	1976
Rivotril	Roche	Switz.	1976
Rivotril	Roche	Japan	1980
Rancedon	Sumitomo	Japan	1981
Antelepsin	Arzneimittelwerk Dresden	E. Germany	-
Clonex	Teva	Israel	-
Iktorivil	Roche	-	-
Landsen	Sumitomo	Japan	-

Raw Materials

Sodium nitrite
Ammonia
Hydrogen chloride
Pyridine
Potassium nitrate
Hydrogen
2-Amino-2'-nitrobenzophenone
Bromoacetyl bromide
Sulfuric acid

Manufacturing Process

The following description is taken from US Patent 3,116,203. A stirred solution of 75 g of 2-amino-2'-nitrobenzophenone in 700 ml of hot concentrated hydrochloric acid was cooled to 0°C and a solution of 21.5 g of sodium nitrite in 50 ml of water was added in the course of 3 hours. The temperature of the suspension was kept at 2° to 7°C during the addition. The resulting clear solution was poured into a stirred solution of 37 g of cuprous chloride in 350 ml of hydrochloric acid 1:1. The solid which had formed after a few minutes was filtered off, washed with water and recrystallized from ethanol. Crystals of 2-chloro-2'-nitrobenzophenone melting at 76° to 79°C were obtained.

A solution of 20 g of 2-chloro-2'-nitrobenzophenone in 450 ml of ethanol was hydrogenated at normal pressure and room temperature with Raney nickel. After uptake of about 6 liters of hydrogen the catalyst was filtered off, and the alcohol then removed in vacuo. The residue was distilled in a bulb tube at 0.4 mm and a bath temperature of 150° to 165°C giving a yellow oil. The oil was dissolved in alcohol, and on addition of water, needles of 2-amino-2'-chlorobenzophenone melting at 58° to 60°C were obtained.

To a solution of 42 g of 2-amino-2'-chlorobenzophenone in 500 ml of benzene, 19 ml of bromoacetyl bromide was added dropwise. After refluxing for 2 hours, the solution was cooled, washed with 2 N sodium hydroxide and evaporated. The residue was recrystallized from methanol giving crystals of 2-bromo-2'-(2-chlorobenzoyl)acetanilide melting at 119° to 121°C.

To a solution of 14.5 g of 2-bromo-2'-(2-chlorobenzoyl)acetanilide in 100 ml of tetrahydrofuran, an excess of liquid ammonia (ca 150 ml) was added. The ammonia was kept refluxing with a dry-ice condenser for 3 hours after which time the ammonia was allowed to evaporate and the solution was poured into water. Crystals of 2-amino-2'-(2-chlorobenzoyl)acetanilide were collected, which after recrystallization from ethanol melted at 162° to 164°C.

A solution of 3 g of 2-amino-2'-(2-chlorobenzoyl)acetanilide in 50 ml of pyridine was refluxed for 24 hours after which time the pyridine was removed in vacuo. The residue was recrystallized from methanol and a mixture of dichloromethane and ether giving crystals of 5-(2-chlorophenyl)-3H-1,4-benzodiazepin-2(1H)-one melting at 212° to 213°C.

To a solution of 13.5 g of 5-(2-chlorophenyl)-3H-1,4-benzodiazepin-2(1H)-one in 60 ml of concentrated sulfuric acid, a solution of 5.5 g of potassium nitrate in 20 ml concentrated sulfuric acid was added dropwise. The solution then was heated in a bath at 45° to 50°C for 2.5 hours, cooled and poured on ice. After neutralizing with ammonia, the formed precipitate was filtered off and boiled with ethanol. A small amount of white insoluble material was then filtered off. The alcoholic solution on concentration yielded crystals of 7-nitro-5-(2-chlorophenyl)-3H-1,4-benzodiazepin-2(1H)-one which, after recrystallization from dichloromethane, melted at 238° to 240°C.

References

Merck Index 2352
Kleeman and Engel p. 232
PDR p. 1481
DOT 9 (6) 237 (1973) and 9 (12) 487 (1973)
I.N.p. 248
REM p. 1077
Kariss, J. and Newmark, H.L.; US Patents 3,116,203; December 31, 1963; and 3,123,529; March 3, 1964; both assigned to Hoffmann-LaRoche, Inc.
Keller, O., Steiger, N. and Sternbach, L.H.; US Patents 3,121,114; February 11, 1964; and 3,203,990; August 31, 1965; both assigned to Hoffmann-LaRoche, Inc.
Focella, A. and Rachlin, A.I.; US Patent 3,335,181; August 8, 1967; assigned to Hoffmann-LaRoche. Inc.

CLONIDINE HYDROCHLORIDE

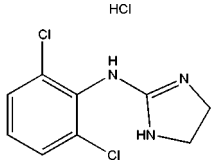
Therapeutic Function: Antihypertensive

Chemical Name: 2-(2,6-Dichloroanilino)-2-imidazoline hydrochloride

Common Name: -

Chemical Abstracts Registry No.: 4205-91-8; 4205-90-7 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Catapresan	Boehringer Ingelheim	W. Germany	1966
Catapresan	Boehringer Ingelheim	Switz.	1966
Catapresan	Boehringer Ingelheim	Italy	1970
Catapres	Tanabe	Japan	1970
Catapres	Boehringer Ingelheim	UK	1971
Catapresan	Boehringer Ingelheim	France	1971
Catapres	Boehringer Ingelheim	US	1974
Bapresan	Chemie Linz	Austria	-
Caprysin	Star	Finland	-
Clonilou	Hermes	Spain	-
Clonisin	Leiras	Finland	-
Clonnirit	Rafa	Israel	-
Dixarit	W.B. Pharm.	UK	-
Haemiton	Arzneimittelwerk Dresden	E. Germany	-
Ipotensium	Pierrel	Italy	-
Isoglaucon	Boehringer Ingelheim	W. Germany	-
Normopresan	Rafa	Israel	-
Tensinova	Cheminova	Spain	-

Raw Materials

2,6-Dichloroaniline
Hydrogen chloride
Ethylenediamine
Methyl iodide
Ammonium thiocyanate

Manufacturing Process

N-(2,6-dichlorophenyl)thiourea (MP 149°C) was prepared in customary manner from 2,6-dichloroaniline (Organic Synthesis III, 262-263) and ammonium thiocyanate. 16.0 g of this thiourea derivative were refluxed for

2.5 hours together with 16 g of methyl iodide in 150 cc of methanol. Thereafter, the methanol was evaporated out of the reaction mixture in vacuo, leaving as a residue 22 g of N-(2,6-dichlorophenyl)-S-methyl-isothiouronium hydroiodide of the formula having a melting point of 170°C. The entire residue was then admixed with an excess (120%) above the molar equivalent of ethylenediamine, and the mixture was heated for about one hour at 130° to 150°C. Methyl mercaptan was given off. Thereafter, the reaction mixture comprising 2-(2',6'-dichloroanilino)-1,3-diazacyclopentene-(2) hydroiodide was taken up in hot dilute acetic acid, and the resulting solution was made alkaline with 2 N NaOH. A precipitate formed which was separated by vacuum filtration, washed with water and dried. 4.0 g of 2-(2',6'-dichloroanilino)-1,3-diazacyclopentene-(2) were obtained. The product had a melting point of 130°C.

The free base was then dissolved in absolute methanol, and the resulting solution was then adjusted to an acid pH value with an ethereal hydrochloric acid solution. The acidified solution was purified with charcoal and then dry ether was added thereto until crystallization took place. The hydrochloride, prepared in this customary manner, had a melting point of 305°C according to US Patent 3,202,660.

References

Merck Index 2353
Kleeman and Engel p. 232
PDR p. 675
OCDS Vol. 1 p. 241 (1977)
DOT 9 (3) 97 (1973)
I.N. p. 249
REM p. 845
Zeile, K., Hauptmann, K.-H. and Stahle, H.; US Patents 3,202,660; August 24, 1965; and 3,236,857; February 22, 1966; both assigned to Boehringer Ingelheim GmbH, Germany

CLOPAMIDE

Therapeutic Function: Diuretic, Antihypertensive

Chemical Name: Benzamide, 3-(aminosulfonyl)-4-chloro-N-(2,6-dimethyl-1-piperidinyl)-, cis-

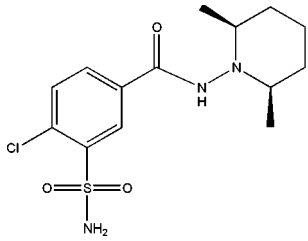
Common Name: Chlosudimeprimylum; Clopamide

Chemical Abstracts Registry No.: 636-54-4

Raw Materials

3-Chlorsulfonyl-4-chlorobenzoylchloride
1-Amino-cis-2,6-dimethylpiperidin-hydrochloride
Ammonium

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Brinaldix	Novartis	-	-
Brinaldix	Egis	-	-
Viskaldix	Novartis (ex.Sandoz)	-	-
Adurix	Benzon	-	-
Adurix	Nycomed Danmark A/S	-	-
Aquex	Sandoz	-	-
Brinaldix	Sandoz	-	-
Clopamide	Interpharma Praha, a.s.	-	-
Clopamide	Polfa	-	-

Manufacturing Process

To a solution of 5.5 g of 3-chlorsulfonyl-4-chlorobenzoylchloride in 20 ml chlorobenzole 3.3 g of 1-amino-cis-2,6-dimethylpiperidin-hydrochloride slowly was added at room temperature. Reaction mixture was heated to 100°-105°C during 8 h, then it was cooled to room temperature. The precipitated crystals of N-[cis-2,6-dimethyl-piperidyl-(1)]-3-chlorsulfonyl-4-chlorobenzoylamide were filtered and dried at 100°C under vacuo, then was treated by ammonium at room temperature. The obtained product was chromatographed (aluminum oxide; eluent: chloroform-methanol 9:1 and methanol-ether) to give N-[cis-2,6-dimethylpiperidyl-(1)]-3-sulfamyl-4-chlorbenzoylamide, melting point 235°-237°C.

References

Lindenmann A.J., Bruschweiler C.; CH Patent No. 436,288; May 31, 1967; Assigned: Sandoz, AG, Basel

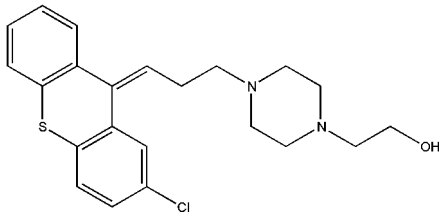
CLOPENTHIXOL

Therapeutic Function: Antipsychotic

Chemical Name: 4-[3-(2-Chloro-9H-thioxanthen-9-ylidene)propyl]-1-piperazineethanol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 982-24-1

Trade Name	Manufacturer	Country	Year Introduced
Ciatyl	Tropon	W. Germany	1961
Sordinol	Bracco	Italy	1967
Clopixol	Lundbeck	UK	1978
Cisordinol	Lundbeck	-	-
Sordenac	Lundbeck	-	-
Thiapax	Ikapharm	Israel	-

Raw Materials

2-Chloro-9-(3'-dimethylaminopropylidene)-thiaxanthene
N-(β-Hydroxyethyl)-piperazine

Manufacturing Process

A mixture of 31 5 g (0.1 mol) of 2-chloro-9-(3'-dimethylaminopropylidene)-thiaxanthene (MP 97°C) and 100 g of N-(β-hydroxyethyl)piperazine is heated to 130°C and boiled under reflux at this temperature for 48 hours. After cooling,the excess of N-(β-hydroxyethyl)piperazine is evaporated in vacuo, and the residue is dissolved in ether. The ether phase is washed with water and extracted with dilute acetic acid, and 2-chloro-9-[3'-N-(N'-β-hydroxyethyl)piperazinylpropylidene]-thiaxanthene separated from the aqueous acetic acid solution by addition of dilute sodium hydroxide solution to basic reaction. The free base is extracted with ether, the ether phase dried over potassium carbonate, the ether evaporated and the residue dissolved in absolute ethanol. By complete neutralization of the ethanolic solution with a solution of dry hydrogen chloride in absolute ethanol, the dihydrochloride of 2-chloro-9-[3'-N-(N'-β-hydroxyethyl)piperazinylpropylidene]-thiaxanthene is produced and crystallizes out as a white substance melting at about 250°C to 260°C with decomposition. The yield is 32 g.

References

Merck Index 2357
Kleeman and Engel p. 234
OCDS Vol. 1 p. 399 (1977)
DOT 9 (6) 229 (1973)
I.N. p. 249
Petersen, P.V., Lassen, N.O. and Holm, T.O.; US Patent 3,149,103; September 15, 1964; assigned to Kefalas A/S (Denmark)

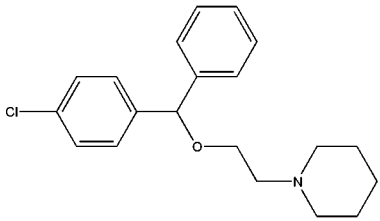
CLOPERASTINE

Therapeutic Function: Antitussive

Chemical Name: 1-[2-[(p-Chloro-α-phenylbenzyl)oxy]ethyl]piperidine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 3703-76-2

Trade Name	Manufacturer	Country	Year Introduced
Hustazol	Yoshitomi	Japan	1972
Seki	Symes	Italy	1981

Raw Materials

p-Chlorobenzhydryl bromide
Ethylene chlorohydrin
Piperidine

Manufacturing Process

The manufacture of a related compound is first described. 28.1 parts of p-chloro-benzhydryl bromide are heated to boiling, under reflux and with stirring, with 50 parts of ethylene chlorohydrin and 5.3 parts of calcined sodium carbonate. The reaction product is extracted with ether and the ethereal solution washed with water and dilute hydrochloric acid. The residue

from the solution in ether boils at 134° to 137°C under 0.2 mm pressure and is p-chloro-benzhydryl-(β-chloroethyl)ether.

28.1 parts of this ether are heated with 12 parts of methylethylamine (100%) in a sealed tube for 4 hours at 110°C. The product of the reaction is extracted several times with dilute hydrochloric acid, the acid solution made alkaline, in the cold, with concentrated caustic soda solution and the base which separates taken up in ether. The ether extract is washed with concentrated potassium carbonate solution, evaporated down, and the residue distilled in vacuo. The product is β-methylethyl aminoethyl p-chlorobenzhydryl ether, BP 152° to 153°C/0.1 mm.

Reaction with dimethylethylamine instead of methylethylamine leads directly to a quaternary compound, which type of compound can also be obtained by reacting the tertiary aminoethyl ether with reactive esters.

If 18 parts of piperidine are used instead of 12 parts of methylethylamine then the same procedure results in the formation of p-chloro-benzyhydril-(β-piperidino-ethyl)ether, boiling at 178° to 180°C under 0.15 mm pressure.

References

Merck Index 2358
Kleeman and Engel p. 234
I.N. p. 250
British Patent 670,622; April 23, 1952; assigned to Parke, Davis and Company

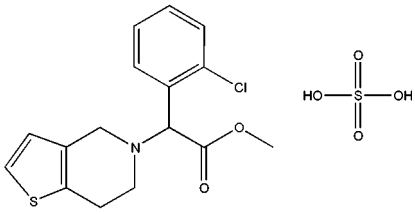
CLOPIDOGREL SULFATE

Therapeutic Function: Platelet aggregation inhibitor

Chemical Name: Thieno(3,2-c)pyridine-5(4H)-acetic acid, α-(2-chlorophenyl)-6,7-dihydro-, methyl ester, (αS)-, sulfate (1:1)

Common Name: Clopidogrel sulfate

Structural Formula:



Chemical Abstracts Registry No.: 120202-66-6

Trade Name	Manufacturer	Country	Year Introduced
Iscover	Bristol-Myers Squibb	-	-
Plavix	Sanofi-Synthelabo	-	-
Plavix	Bristol-Myers Squibb	-	-

Raw Materials

Racemic methyl-α-5-(4,5,6,7-tetrahydro-thieno(3,2-c)pyridyl)(2-chlorophenyl)-acetate
Ammonium camphor-10-sulfonate, L-
Saturated aqueous solution of sodium hydrogen carbonate
Sulfuric acid

Manufacturing Process

Levo-rotatory ammonium camphor-10-sulfonate is dissolved in a minimum of water and applied to the column of Amberlite IRN-77 resin. Elution is carried out with water. The eluted fractions containing the levo-rotatory camphor-10-sulfonic acid are lyophilized, melting point 198°C.

32 g (0.0994 mole) of racemic methyl-α-5-(4,5,6,7-tetrahydro-thieno(3,2-c)pyridyl)(2-chlorophenyl)-acetate are dissolved in 150 ml of acetone. 9.95 g (0.0397 mole) of levo-rotatory camphor-10-sulfonic acid monohydrate are added. The clear solution is left to stand at room temperature. After 48 hours the reaction mixture is concentrated to 50 ml and left to stand at room temperature for 24 hours. The obtained camphor-10-sulfonic acid salt of methyl-α-5-(4,5,6,7-tetrahydro-thieno(3,2-c)pyridyl)(2-chlorophenyl)-acetate (SR 25990) are filtered off, washed with acetone and dried (yield: 55% on the basis of the starting racemate), melting point 165°C, $[\alpha]_D^{20}$=+24.67 (c=1.58 g/100 ml; methanol). The crystals obtained above are redissolved in the minimum of boiling acetone (50 ml). The crystals obtained after cooling are filtered off, washed with acetone and dried (yield: 88%), m.p. 165°C, $[\alpha]_D^{20}$=+24.75 (c=1.68 g/100 ml; methanol).

12 g (0.022 mole) of the pure camphor-10-sulfonic acid salt of methyl-α-5-(4,5,6,7-tetrahydro-thieno(3,2-c)pyridyl)(2-chlorophenyl)-acetate are dissolved in a minimum of water. After cooling to 5°C, the aqueous solution obtained is made alkaline with a saturated aqueous solution of sodium hydrogen carbonate. The alkaline aqueous phase is extracted with dichloromethane. The organic extracts are dried over anhydrous sodium sulfate. On evaporation of the solvent a colorless oil of dextro-rotatory methyl-α-5-(4,5,6,7-tetrahydro-thieno(3,2-c)pyridyl)(2-chlorophenyl)-acetate is obtained (quantitative yield). Oil, $[\alpha]_D^{20}$=+51.52 (c=1.61 g/100 ml; methanol).

800 ml of a saturated aqueous solution of sodium bicarbonate are added to a suspension of 200 g of SR 25990 in 800 ml of dichloromethane. After vigorous shaking, the organic phase is separated, dried over sodium sulfate and the solvent is removed under reduced pressure. The residue is dissolved in 500 ml of ice-cold acetone and 20.7 ml of concentrated sulfuric acid (93.64%) are

added drop-wise. The precipitate formed is isolated by filtration and washed with 1 L of acetone, then dried in a vacuum oven at 50°C. 139 g of pure white crystals of hydrogen sulfate of dextro-rotatory methyl-α-5-(4,5,6,7-tetrahydro-thieno(3,2-c)pyridyl)(2-chlorophenyl)-acetate (SR 25990 C) are thus obtained, m.p. 184°C, $[\alpha]_D^{20}$=+55.10 (c=1.891 g/100 ml; methanol).

References

Badore A., Frehel D., US Patent No. 4,847,265; 07.11.1989; Assigned to Sanofi, France

Pandey B. et al., US Patent No. 6,635,763 B2; 10.21.2003; Assigned to Cadila Health Care Ltd.

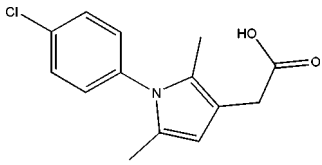
CLOPIRAC

Therapeutic Function: Antiinflammatory

Chemical Name: 1H-Pyrrole-3-acetic acid, 1-(4-chlorophenyl)-2,5-dimethyl-

Common Name: Clopirac

Structural Formula:



Chemical Abstracts Registry No.: 42779-82-8

Trade Name	Manufacturer	Country	Year Introduced
Nidran	Cont. Pharma	-	-
Nidran	Sankyo	-	-

Raw Materials

Dimethylamine
Acetic acid
Sodium hydroxide
Sodium cyanide
p-Chloroaniline
Morpholine
Sodium bicarbonate
1-p-Chlorophenyl-2,5-dimethylpyrrole
Formaldehyde
Methyl iodide
Potassium hydroxide
3-Acetyl-2,5-hexanedione
Hydrogen chloride

Manufacturing Process

2 Methods of producing of 1-p-chlorophenyl-2,5-dimethyl-3-pyrroleacetic acid

1. To 47.0 g (0.23 mol) of finely ground 1-p-chlorophenyl-2,5-dimethylpyrrole, a solution of 47.5 ml of an aqueous solution of 40% dimethylamine, 57.5 ml of acetic acid and 27.5 ml of 35% formaldehyde is slowly added while stirring. The mixture is stirred overnight at room temperature and extraction is made with 2 x 100 ml of ether. To the aqueous phase, 700 ml of 20% NaOH are added and extraction is made with ether. The organic phase is dried on $MgSO_4$, filtered and evaporated. To the residue obtained, 60 ml of absolute ethanol are added, then dropwise while stirring 34.1 g of methyl iodide. The mixture is stirred for 1 h, then the precipitate obtained is filtered; 85.9 g (yield: 92.5%) of methiodide of 1-p-chlorophenyl-2,5-dimethyl-3-dimethylaminomethylpyrrole are thus obtained, melting point 197°-201°C (dec).

To 166.0 g (0.41 mol) of the methiodide of 1-p-chlorophenyl-2,5-dimethyl-3-dimethylaminomethylpyrrole in 600 ml of dimethylsulfoxide, 66.6 g of sodium cyanide are added and the mixture is heated to 100°C with stirring and under a nitrogen stream for 3.5 h. After cooling, the mixture is poured into 1500 ml of water and extracted with ether. The ethereal phase is washed with water, dried on $MgSO_4$ and evaporated. The residue is vacuum stripped; 62.1 g of a yellow oil are thus obtained, which rapidly solidifies and which is recrystallized from aqueous methanol, 57.4 g (yield: 56%) of 1-p-chlorophenyl-2,5-dimethyl-3-pyrrole acetonitrile are obtained, melting point 86°-88°C, boiling point 158°-161°C (0.4 mm).

To 64.0 g of 1-p-chlorophenyl-2,5-dimethyl-3-pyrrole acetonitrile, 64.0 g of KOH and 300 ml of ethanol are added and the mixture is refluxed for 15 h. The alcohol is evaporated and one dilutes with 300 ml of water. The aqueous phase is washed with ether, and then acidified with 20% HCl. The precipitated obtained is filtered and one washes with petroleum ether and a minimum of ether. 58.5 g (yield: 85%) of 1-p-chlorophenyl-2,5-dimethyl-3-pyrroleacetic acid are thus obtained, melting point 99.5°-101°C.

2. To 9.5 g of 3-acetyl-2,5-hexanedione in 50 ml of benzene, 7.7 g of p-chloroaniline are added and the mixture is refluxed for 5 h with azeotropic removal of the water formed. The excess solvent is evaporated and residue is vacuum stripped: 12.0 g (yield: 80%) of 1-p-chlorophenyl-2,5-dimethyl-3-acetylpyrrole as an orange oil which rapidly crystallizes are thus obtained, boiling point 144°-146°C. Melting point of it 80°-81°C (recrystallization from hexane).

To 5.0 g of the 1-p-chlorophenyl-2,5-dimethyl-3-acetylpyrrole, 0.7 g of sulfur and 2.7 ml of morpholine are added and the mixture is refluxed for 5 h. Then, 20 ml of an aqueous solution of 20% are added and the mixture is refluxed for 4 h. The mixture is washed with ether, acidified with 20% HCl, and then extracted with ether. The organic phase is extracted with a 10% sodium bicarbonate solution which is acidified with 5% HCl. The solid obtained is filtered and recrystallized several times from a diethyl ether-pentane mixture. 1.1 g (yield: 20%) of 1-p-chlorophenyl-2,5-dimethyl-3-pyrroleacetic acid are thus obtained, melting point 100°-103°C.

References

GB Patent No. 1,406,330; Dec. 20, 1972; Assigned: Continental Pharma, a Belgian Body Corporate, Brussels, Begium

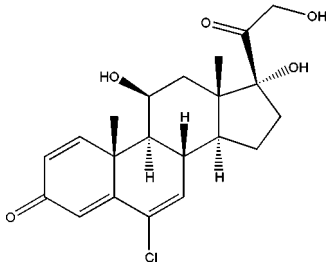
CLOPREDNOL

Therapeutic Function: Glucocorticoid

Chemical Name: 6-Chloro-11,17,21-trihydroxypregna-1,4,6-triene-3,20-dione

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 5251-34-3

Trade Name	Manufacturer	Country	Year Introduced
Syntestan	Syntex	W. Germany	1980
Novacort	Syntex	Switz.	1983
Synclopred	Syntex	-	-

Raw Materials

6α-Chlorohydrocortisone 21-acetate
Chloranil

Manufacturing Process

A mixture of 5 g of the 21-acetate of 6α-chlorohydrocortisone, 7 g of chloranil and 100 cc of n-amyl alcohol was refluxed for 16 hours, cooled and diluted with ether. The solution was successively washed with water, 5% sodium carbonate solution and water, dried over anhydrous sodium sulfate, filtered and evaporated to dryness under reduced pressure. Chromatographic purification of the residue yielded the 21-acetate of 6-chloro-$\delta^{1,4,6}$-pregnatriene-11β,17α,21-triol-3,20-dione.

References

Merck Index 2361
DFU 2 (1) 18 (1977)
OCDS Vol. 2 p. 182 (1980)
DOT 17 (10) 393 (1981)
I.N.p.250
Ringold, H.J. and Rosenkranz, G.; US Patent 3,232,965; February 1, 1966; assigned to Syntex Corp.

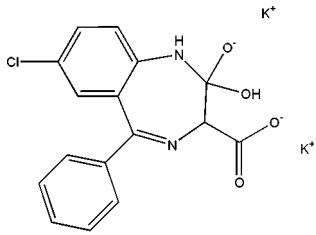
CLORAZEPATE DIPOTASSIUM

Therapeutic Function: Tranquilizer

Chemical Name: 7-Chloro-2,3-dihydro-2,2-dihydroxy-5-phenyl-1H-1,4-benzodiazepine-3-carboxylic acid dipotassium salt

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 15585-90-7; 20432-69-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Tranxene	Clin-Comar-Byla	France	1968
Tranxilium	Mack	W. Germany	1969
Tranxilium	Cun Midy	Switz.	1969
Transene	Zambeletti	Italy	1970
Tranxene	Abbott	US	1972
Tranxene	Boehringer Ingelheim	UK	1973
Mendon	Dainippon	Japan	1980
Anxidin	Orion	Finland	-
Azene	Endo	US	-
Belseren	Mead Johnson	-	-
Enadine	York	Argentina	-
Nansius	Prodes	Spain	-

Trade Name	Manufacturer	Country	Year Introduced
Noctran	Clin-Comar-Byla	France	-
Tranex	Idravlje	Yugoslavia	-
Tranxilen	Leo	Sweden	-

Raw Materials

2-Amino-5-chlorobenzonitrile
Potassium hydroxide
Magnesium
Methyl aminomalonate
Bromobenzene

Manufacturing Process

(A) Preparation of (2-Amino-5-Chlorophenyl)Phenylmethaneimine (4356 CB): A solution of 228.7 g (1.5 mold of 2-amino-5-chlorobenzonitrilein 1,800 ml of dry ether is added slowly in the course of about 3.5 hours to a solution of phenyl magnesium bromide prepared from 109 g (4.5 g-atoms) of magnesium turnings and 848 g (5.4 mols) of bromobenzene in 3,600 ml of anhydrous ether, and the mixture then heated under reflux for 15 hours.

The complex is decomposed by stirring the reaction mixture into a solution prepared from 500 g of ammonium chloride in 2,000 mi of water to which 3 kg of crushed ice have been added. After extraction and washing, the ether is evaporated in vacuo at 40°C. The oily residue is taken up in 500 ml of petroleum ether and left to crystallize by cooling at -20°C. The yellowish crystals formed are dried (309 g); MP_k (Kofler block): 74°C; yield: 92%.

(B) Preparation of 7-Chloro-3-Methoxycarbonyl-5-Phenyl-2-Oxo-2,3-Dihydro-1H-Benzo[f]-1,4-Diazepine (4347 CB): A solution of 9.2 g (0.04 mol) of compound 4356 CB in 20 ml of methanol is added dropwise, in the course of one hour and 30 minutes, to a boiling solution of 9.2 g (0.05 mol) of the hydrochloride of methyl aminomalonate in 30 ml of methanol. When this is completed, heating under reflux is continued for 30 minutes and the product then concentrated to dryness under reduced pressure. The residue is taken up in water and ether, the ethereal layer separated, the product washed with water and dried over sodium sulfate. The solvent is evaporated under reduced pressure. The residue, which consists of the methyl ester, could not be obtained in the crystalline state. It is dissolved in 25 ml of acetic acid, heated under reflux for 15 minutes, the product evaporated to dryness and the residual oil taken up in ether. A colorless solid separates which is filtered by suction and recrystallized from methanol. Colorless crystals are obtained (4.7 9); MP_k (Kofler block): 226°C. A second crop (1.5 g) is obtained on concentration of the mother liquor; MP_k (Kofler block): 222°C; total quantity 6.2 g, corresponding to a yield of 47%.

(C) Preparation of Dipotassium Salt of [2-Phenyl-2-(2-Amino-5-Chlorophenyl)-1-Azavinyl] Malonic Acid (4306 CB): 50 g of caustic potash are dissolved in 1,350 ml of 96% ethyl alcohol, and 82 g (0.25 mol) of compound 4347 CB are then added all at once at a temperature of about 70°C. The solid dissolves rapidly to form a yellow solution which then loses color while simultaneously an abundant colorless precipitate appears.

After cooling, the solid is filtered by suction and washed with alcohol at 96°C. The product is dried at ordinary temperature in a high vacuum. A colorless solid is obtained (quantitative yield), which is completely soluble in water. The aqueous solution is strongly alkaline in reaction; when acidified with acetic acid and heated on a water bath, it yields a precipitate of 7-chloro-5-phenyl-2-oxo-2,3-dihydro-1H-benzo[f]-1,4-diazepine.

References

Merck Index 2364
Kleeman and Engel p. 311
PDR p. 553
DOT 4 (4) 137 (1968) and 9 (6) 238 (1973)
I.N. p. 251
REM p. 1061
Schmitt, J.; US Patent 3,516,988; June 23, 1970

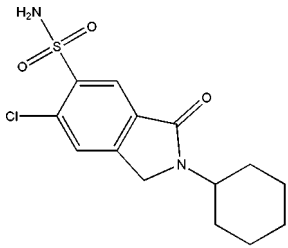
CLOREXOLONE

Therapeutic Function: Diuretic

Chemical Name: 6-Chloro-2-cyclohexyl-2,3-dihydro-3-oxo-1H-isoindole-5-sulfonamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 2127-01-7

Trade Name	Manufacturer	Country	Year Introduced
Speciatensol	Specia	France	1966
Flonatril	Specia	France	-
Nefrolan	May and Baker	UK	-
Nefrolan	Teikoku Zoki	Japan	-

Raw Materials

4-Chlorophthalimide	Sulfuric acid
Cyclohexylamine	Stannous chloride
Tin	Sodium nitrite
Hydrogen chloride	Sulfur dioxide
Potassium nitrate	Ammonia

Manufacturing Process

4-Chlorophthalimide (263 g) was reacted in amyl alcohol (2.6 l) with cyclohexylamine (143.5 g, 1 mol) at reflux temperature for 16 hours to give N-cyclohexyl-4-chlorophthalimide (250 g, 66%) as a solid, MP 134°C to 136°C.

N-Cyclohexyl-1-chlorophthalimide (250 g) was dissolved in glacial acetic acid (2.5 l), concentrated hydrochloric acid (555 ml) and tin (278 g) were added and the suspension was heated on a steam bath for 16 hours. The cooled solution was filtered and concentrated to dryness in vacuo to give a white solid. This solid was dissolved in water and the precipitated oil extracted with chloroform. The chloroform solution was dried and concentrated in vacuo to give a solid which, after recrystallization, yielded 5-chloro-2-cyclohexylisoindolin-1-one (43%), MP 140°C to 142°C.

5-Chloro-2-cyclohexylisoindolin-1-one (102.9 g) was dissolved in concentrated sulfuric acid (665 ml); potassium nitrate (723 g) in concentrated sulfuric acid (166 ml) was added at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred at 25°C for 12 hours. The reaction mixture was poured onto ice to give a cream solid which, after recrystallization from benzene, gave 5-chloro-2-cyclohexyl-6-nitroisoindolin-1-one (46.7 g, 44%) as a white solid, MP 164°C to 168°C.

5-Chloro-2-cyclohexyl-6-nitroisoindolin-1-one (93.9 g) was reduced in concentrated hydrochloric acid (1,970 ml) with stannous chloride (376 g). The reaction temperature rose to 70°C. The resulting solution was cooled in ice and filtered. The product was washed well with water, filtered and dried to give 6-amino-5-chloro-2-cyclohexylisoindolin-1-one (74.1 g, 87.6%) which, after recrystallization from benzene, had a MP of 216°C to 218°C.

6-Amino-5-chloro-2-cyclohexylisoindolin-1-one (42.5 g) was dissolved in concentrated hydrochloric acid (425 ml) and the solution diazotized by the addition of sodium nitrite (21.25 g) in water (125 ml). The resulting diazonium salt solution was added to a solution of liquid sulfur dioxide (93 ml) in glacial acetic acid (243 ml) containing cuprous chloride (2.25 g). A yellow solid was precipitated; this was filtered off, washed, dried and recrystallized from benzene to give 5-chloro-2-cyclohexylisoindolin-1-one-6-sulfonyl chloride (45 g, 80%) as a cream solid, MP 171°C to 174°C.

This sulfonyl chloride (23.7 g) was reacted with liquid ammonia (237 ml) to give 5-chloro-2-cyclohexyl-6-sulfamoylisoindolin-1-one (14.2 g, 53%). MP 259°C to 261°C.

References

Merck Index 2365
Kleeman and Engel p. 235
DOT 2 (4) 128 (1966)
I.N. p.251
Lee, G.E. and Wragg, W.R.; US Patent 3,183,243; May 11, 1965; assigned to May and Baker, Ltd.

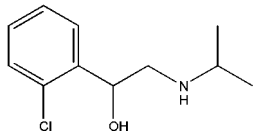
CLORPRENALINE

Therapeutic Function: Bronchodilator

Chemical Name: 2-Chloro-α-[(1-methylethyl)amino]methyl]benzenemethanol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 3811-25-4; 5588-22-7 (Hydrochloride monohydrate)

Trade Name	Manufacturer	Country	Year Introduced
Asthone	Eisai	Japan	1970
Aremans	Zensei	Japan	-
Asnormal	Sawai	Japan	-
Bronocon	Wakamoto	Japan	-
Clopinerin	Nippon Shoji	Japan	-
Clorprenaline	Kongo	Japan	-
Conselt	Sana	Japan	-
Cosmoline	Chemiphar	Japan	-
Fusca	Hoei	Japan	-
Kalutein	Tatsumi	Japan	-
Pentadoll	Showa	Japan	-
Propran	Kobayashi Kako	Japan	-
Restanolon	Isei	Japan	-
Troberin	Nippon Zoki	Japan	-

Raw Materials

o-Chloroacetophenone
Bromine
Sodium borohydride
Isopropylamine

Manufacturing Process

To a solution of 279 g of o-chloroacetophenone in 2 liters of anhydrous diethyl ether were added about 3 g of dibenzoyl peroxide. 5 g of bromine were added to the resulting solution, and after 3 minutes, the color of bromine had been discharged, indicating that the formation of ω-bromo-o-chloroacetophenone had been initiated. A further amount of 288 g of bromine was added dropwise to the reaction mixture over a 1.5 hour interval. After the addition of the bromine had been completed, the reaction mixture was stirred for one-half hour and poured over about 1 kg of crushed ice.

After the ice had melted, the resulting aqueous and ethereal layers were separated. The ethereal layer containing ω-bromo-o-chloroacetophenone was washed with successive 500 ml quantities of water, 5% sodium carbonate solution and again with water to remove the hydrogen bromide formed as a by-product in the reaction. The ethereal layer was dehydrated by contacting with anhydrous magnesium sulfate. The drying agent was removed by filtration and the ether was evaporated from the filtrate. The residue remaining after the evaporation consisted of about 400 g of ω-bromo-o-chloroacetophenone.

A solution of 400 g of ω-bromo-o-chloroacetophenone in one liter of methanol was cooled to about 25°C. A cold solution of 92.5 g of sodium borohydride in one liter of methanol was added as rapidly as possible to this cooled solution while maintaining the temperature below about 25°C. After the addition had been completed, the reaction mixture was allowed to stand for 4 hours at ambient room temperature, to complete the reduction of the keto group of the ω-bromo-o-chloroacetophenone. The reaction mixture containing a mixture of o-chlorophenyl ethylene-β-bromohydrin and o-chlorophenyl ethylene oxide was then evaporated in vacuo at room temperature to a syrup which was poured into about one liter of 5% hydrochloric acid to decompose any borate-alcohol complexes.

The two compounds were dissolved in diethyl ether by extracting the acidic layer three times with successive 500 ml portions of diethyl ether. The combined ether extracts were dried over anhydrous magnesium sulfate and filtered, and the ether was removed by evaporation in vacuo. A residue consisting of 400 g of a mixture of o-chlorophenyl ethylene-β-bromohydrin and o-chlorophenyl ethylene oxide was obtained.

400 g of a mixture of o-clilorophenyl ethylene-β-bromohydrin and o-chlorophenyl ethylene oxide were dissolved in one liter of anhydrous ethanol. To this solution was added a solution of 306 g of isopropylamine in one liter of anhydrous ethanol. The reaction mixture was heated at refluxing temperature for about 16 hours, thus forming N-[β-(o-chlorophenyl)-β-hydroxyethyl]-isopropylamine. The solvent was removed in vacuo, and to the residue was added a solution containing 200 ml of 12 N HCl in 2,500 ml of water.

The acidic solution was washed twice with 500 ml portions of ether which were discarded. The acidic layer was then made basic by the addition of 250 ml of 5% (w/v) sodium hydroxide, thus liberating the free base of N-[β-(o-chlorophenyl)-β-hydroxyethyl]-isopropylamine. The free base was extracted with two successive one liter portions of diethyl ether. The combined ether extracts were dried over anhydrous magnesium sulfate, filtered and

concentrated in vacuo to remove all of the solvents. N-[β-(o-chlorophenyl)-β-hydroxyethyl]-isopropylamine was thus obtained, according to US Patent 2,887,509.

The N-[β-(o-chlorophenyl)-β-hydroxyethyl]-isopropylamine obtained by the foregoing procedure was dissolved in about 3 liters of ether and dry hydrogen chloride gas was bubbled into the solution until it was saturated, whereupon the hydrochloride salt of N-[β-(o-chlorophenyl)-β-(hydroxy)-ethyl]isopropylamine precipitated. The salt was separated from the ether by filtration, and was dissolved in two liters of anhydrous ethanol. The alcoholic solution was decolorized with charcoal and filtered.

Three liters of anhydrous ether were added thereto and the N-[β-(o-chlorophenyl)-β-hydroxyethyl]-isopropylamine hydrochloride precipitated in crystalline form as the monohydrate. The mixture was maintained at about 0°C for 40 hours and then filtered. The filter cake was washed with ether and dried. About 209 g of N-[β-(o-chlorophenyl)-β-(hydroxy)-ethyl]isopropylamine hydrochloride monohydrate, melting at about 163° to 164°C, were obtained according to US Patent 2,816,059.

References

Merck Index 2368
Kleeman and Engel p. 236
OCDS Vol. 2 p. 39 (1980)
I.N . p. 252
Mills, J.; US Patent 2,816,059; December 10, 1957; assigned to Eli Lilly and Company
Nash, J.F.; US Patent 2,887,509; May 19, 1959; assigned to Eli Lilly and Company

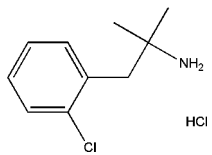
CLORTERMINE HYDROCHLORIDE

Therapeutic Function: Antiobesity

Chemical Name: 2-Chloro-α-α-dimethylbenzeneethanamine hydrochloride

Common Name: 1-(o-Chlorophenyl)-2-methyl-2-aminopropane hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 10389-72-7; 10389-73-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Voranil	U.S.V.	US	1973

Raw Materials

o,α-Dichlorotoluene	Acetone
Sodium cyanide	Magnesium
Sulfuric acid	Hydrogen chloride

Manufacturing Process

To a Grignard reagent (prepared from 50.0 g of o,α-dichloro-toluene and 7.45 g of magnesium in diethyl ether) is added 18.0 g of acetone at such rate that constant reflux is maintained. The reaction mixture is allowed to stand overnight at room temperature, and is then poured onto a mixture of 20% sulfuric acid and ice. The organic layer is separated, washed with water, an aqueous solution of sodium hydrogen carbonate and again with water, dried over magnesium sulfate and evaporated to dryness. The residue is distilled under reduced pressure to yield 42.6 g of 1-(o-chlorophenyl)-2-methyl-2-propanol, BP 120° to 122°C/12.5 mm.

To 29.0 ml of glacial acetic acid, cooled to 15°C, is added 11.5 g of sodium cyanide (98%) while stirring, and then dropwise 32.4 ml of concentrated sulfuric acid, dissolved in 29 ml of glacial acetic acid, while maintaining a temperature of 20°C. The 1-(o-chlorophenyl)-2-methyl-2-propanol is added moderately fast, allowing the temperature to rise spontaneously. After completing the addition, the reaction mixture is heated to 70°C and stirred, and is then poured onto a mixture of water and ice. The aqueous mixture is neutralized with sodium carbonate and extracted with diethyl ether. The organic solution is washed with water, dried over magnesium sulfate and evaporated to dryness.

The oily residue is taken up in 100 ml of 6 N aqueous hydrochloric acid and refluxed until a clear solution is obtained. The latter is made basic with aqueous ammonia and extracted with diethyl ether; the organic solution is separated, washed, dried and evaporated. The residue is distilled under reduced pressure to yield 26.3 g of 1-(o-chlorophenyl)-2-methyl-2-propylamine, BP 116° to 118°C/16 mm.

The 1-(o-chlorophenyl)-2-methyl-2-propylamine hydrochloride is prepared by adding ethanolic hydrogen chloride to an ice-cold solution of the free base in ethanol; the desired salt precipitates and is recrystallized from ethanol, MP 245° to 246°C.

References

Merck Index 2369
Kleeman and Engel p. 236
I.N. p. 253
REM p.891
Finocchio, D.V. and Heubner, C.F.; US Patent 3,415,937; December 10, 1968; assigned to Ciba Corporation

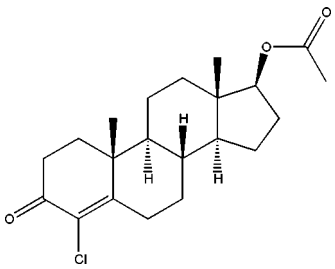
CLOSTEBOL ACETATE

Therapeutic Function: Anabolic

Chemical Name: Androst-4-en-3-one, 17-(acetyloxy)-4-chloro-, (17-β)-

Common Name: Chlortestesterone acetate; Clostebol acetate

Structural Formula:



Chemical Abstracts Registry No.: 855-19-6

Trade Name	Manufacturer	Country	Year Introduced
Clostebol acetate	Hunan Steroid Chemicals Co., Ltd.	-	-
Clostebol acetate	UCC Pharm Co., Ltd.	-	-
Alfa-Trofodermin	Pharmacia	-	-
Alfa-Trofodermin	Farmitalia	-	-
Steranabol	Farmitalia	-	-
Megagrisevit-Mono	Pharmacia	-	-
Turinabol	British Dragon	-	-

Raw Materials

Hydrogen chloride
Sodium bicarbonate
Acetic anhydride
4β,5-Epoxy-etiocholane-17β-ol-3-one
4α,5-Epoxy-androstane-17β-ol-3-one
Pyridine

Manufacturing Process

15 g of a mixture of 4β,5-epoxy-etiocholane-17β-ol-3-one and 4β,5-epoxy-androstane-17β-ol-3-one, dissolved in 375 ml chloroform, are treated with a stream of gaseous HCl at room temperature for about 2 h. The chloroform solution is neutralized with a sodium bicarbonate solution, washed with water and dried. The residue is crystallized from benzene or aqueous methanol and 9 g of needle-shaped crystals of 4-chloro-testosterone, melting point 186°-188°C, are obtained. Upon concentrating the mother-liquor, 3.2 g of this

product, melting point 180°-184°C, are covered.

1 g 4-chloro-testosterone are acetylated with 1 ml acetic anhydride and 5 ml pyridine at room temperature for 16 h. Ice is added to the solution, and the precipitate is filtered off and recrystallized from chloroform-ethanol; 1 g 4-chloro-testosterone-acetate, melting point 228°-230°C, is obtained.

References

Camerino B.; US Patent No. 2,953,582; Sep. 20, 1960; Assigned: Societa Farmaceutici Italia, a corporation of Italy

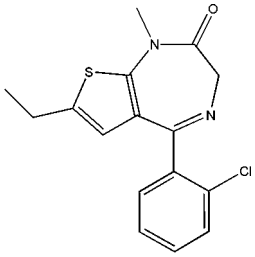
CLOTIAZEPAM

Therapeutic Function: Tranquilizer

Chemical Name: 5-(o-Chlorophenyl)-7-ethyl-1,3-dihydro-1-methyl-1H-thieno[2,3-e]-1,4-diazepin-2-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 33671-46-4

Trade Name	Manufacturer	Country	Year Introduced
Rize	Yoshitomi	Japan	1979
Trecalmo	Tropon	W. Germany	1979

Raw Materials

2-N-Methyiaminoacetamido-3-o-chlorobenzyl-5-ethylthiophene
Acetic acid

Manufacturing Process

To a solution of 10 g of 2-N-methylaminoacetamido-3-o-chlorobenzoyl-5-

ethylthiophene in 50 ml of pyridine are added 20 ml of benzene and 1.9 g of acetic acid. The resulting mixture is refluxed with stirring for 10 hours in a flask provided with a water-removing adaptor. The reaction mixture is concentrated, and the residue is extracted with chloroform. The chloroform layer is washed with water and then with a sodium hydrogen carbonate solution, then dried over magnesium sulfate. The chloroform is distilled off under reduced pressure, and toluene is added to the residue. Thus is precipitated white crystalline-5-o-chlorophenyl-7-ethyl-1-methyl-1,2-dihydro-3H-thieno-[2,3-e][1,4]diazepin-2-one, MP 105°C to 106°C.

References

Merck Index 2373
DFU 1 (8) 363 (1976)
Kleeman and Engel p. 237
DOT 16 (1) 13 (1980)
I.N. p. 254
Nakanishi, M., Araki, K.,Tahara, T. and Shiroki, M.; US Patent 3,849,405; November 19, 1974; assigned to Yoshitomi Pharmaceutical Industries, Ltd.

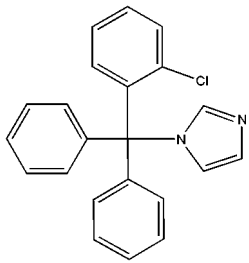
CLOTRIMAZOLE

Therapeutic Function: Antifungal

Chemical Name: 1-[(2-Chlorophenyl)diphenylmethyl]-1H-imidazole

Common Name: 1-(o-Chlorotrityl)imidazole

Structural Formula:



Chemical Abstracts Registry No.: 23593-75-1

Trade Name	Manufacturer	Country	Year Introduced
Canesten	Bayer	UK	1973
Canesten	Bayer	Italy	1973
Canesten	Bayer	W. Germany	1973
Lotrimin	Schering	US	1975

Trade Name	Manufacturer	Country	Year Introduced
Empecid	Bayer	Japan	1976
Trimysten	Bellon	France	1978
Mycelex	Miles	US	1979
Baycuten	Bayropharm	W. Germany	-
Gyne-Lotrimin	Debay	US	-
Micoter	Cusi	Spain	-
Myclo	Boehringer Ingelheim	-	-
Mycosporin	Bayer	-	-

Raw Materials

o-Chlorophenyldiphenylmethyl chloride
Imidazole

Manufacturing Process

156.5 g (0.5 mol) o-chlorophenyldiphenylmethyl chloride and 34 g (0.5 mol) imidazole are dissolved in 500 ml acetonitrile, with stirring, and 51 g (0.5 mol) triethylamine are added, whereupon separation of triethylamine hydrochloride occurs even at room temperature. In order to complete the reaction, heating at 50°C is carried out for 3 hours. After cooling, one liter of benzene is added and the reaction mixture is stirred, then washed salt-free with water. The benzene solution is dried over anhydrous sodium sulfate, filtered and concentrated by evaporation; giving 167 g crude 1-(o-chlorophenylbisphenylmethyl)-imidazole. By recrystallization from acetone, 115 g (= 71% of the theory) of pure 1-(o-chlorophenylbisphenylmethyl)-imidazole of MP 154° to 156°C are obtained.

References

Merck Index 2374
Kleeman and Engel p. 238
PDR pp. 1257, 1631
DOT 10 (1) 32 (1974)
I.N. p. 254
REM p. 1227
Buechel, K.H., et al; South African Patent 69/0039; January 3, 1969; assigned to Farbenfabriken Bayer AG, Germany
Buechel, K.H., Regel, E. and Plempel, M.; US Patent 3,660,577; May 2, 1972; and US Patent 3,705,172; Dec. 5, 1972; both assigned to Farbenfabriken Bayer A.G. (Germany)

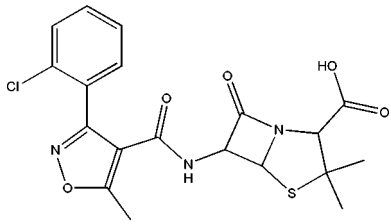
CLOXACILLIN

Therapeutic Function: Antibacterial

Chemical Name: 6-[[[[3-(2-Chlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]-amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid

Common Name: [3-(o-Chlorophenyl)-5-methyl-4-isoxazolyl]penicillin

Structural Formula:



Chemical Abstracts Registry No.: 61-72-3; 642-78-4 (Sodium Salt)

Trade Name	Manufacturer	Country	Year Introduced
Orbenin	Beecham	UK	1962
Cloxypen	Allard	France	1964
Orbenin	Beecham	W. Germany	1964
Tegopen	Bristol	US	1965
Cloxapen	Beecham	US	1976
Acucillin	Fuji	Japan	-
Ampiclox	Beecham	W. Germany	-
Austrastaph	C.S.L.	Australia	-
Benicil	Ibsa	Switz.	-
Ellecid	Pharmax	Italy	-
Ekvacilline	Astra	-	-
Gelstaph	Beecham	-	-
Kloxerate	Duphar	UK	-
Methocillin-S	Meiji	Japan	-
Novocloxin	Novopharm	Canada	-
Orbenil	Teva	Israel	-
Orbenine	Beecham-Sevigne	France	-
Penstapho-N	Bristol	-	-
Prostaphlin	Galenika	Yugoslavia	-
Prostaphlin	Banyu	Japan	-
Rivoclox	Rivopharm	Switz.	-
Solcillin-C	Takeda	Japan	-
Staphybiotic	Delagrange	France	-
Syntarpen	Polfa	Poland	-
Totaclox	Beecham	Japan	-

Raw Materials

Ethyl acetoacetate
o-Chlorobenzohydroxamic acid chloride
6-Aminopenicillanic acid

Manufacturing Process

The reaction between 6-aminopenicillanic acid (6.5 g) and 3-o-chlorophenyl-5-methylisoxazole4-carbonyl chloride (7.66 g) gave the sodium salt of 3-o-chlorophenyl-5-methyl-4-isoxazolylpenicillin (9.98 g) as a pale yellow solid. Colorimetric assay with hydroxylamine against a benzylpenicillin standard indicated a purity of 68%.

The 3-o-chlorophenyl-5-methylisoxazole-4-carboxylic acid, from which the acid chloride was prepared, was obtained by hydrolysis of the ester product of the reaction between o-chlorobenzohydroxamic chloride and ethyl acetoacetate in methanolic sodium methoxide. Reaction with thionyl chloride gave the starting material.

References

Merck Index 2376
Kleeman and Engel p. 239
PDR pp. 673, 1606
OCDS Vol. 1 p. 413 (1977)
I.N.p.254
REM p. 1195
Doyle, F.P. and Nayler, J.H.C.; British Patent 905,778; September 12, 1962; assigned to Beecham Research Laboratories, Ltd.
Doyle, F.P. and Nayler, J.H.C.; US Patent 2,996,501; August 15, 1961

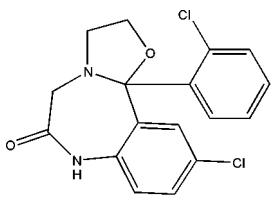
CLOXAZOLAM

Therapeutic Function: Tranquilizer

Chemical Name: 10-Chloro-11b-(2-chlorophenyl)-2,3,7,11b-tetrahydrooxazolo[3,2-d][1,4]benzodiazepin-6(5H)-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 24166-13-0

Trade Name	Manufacturer	Country	Year Introduced
Sepazon	Sankyo	Japan	1974
Enadel	Pfizer Taito	Japan	1974
Lubalix	Lubapharm	Switz.	1983
Betavel	Pharm. Investi	Spain	-
Olcadil	Sankyo	Japan	-
Tolestan	Roemmers	Argentina	-

Raw Materials

5-Chloro-2-bromoacetylamino-o-chlorobenzophenone
Ethanolamine

Manufacturing Process

As described in US Patent 3,772,371: To a solution of 5.8 g of 5-chloro-2-bromoacetylamino-o-chlorobenzophenone in 120 ml of ethanol were added 0.95 g of ethanolamine and 1.3 g of sodium acetate. The resulting mixture was heated under reflux for 16 hours.

After completion of the reaction, the solvent was distilled off and the residue was extracted with dichloromethane. The extract was washed with water, dried over anhydrous sodium sulfate and the solvent was distilled off to give 3.25 g of the desired product melting at 202° to 204°C with decomposition.

References

Merck Index 2377
Kleeman and Engel p. 240
DOT 11 (1) 35 (1975)
I.N. p. 254
Tachikawa, R., Takagi, H., Kamioka, T., Fukunaga, M., Kawano, Y. and Miyadera, T.; US Patents 3,696,094; October 3, 1972; and 3,772,371; November 13, 1973; both assigned to Sankyo Company Limited, Japan

CLOZAPINE

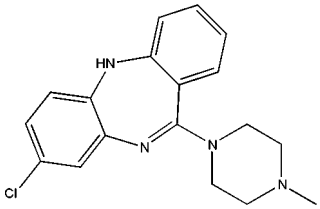
Therapeutic Function: Tranquilizer

Chemical Name: 8-Chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4] diazepine

Common Name: -

Chemical Abstracts Registry No.: 5786-21-0

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Leponex	Wander	W. Germany	1974
Leponex	Wander	Switz.	1975
Clozaril	Sandoz	-	-

Raw Materials

2-Amino-4-chlorodiphenylamine-2'-carboxylic(4"-methyl)piperazide
Phosphoroxychloride

Manufacturing Process

7.4 g of 2-amino-4-chlorodiphenylamine-2'-carboxylic acid (4"-methyl) piperazide and 35 ml of phosphoroxychloride are heated for 3 hours under reflux in the presence of 1.4 ml of N,N-dimethylaniline. Upon concentration of the reaction mixture in vacuo as far as possible, the residue is distributed between benzene and ammonia/ice water. The benzene solution is extracted with dilute acetic acid. The acid extract is clarified with charcoal and treated with concentrated ammonia water to precipitate the alkaline substance, which is dissolved in ether. The ethereal solution is washed with water and dried over sodium sulfate. The residue obtained yields, after recrystallization from ether/petroleum ether 2.9 g (41% of the theoretical yield) of 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine in the form of yellow grains of melting point 182° to 184°C (from acetone/petroleum ether).

References

Merck Index 2378
Kleeman and Engel p. 240
OCDS Vol. 2 p. 425 (1980)
DOT 9 (1) 17 and (6) 232 (1973)
I.N. p.255
Schmutz, J. and Hunziker, F.;US Patent 3,539,573; November 10, 1970

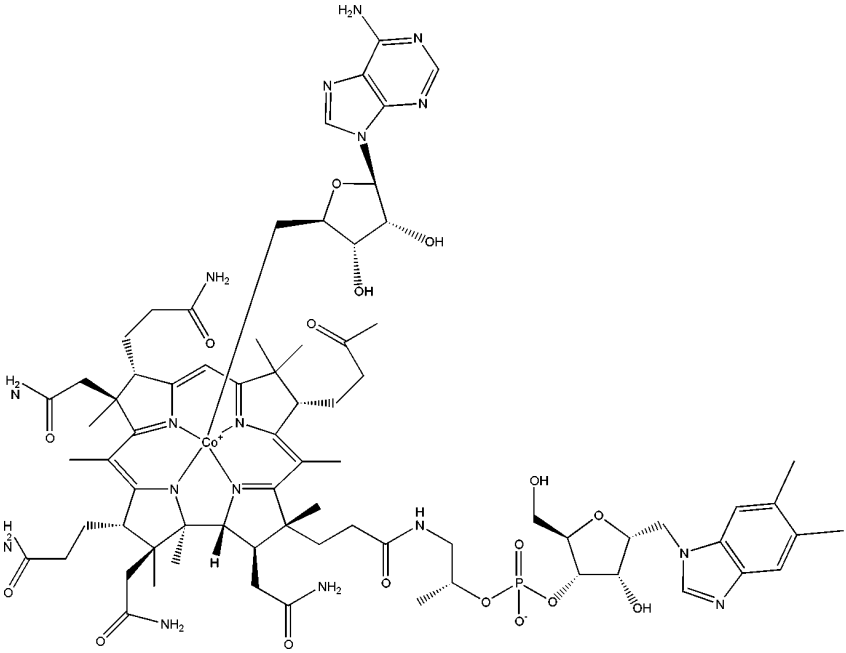
COBAMAMIDE

Therapeutic Function: Anabolic, Analgesic

Chemical Name: Cobinamide, O-(5'-deoxyadenosine-5') deriv., hydroxide, dihydrogen phosphate (ester), inner salt, 3'-ester with 5,6-dimethyl-1-alpha-D-ribofuranosylbenzimidazole

Common Name: Adenosylcobalamin; Cobamamide; Coenzima B12; Coenzym B12; Dibencozide; Dibenzcozamide; Dimebenzcozamide

Structural Formula:



Chemical Abstracts Registry No.: 13870-90-1

Trade Name	Manufacturer	Country	Year Introduced
Actimide	Tobishi	-	-
Ademide	Toyo Jozo	-	-
Betarin	Beta	-	-
Calomide	Yamanouchi	-	-
Cobamamide	Hebei Huarong Pharmaceutical Co., Ltd.	-	-
Cobamamide	Shijiazhuang Pharmaceutical Group Co., Ltd.	-	-
Cobamamide	Thorne Research	-	-
Cobamamide	Recordati SpA	-	-
Mecobal OD	Rapross Pharmaceuticals Pvt. Ltd.	-	-

Trade Name	Manufacturer	Country	Year Introduced
Vitamin B12 Depot	Siegfried	-	-
Cobalin	Laboratorios Finlay, S.A.	-	-

Raw Materials

Isopropylidine adenosine
Hydroxocobalamin
Hydrochloric acid
Tosyl chlorine
Sodium borohydride

Manufacturing Process

Isopropylidine adenosine was converted to the p-toluene sulphonyl (tosyl) ester by reaction with tosyl chlorine solution, following the method of Clark et al. (1951) [J. Chem. Soc. 2952]. Because of its tendency to cyclization, the reagent was used directly it was ready. A reaction flask with separating funnels was set up in such a way that the whole system could be evacuated and filled with pure nitrogen two or three times, to eliminate all oxygen, and reagents could then be added when desired, in the closed system.

The flask contained 700.0 mg hydroxocobalamin in 20 ml of water, one funnel 200.0 mg sodium borohydride in 10 ml of water, and another the crude isopropylidine adenosine tosyl ester made from 500 mg isopropylidine adenosine dissolved in 10 ml of 50% aqueous methanol. On adding the borohydride to the vitamin, the color changed instantly from red to brown, then slowly to a greenish black. After 15 min the isopropylidine adenosine tosyl ester was added, and the colour slowly changed to a red-brown. After 45 min at room temperature air was admitted and the mixture was shaken to reoxidise any remaining reduced vitamin B_{12}. The alkaline solution was neutralized with dilute hydrochloric acid and extracted with phenol carbon tetrachloride 3:1 in small portions till the aqueous layer was nearly colorless. The combined extracts were washed with water, mixed with about ten parts of carbon tetrachloride-acetone 10:1 and shaken with small portions of water till all red color was removed.

The product was purified by chromatography on columns of DEAE (diethyl aminoethyl) cellulose (3 x 1) followed by CM (carboxymethyl) cellulose (6 x 1), developed with water. Nearly all the color washed quickly through DEAE cellulose. The effluent and washes were applied to the CM cellulose column, which was further developed with water. Elution was continued as long as this fraction continued to emerge, in a total of 850 ml. One half of this fraction (425 ml) was concentrated to a few ml under reduced pressure; it crystallized slowly after adding acetone to slight turbidity. So cobamamide was obtained.

References

Smith E.L. et al.; US Patent No. 3,213,082; Oct. 19, 1965; Assigned: Glaxo Group Limited, Middlesex, England, a British company

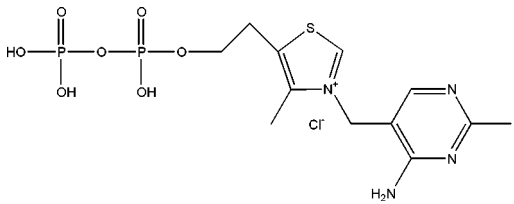
COCARBOXYLASE CHLORIDE

Therapeutic Function: Coenzyme, Metabolic

Chemical Name: Thiazolium, 3-((4-amino-2-methyl-5-pyrimidinyl)methyl)-4-methyl-5-(4,6,6-trihydroxy-3,5-dioxa-4,6-diphosphahex-1-yl)-, chloride, P,P'-dioxide

Common Name: Cocarbossilasi; Cocarboxylase; Diphosphothiamine; Pyruvodehydrase; Thiamine pyrophosphate

Structural Formula:



Chemical Abstracts Registry No.: 154-87-0

Trade Name	Manufacturer	Country	Year Introduced
Actimide	Tobishi	-	-
Ademide	Toyo Jozo	-	-
Betarin	Beta	-	-
Calomide	Yamanouchi	-	-
Cobamamide	Hebei Huarong Pharmaceutical Co., Ltd.	-	-
Cobamamide	Shijiazhuang Pharmaceutical Group Co., Ltd.	-	-
Cobamamide	Thorne Research	-	-
Cobamamide	Recordati SpA	-	-
Mecobal OD	Rapross Pharmaceuticals Pvt. Ltd.	-	-
Vitamin B12 Depot	Siegfried	-	-
Cobalin	Laboratorios Finlay, S.A.	-	-

Raw Materials

Phosphoric acid
Hydrochloric acid
Phosphorous pentoxide
Thiamine chloride hydrochloride

Manufacturing Process

4.5 kg of aqueous 89% orthophosphoric acid are heated to 135°C, and kept at this temperature for about 3 h while being actively stirred. Then, the heating is discontinued and 3.5 kg of phosphorouspentoxide are added during a period of 2.5 to 3 h, while being actively stirred. During this period, the interior temperature rises to 165°-175°C. After completion of the addition of phosphorouspentoxide, the stirring is continued until all phosphorouspentoxide is dissolved. The phosphoric acid mixture thus produced is subsequently cooled down to 130°C.

At this temperature 2.0 kg of thiamine chloride hydrochloride (vitamin B_1) were added during 2 to 3 h while being well stirred. The stirring is continued at 130°C until the phosphorylated mixture no longer contains chlorine ions. A phosphorylated melt is thus obtained. The thus obtained phosphorylation melt is dissolved in 6-8 L of water (with ice) at a temperature below 10°C, while being vigorously stirred. The aqueous solution is stirred into 100 L of 96% alcohol and left standing overnight. The supernatant solvent is decanted from the separated syrup; the latter is taken up in 4 L of water. The solution thus obtained is fed, depending upon the volume of phosphoric acid contained therein, to an exchanger column filled with anion exchanger (weak basic, for instance Amberlite IRA 45, 20-30 L) (a polystyrene resin with primary, secondary and quaternary amino groups). The solution is caused to seep into the column from the top thereof and is then washed with water until the run-off at the bottom no longer shows any thiamine reaction. About 25 L of the solution are obtained, which are concentrated to 6 L at 30°C and 12 Torr. The concentrated residue is added to 20 to 30 L of a cationic exchanger (Amberlite IRC 50) in order to separate the thiamine-orthophosphoric acid ester from the thiamine-pyrophosphoric acid ester, and subsequently washed with water until the eluate is free of thiamine.

70-80 L of a solution are obtained which are concentrated to 1.5 L in a circulation evaporator at 30°C and 12 Torr. 7.5 L of 96% ethanol are slowly added to a concentrate while being stirred. The cocarboxylase-tetrahydrate separates in the form of fine needles. The yield is 530.0 g with a melting point of 220°-225°C (dec.).

10.0 g of cocarboxylase-tetrahydrate are dissolved in 25 ml of 5% aqueous hydrochloric acid, and 75 ml acetone are added dropwise while being stirred. The precipitated hydrochloride of the cocarboxylase, melting point 240°C is sucked off. The yield is 9.5 g.

References

Wenz A. et al.; US Patent No. 2,991,284; July 4, 1961; Assigned: E. Merck, Aktiengesellschaft, Darmstadt, Darmstadt, Germany, a corporation of Germany

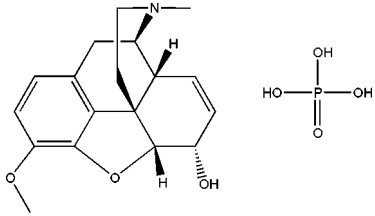
CODEINE PHOSPHATE

Therapeutic Function: Narcotic analgesic, Antitussive

Chemical Name: Morphinan-6-ol, 7,8-didehydro-4,5-epoxy-3-methoxy-17-methyl-, (5α,6α)-, phosphate (1:1) (salt)

Common Name: Codeinum phosphoridum

Structural Formula:



Chemical Abstracts Registry No.: 52-28-8

Trade Name	Manufacturer	Country	Year Introduced
Actacode Linctus	Sigma Pharmaceuticals	-	-
Bronchodine	Pharmethic	Belgium	-
Bronchosedal codeine	Janssen-Cilag	-	-
Galcodine	Galena a.s.	Czech Republic	-

Raw Materials

Morphine
Trimethylphenylammonium chloride
Sodium hydroxide

Manufacturing Process

Interaction of morphin, trimethylphenylammonium chloride and sodium hydroxide in methanol give the morphinan-6-α-ol, 7,8-didehydro-4,5-α-epoxy-3-methoxy-17-methyl. Then the free base was converted into phosphate.

References

Boheringer H., DE 247,180, 1912
Ullmann 3, Aufl., Bd.3, 232

COLESTIPOL

Therapeutic Function: Antihyperlipoproteinemic

Chemical Name: N-(2-Aminoethyl)-1,2-ethanediamine polymer with (chloromethyl) oxirane

Common Name: -

Structural Formula: See Chemical Name

Chemical Abstracts Registry No.: 26658-42-4

Trade Name	Manufacturer	Country	Year Introduced
Colestid	Upjohn	US	1977
Colestid	Upjohn	UK	1978
Colestid	Upjohn	W. Germany	1978
Colestid	Upjohn	Switz.	1978
Lestid	Upjohn	-	-

Raw Materials

Epichlorohydrin
Tetraethylene pentamine

Manufacturing Process

Into a 1,000 gallon, jacketed, glass-lined reactor equipped with baffles and a two-speed (67 and 135 rpm) reversed impeller is introduced 200 g of Richonate 60B (a 60% aqueous slurry of sodium salts of alkylbenzenesulfonic acids) and 364 liters of deionized water, followed by 90.5 kg of tetraethylenepentamine rinsed in with 5 gallons of toluene. The solution is stirred at the low speed and then 500 gallons of toluene are added to form a dispersion. To the stirred dispersion is added 109 kg of epichlorohydrin, rinsed in with 5 gallons of toluene, and the resulting mixture is heated at reflux for two hours. The reaction mixture is cooled to about 20°C and then treated with 58.5 kg of a filtered 50% aqueous solution of sodium hydroxide. The mixture is removed from the reactor and filtered, and the copolymer is collected and dried by treating it first with hot (75°C to 80°C) filtered nitrogen and then with an 80°C air stream. The resulting crude product is returned to the reactor, washed extensively with filtered deionized water (at the low speed), dried with an 80°C air stream and blended until homogeneous to give about 155 kg of a dry tetraethylenepentamine-epichlorohydrin copolymer hydrochloride, particle diameter 0.002-0.02 inch.

References

Merck Index 2440
PDR p. 1832
DOT 14 (2) 69 (1978)
I.N. p. 259
REM p.864
Lednicer, D. and Peery, C.Y.; US Patent 3,803,237; April 9, 1974; assigned to The Upjohn Co.

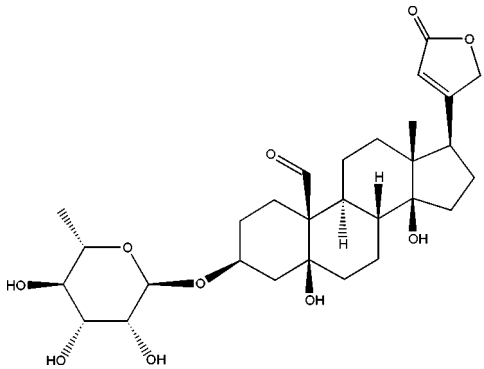
CONVALLATOXIN

Therapeutic Function: Cardiotonic

Chemical Name: Card-20(22)-enolide, 3-((6-deoxy-α-L-mannopyranosyl) oxy)-5,14-dihydroxy-19-oxo-, (3β,5β)-

Common Name: Convallatoxin; Corglykon

Structural Formula:



Chemical Abstracts Registry No.: 508-75-8

Trade Name	Manufacturer	Country	Year Introduced
Convallatoxin	C-Strong Co., Ltd.	-	-

Raw Materials

Flowers Convallaria majalis, lily of valley
Lead(II) acetate

Manufacturing Process

1 part of grinded flowers Convallaria majalis and 12 parts of water was stirred for 15 hours at ambient temperature. After a filtration and washing with water, a clear brown filtrate was mixed with a concentrate solution of lead acetate. A lead consisted precipitate was filtered off and sodium phosphate was added to filtrate for removing the remaining lead. The solution was filtered again and 0.5 - 0.6 parts of a coal was added and the mixture was stirred for 3 hours at ambient temperature. The coal was filtered off, washed with a little water and dried at 30°-40°C. A hot $CHCl_3$ was added to dry coal adsorbent. $CHCl_3$ was distilled off to dryness in vacuum. The residue was dissolved in a little methanol and the obtained solution was shook 3 times with 2 volumes of petrol ether and then distilled to dryness in vacuum. This product was dissolved in minimum absolute ethanol and added to 10 volumes of dry ether. The formed precipitate was filtered and washed with ether to

give the glycoside as a gray powder. It was crystallized from diluted ethanol as colorless needles.

References

DR Patent No. 490,648; Jan. 31, 1930; F. Hoffmann-la Roche and Co. Akt.-Ges. in Basel, Schweiz.

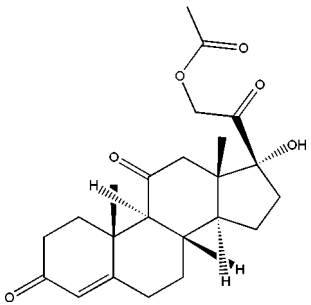
CORTISONE ACETATE

Therapeutic Function: Glucocorticoid

Chemical Name: 17α,21-Dihydroxy-4-pregnene-3,11,20-trione-21-acetate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 50-04-4; 53-06-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Cortone Acetate	MSD	US	1950
Acetisone	Farmigea	Italy	-

Raw Materials

Potassium cyanide	3(α)-Hydroxy-21-acetoxy-11,20-diketopregnane
Acetic acid	Phosphorus oxychloride
Chromic acid	Osmium tetroxide

Manufacturing Process

The following technique is described in US Patent 2,541,104. A solution of 2.0 g of 3(α)-hydroxy-21-acetoxy-11,20-diketo-pregnane, which can be prepared as described in Helv. Chim. Acta 27, 1287 (1944), is treated in a mixture of 25 cc of alcohol and 6.4 cc of acetic acid at 0°C with 6.0 g of potassium

cyanide. The solution is allowed to warm to room temperature and after 3 hours is diluted with water. The addition of a large volume of water to the alcohol-hydrogen cyanide mixture precipitates a gum which is extracted with chloroform or ethyl acetate. The extract is washed with water, and evaporated to small volume under reduced pressure. The crystalline precipitate (1.3 g) consists of 3(α),20-dihydroxy-20-cyano-21-acetoxy-11-keto-pregnane; dec. 175° to 185°C.

A solution of 0.60 g of chromic acid in 1.2 cc of water and 11 cc of acetic acid is added to a solution containing about 1.2 g of 3(α),20-dihydroxy-20-cyano-21-acetoxy-11-ketopregnane at room temperature. After 1 hour, water is added and the product, which precipitates, is filtered and recrystallized from ethyl acetate to produce 3,11-diketo-20-hydroxy-20-cyano-21-acetoxy-pregnane; dec. 214° to 217°C.

0.40 cc of phosphorus oxychloride is added to a solution containing about 950 mg of 3,11-diketo-20-hydroxy-20-cyano-21-acetoxy-pregnane dissolved in 3 cc of pyridine. After standing at room temperature for 24 hours, the solution is poured into water and dilute hydrochloric acid, extracted with benzene and concentrated to dryness. The crude product, after chromatography gives one main constituent, namely δ^{17}-3,11-diketo-20-cyano-21-acetoxy-pregnene; MP 189° to 190°C.

A solution of 1.0 g of δ^{17}-3,11-diketo-20-cyano-21-acetoxy-pregnene in 10 cc of benzene is treated with 1.0 g of osmium tetroxide and 0.43 g of pyridine. After standing at room temperature for 18 hours, the resulting solution is treated successively with 50 cc of alcohol, and with 50 cc of water containing 2.5 g of sodium sulfite. The mixture is stirred for 30 hours, filtered, and the filtrate acidified with 0.5 cc of acetic acid and concentrated to small volume in vacuo. The aqueous suspension is then extracted four times with chloroform, the chloroform extracts are combined, washed with water and concentrated to dryness in vacuo. Recrystallization of the residue from acetone gives 9°C. This compound is then treated with acetic anhydride and pyridine for 15 minutes at room temperature to produce 3,11,20-triketo-17(α)-hydroxy-21-acetoxy-pregnane or cortisone acetate.

References

Merck Index 2510
Kleeman and Engel p. 246
OCDS Vol. 1 pp. 188, 190 (1977)
I.N . p. 265
REM p.964
Reichstein, T.; US Patent 2,403,683; July 9, 1946
Gallagher, T.F.; US Patent 2,447,325; August 17, 1948; assigned to Research Corporation
Sarett, L.H.; US Patent 2,541,104; February 13, 1951; assigned to Merck and Co., Inc

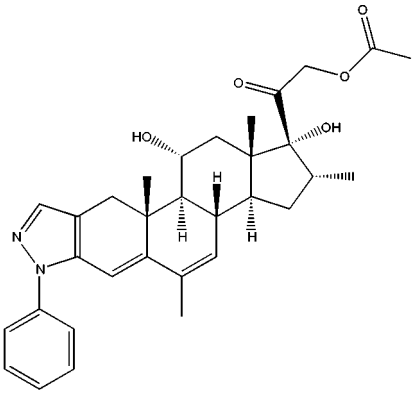
CORTIVAZOL

Therapeutic Function: Glucocorticoid

Chemical Name: 11β,17,21-Trihydroxy-6,16α-dimethyl-2'-phenyl-2'H-pregna-2,4,6-trieno-[3,2-c]pyrazol-20-one-21-acetate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 1110-40-3

Trade Name	Manufacturer	Country	Year Introduced
Diaster	Diamant	France	1972
Altim	Roussel	France	-
Idaitim	Roussel	-	-
Dilaster	Roussel	-	-

Raw Materials

11β,17α,21-Trihydroxy-6,16α-dimethyl-4,6-pregnadiene-3,20-dione
Phenyl hydrazine
Acetic anhydride
Formaldehyde
Hydrogen chloride
Ethyl formate
Formic acid

Manufacturing Process

To a suspension of 25.0 g of 11β,17α,21-trihydroxy-6,16α-dimethyl-4,6-pregnadiene-3,20-dione in 1.5 liters of alcohol-free chloroform cooled to about 5°C in an ice bath is added with constant stirring 750 ml of cold, concentrated hydrochloric acid and then 750 ml of formalin (low in methanol). The mixture is removed from the ice bath and stirred at room temperature for 7 hours.

The layers are separated and the aqueous phase is back-extracted twice with chloroform. The combined organic layers are washed twice with a 5% solution of sodium bicarbonate, and twice with a saturated salt solution. The solution is dried over magnesium sulfate and evaporated to dryness under reduced pressure.

The residue is triturated with methanol to afford a crystalline solid. This material contains no detectable amount of starting material by paperstrip chromatography but shows two UV absorbing spots near the solvent front (methanol-formamide 2:1 vs benzene-n-hexane 1:1). An aliquot is recrystallized three times from a mixture of benzene and n-hexane to give 17α,20,20,21-bis(methylenedioxy)-11β-hydroxy-6,16α-dimethyl-4,6-pregnadiene-3-one which is used in the subsequent step of the synthesis without further purification.

17α,20,20,21-bis(methylenedioxy)-11β-hydroxy-6,16α-dimethyl-4,6-pregnadiene-3-one (500 mg) is dissolved in 25 cc of benzene and then about 5 cc of benzene is removed by distillation at normal pressure. The resulting solution is cooled to room temperature. Then 0.75 cc of freshly distilled ethyl formate is added. The air in the system is replaced with nitrogen and 150 mg of sodium hydride (as a 57% dispersion in mineral oil) is added. The mixture is stirred under nitrogen at room temperature for three hours. Then 15 cc of a saturated aqueous solution of sodium dihydrogen phosphate is added and the product is extracted into ether.

The ether extracts are extracted with 2 N sodium hydroxide and the sodium hydroxide extracts are acidified with sodium dihydrogen phosphate and extracted again into ether. The ether extract is evaporated to dryness to give about 500 mg of a crude product. From the ether solution there is obtained about 290 mg of yellow crystals, MP 220° to 236°C which is 17α,20,20,21-bis(methylenedioxy)-11β-formyloxy-2-hydroxy-methylene-6,16α-dimethyl-4,6-pregnadiene-3-one. The analytical sample is recrystallized from ethyl acetate and has a melting point of 249° to 255°C, $[\alpha]_D^{27}$ -217°, I R 5.81 and 8.37 μm. From the mother liquor is obtained about 127 mg of 17α,20,20-21-bis(methylenedioxy)-11β-hydroxy-2-hydroxymethylene-6,16α-dimethyl-4,6-pregnadiene-3-one. The analytical sample is recrystallized from ether and has a melting point of 200° to 204°C, $[\alpha]_D^{27}$ -197°, IR 6.05 to 6.2 and 6.4 μ.

The 17α,20,20,21-bis(methylenedioxy)-11β-hydroxy-2-hydroxymethylene-6,16α-dimethyl-4,6-pregnadiene-3-one (1.19 g) is dissolved in 25 cc of ethanol. 300 mg of phenyl hydrazine is added and the mixture is refluxed under nitrogen for one hour. About 25 cc of water is added. The product is then extracted into 150 cc of ether. The extracts are washed with 2N HCl, with saturated sodium bicarbonate, water and saturated sodium chloride solution, and then dried over sodium sulfate and evaporated to dryness to give about 1.2 g of crude product. On crystallization from ether there is obtained as a major component the 17α,20,20,21-bis(methylenedioxy)-11β-hydroxy-6,16α-dimethyl-2'-phenyl-4,6-pregnadieno-[3,2-c] pyrazole.

17α,20,20,21-bis(methylenedioxy)-11β-hydroxy-6,16α-dimethyl-2'-phenyl-4,6-pregnadieno[3,2-c] pyrazole (430 mg), is heated on a steam bath under nitrogen with 40 cc of a 60% aqueous solution of formic acid for about 30 minutes. About 40 cc of water is added and the mixture is then extracted into 200 cc of chloroform. The chloroform solution is washed with water, saturated

sodium bicarbonate solution and water, then dried over sodium sulfate and evaporated under vacuum to give 430 mg of crude product. This is dissolved in 60 cc of absolute methanol, and 0.1 equivalent of sodium methoxide in methanol is added.

The mixture is stirred under nitrogen at room temperature for 15 minutes. It is then acidified with acetic acid and the solvent is removed under vacuum at room temperature. About 20 cc of water is added and the product is extracted into 150 cc of ethyl acetate. The ethyl acetate solution is washed with saturated sodium bicarbonate and then with water. It is then dried over sodium sulfate and taken to dryness to give an amorphous solid.

The crude product obtained above is dried in high vacuum and then dissolved in 4 cc of pyridine. About 3 cc of acetic anhydride is added. The mixture is then heated on the steam bath for about 15 minutes and then evaporated to dryness in vacuo. About 20 cc of water is added. The product is then extracted into 150 cc of ethyl acetate, washed with saturated sodium bicarbonate solution and water, and dried over sodium sulfate. The solvent is removed in vacuo to give a residue which is crystallized from ethyl acetate-benzene to yield about 250 mg of 11β,17α,21-trihydroxy-6,16α-dimethyl-20-oxo-2'-phenyl-4,6-pregnadieno-[3,2-c]pyrazole 21-acetate, as described in US Patent 3,300,483.

References

Merck Index 2513
Kleeman and Engel p. 248
OCDS Vol. 2 p. 191 (1980)
DOT 8 (10) 374 (1972)
I.N. p. 265
Tishler, M., Steinberg, N.G. and Hirschmann, R.F.; US Patents 3,067,194; December 4, 1962; and 3,300,483; January 24, 1967; both assigned to Merck and Co., Inc.

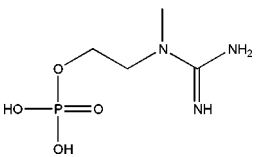
CREATINOLFOSFATE

Therapeutic Function: Cardiotonic

Chemical Name: 1-(2-Hydroxyethyl)-1-methylguanidine dihydrogen phosphate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 6903-79-3

Trade Name	Manufacturer	Country	Year Introduced
Aplodan	Simes	Italy	1968
Dragosil	Farmasimes	Spain	-
Nergize	Byk Liprandi	Argentina	-

Raw Materials

Creatinol phosphate
Polyphosphoric acid

Manufacturing Process

In a reactor put 80 kg of polyphosphoric acid having the following composition: $H_5P_3O_{10}$ - 60%; $(HPO_3)_6$ - 10%; $H_4P_2O_7$ - 15%; $(HPO_3)_x$ - 10%; total content in P_2O_5 about 83%; this is heated to about 160°C.

Then 360 kg of creatinol phosphate are added to the polyphosphoric acid; continue to heat for about two hours under vacuum until the reaction water is eliminated.

The molten mass is then poured into ethanol at 95°C, the solution cooled down to 10°C and the precipitated product separated by centrifugation. The resulting product is dissolved in the minimum quantity of warm water and the solution poured into ethanol.

Thus 297 kg of the phosphoric ester of the creatinol are obtained having these characteristics: MP 240°C to 243°C.

References

Kleeman and Engel p. 249
I.N. p. 268
Allievi, E.; US Patent 4,012,467; March 15, 1977

CROMOLYN SODIUM

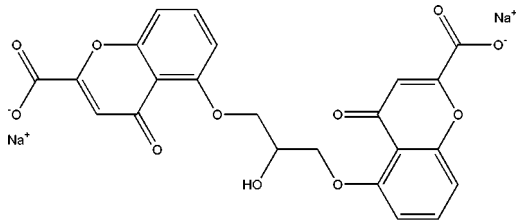
Therapeutic Function: Bronchodilator

Chemical Name: 5,5'-[(2-Hydroxy-1,3-propanediyl)bis-(oxy)]bis[4-oxo-4H-1-benzopyran-2-carboxylic acid] disodium salt

Common Name: Cromogycinic acid sodium salt; Disodium cromogycate

Chemical Abstracts Registry No.: 15826-37-6; 16110-51-3 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Intal	Fisons	UK	1969
Intal	Fisons	W. Germany	1970
Lomudal	Fisons	Switz.	1970
Intal	Fujisawa	Japan	1971
Frenasma	Italseber	Italy	1971
Lomudal	Fisons	France	1972
Intal	Fisons	US	1973
Aarane	Fisons	US	1973
Nalcrom	Fisons	Italy	1983
Aarane	Syntex	US	-
Alercrom	Osiris	Argentina	-
Colimone	Fisons	W. Germany	-
Cromo-Asma	Aldo Union	Spain	-
Cusicrom	Cusi	Spain	-
Frenal	I.S.F.	Italy	-
Gastrofrenal	I.S.F.	Italy	-
Kromolin	Iltas	Turkey	-
Lomupren	Fisons	W. Germany	-
Nalcrom	Fisons	UK	-
Nasmil	Lusofarmaco	Spain	-
Nebulasma	Septa	Spain	-
Opticron	Fisons	France	-
Rynacrom	Fisons	UK	-

Raw Materials

2,6-Dihydroxyacetophenone
Epichlorohydrin
Diethyl oxalate
Sodium hydroxide

Manufacturing Process

To a solution of 970 parts of 2,6-dihydroxyacetophenone and 325 parts of epichlorohydrin in 1,500 parts of hot isopropanol was added, with stirring

under reflux, a solution of 233 parts of 85% KOH in 2,500 parts of isopropanol and sufficient water (ca 100 parts) to dissolve the solid. The mixture was heated, with stirring, under reflux for 48 hours. Half the solvent was then distilled off and 5,000 parts of water were added. The mixture was cooled and the solid filtered off and washed with isopropanol and ether. It was then recrystallized from 12,500 parts of isopropanol to obtain a first crop of 380 parts and a second crop, after concentration, of 300 parts of 1,3-bis(2-acetyl-3-hydroxyphenoxy)-2hydroxypropane.

4.6 parts of 1,3-bis(2-acetyl-3-hydroxyphenoxy)-2-hydroxypropane were reacted with diethyl oxalate and the product cyclized to obtain 4.4 parts of pure diethyl ester of 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane as pale yellow crystals melting between 180° and 182°C from a mixture of benzene and petrol, 4 parts of the diethyl ester of 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane were saponified with sodium hydroxide to obtain 3.2 parts of the disodium salt tetrahydrate as colorless crystals from aqueous alcohol.

References

Merck Index 2580
Kleeman and Engel p. 250
PDR p. 876
OCDS Vol. 3 pp. 66, 235 (1984)
DOT 10 (7) 246 (1974) and 14 (7) 283 (1978)
I.N. p. 19
REM p. 1131
Fitzmaurice, C. and Lee, T.B.; US Patent 3,419,578; December 31, 1968; assigned to Fisons Pharmaceuticals Limited, England

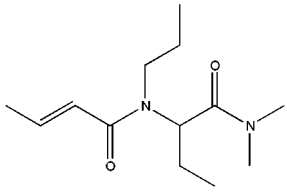
CROPROPAMIDE

Therapeutic Function: Respiratory stimulant

Chemical Name: 2-Butenamide, N-(1-((dimethylamino)carbonyl)propyl)-N-propyl-

Common Name: Cropropamide; Propylbutamidum

Structural Formula:



Chemical Abstracts Registry No.: 633-47-6

Trade Name	Manufacturer	Country	Year Introduced
Cropropamide	Geigy (Novartis)	-	-

Raw Materials

2-Chlorbutyric acid dimethyl amide
Propylamine
Crotonic acid chloride

Manufacturing Process

2-Chlorbutiric acid dimethyl amide are dissolved in absolute benzene and heated to 110°C with propylamine in the autoclave. After cooling the propylamine hydrochloride is filtered off, then the benzene solution is treated with water and freed from any dissolved propylamine hydrochloride by means of potassium lye. After distillation of the benzene the 2-propylaminobutyric acid dimethyl amide is rectified in vacuum.

2-Propylaminobutyric acid dimethyl amide is dissolved in benzene and while cooling, crotonic acid chloride is added and mixed. Then, reaction mixture is filtered and freed from benzene to give 2-(N-propyl-crotonylamido)butyric acid dimethyl amide, melting point 128°-130°C.

References

Martin H., Gysin H.; US Patent No. 2,447,587; August 24, 1948; Assigned: J. R. Geigy A.G., Basel, Switzerland

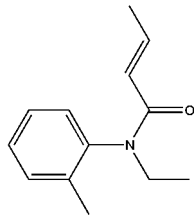
CROTAMITON

Therapeutic Function: Scabicide

Chemical Name: N-Ethyl-N-(2-methylphenyl)-2-butenamide

Common Name: Crotonyl-N-ethyl-o-toluidine

Structural Formula:



Chemical Abstracts Registry No.: 483-63-6

Trade Name	Manufacturer	Country	Year Introduced
Eurax	Ciba Geigy	France	1949
Eurax	Ciba Geigy	US	1949
Crotan	Owen	US	1982
Crotamitex	Tropon	W. Germany	-
Euraxil	Geigy	W. Germany	-
Servitamitone	Servipharm	Switz.	-
Veteusan	Veterinaria	Switz.	-

Raw Materials

Crotonyl chloride
N-Ethyl-o-toluidine

Manufacturing Process

10.5 parts of crotonyl chloride are dropped in such a manner into 27 parts of N-ethyl-o-toluidine, white stirring, that the temperature rises to 130° to 140°C. After cooling, the reaction product is dissolved in ether or other solvent that is immiscible with water, and the solution is washed successively with hydrochloric acid, alkali solution and water. After distilling off the solvent, the residue is distilled in vacuo. The crotonic acid N-ethyl-o-toluidide boils at 153° to 155°C at a pressure of 13 mm and is a slightly yellowish oil. Instead of carrying the reaction out in the presence of an excess of N-ethyl-o-toluidine, it may be carried out in the presence of an acid-combining agent, for example, potash, advantageously in a solvent (e.g., acetone).

References

Merck Index 2583
Kleeman and Engel p. 251
I.N. p. 269
REM p. 1239
British Patent 615,137; January 3, 1949; assigned to J.R. Geigy AG, Switzerland

CROTETHAMIDE

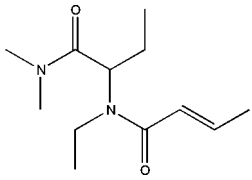
Therapeutic Function: Respiratory stimulant

Chemical Name: N-(1-(Dimethylcarbamoyl)propyl)-N-ethylcrotonamide

Common Name: Crotetamide; Crotethamide

Chemical Abstracts Registry No.: 6168-76-9

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Micorene	Geisy	-	-
Micoren	Novartis Consumer	-	-

Raw Materials

2-Clorobutiric acid dimethyl amide
Ethylamine
Crotonic acid chloride

Manufacturing Process

2-Clorobutiric acid dimethyl amide is dissolved in absolute benzene and heated to 110°-120°C with ethylamine in the autoclave. After cooling the ethylamine hydrochloride is filtered off, then the benzene solution is treated with water and freed from any dissolved ethylamine hydrochloride by means of potassium lye. After distillation of the benzene the 2-ethylaminobutyric acid dimethyl amide is rectified in vacuum.

2-Ethylaminobutyric acid dimethyl amide is dissolved in absolute ether, then the mixture is well cooled and treated drowsy under stirring with crotonic acid chloride. After a stirring reaction mixture is filtered and residue obtained is dissolved in water and treated by potassium hydroxide. The remaining product is finally rectified in high vacuum to give 2-(N-ethyl-crotonylamido)butyric acid dimethyl amide.

References

Martin H., Gysin H.; US Patent No. 2,447,587; August 24, 1948; Assigned: J. R. Geigy A.G., Basel, Switzerland

CRYPTENAMINE TANNATES

Therapeutic Function: Antihypertensive

Chemical Name: Complex alkaloid mixture

Common Name:

Structural Formula: $C_{32}H_{49}O_6N$-tannate

Chemical Abstracts Registry No.: 1405-40-9

Trade Name	Manufacturer	Country	Year Introduced
Unitensen	Neisler	US	1954

Raw Materials

Veratrum viride
Tannic acid
Hydrogen chloride
Triethylamine
Benzene

Manufacturing Process

Initial Extraction Technique: Continuous extraction apparatus was employed, including an extractor designed to contain the starting plant materials, a distillation flask to hold the solvent mixture, the flask being equipped with a reflux condenser, a drip device to facilitate the removal of the volatilized mixture from the condenser and to percolate it through the continuous extractor, and a Soxhlet type return. Means for heating the continuous extraction system were provided.

1,000 g of Veratrum viride powder was placed in a continuous plant extractor and a mixture of 2,000 ml of benzene and 20 ml of triethylamine was poured over a Veratrum powder in the reactor and permitted to siphon into the distillation flask. Approximately 50 g of an inert desiccant (Drierite) was added to the distillation flask, heat applied to initiate the distillation of the reaction mixture in the flask, and the continuous extraction procedure continued for 8 hours, during which time constant, gentle heat was applied to insure refluxing of the mixture (about 80° to 90°C). The extraction procedure was discontinued and the contents of the distillation flask filtered. The resulting filtrate was concentrated by distilling off and recovering a large portion of the benzene solvent together with virtually all of the triethylamine base. 50 ml of the concentrated benzene solution was thus obtained.

Preparation of Alkaloid Mixture: 50 ml of the concentrated benzene solution, obtained as described was rapidly stirred, and a saturated solution of hydrogen chloride in ether added to the concentrated benzene solution until no more precipitate was obtained. The resulting precipitate was recovered by filtration and comprised the crude hydrochlorides of the extracted alkaloids and the hydrochloride of any unrecovered triethylamine. This material was dried by heating at a temperature of about 75°C for 6 hours, the crude, dried precipitate ground with 50 ml of isopropanol and to this slurry was added 1,000 ml of water. The resulting mixture was filtered. To the clear filtrate, cooled to 5°C, there was slowly added with rapid stirring, a 10% aqueous solution of ammonium hydroxide, until complete precipitation was accomplished. The precipitate was filtered off, washed with water and dried by heating at about 75°C for 6 hours.

There was thus obtained a mixture of Veratrum viride alkaloids having substantial utility as a hypertension reducing agent, without the concomitant

marked side-actions normally associated with the clinical use of Veratrum viride extracts. This material may be clinically administered in this form, or further purification may be performed as described hereinafter.

Preparation of Alkaloid III : 100 g of the alkaloid mixture was dissolved in a liter of benzene and the resulting mixture filtered. The filtrate was diluted with approximately 4 liters of an aliphatic hydrocarbon solvent (Skellysolve B) and the resulting mixture filtered. The filtrate was cooled with Dry Ice to cause precipitation, and the alkaloid removed by filtration. There was thus obtained an alkaloid, which, for convenience, is called Alkaloid III, having analytical values consistent with a molecular formula $C_{32}H_{49}O_6N$, apparently an ester of a tertiary alkamine.

This material sinters at a temperature above about 125°C and melts at 130° to 135°C; UV absorption; lambda maximum 255 nm, lamda minimum 240 nm. It contains one ester group and no N-methyl groups.

Preparation of Alkaloid III Tannate: 20 g of Alkaloid III was dissolved in 200 ml of isopropyl alcohol at room temperature and a mixture of 30 g of tannic acid dissolved in 300 ml of isopropyl alcohol, maintained at 40° to 50°C was added thereto with rapid stirring. The mixture was cooled to 20°C, filtered and the precipitate dried at about 80°C. There was thus obtained 33.5 g of the tannate salt of Alkaloid III, as a pale yellow amorphous powder, relatively insoluble in water, and having an indefinite melting point.

References

Merck Index 2596
PDR p. 1875
I.N. p. 270
REM p. 850
Cavallito, C.J.; USPatent 2,789,977; April 23, 1957; assigned to Irwrin, Neisler and Company

CYAMEMAZINE

Therapeutic Function: Tranquilizer

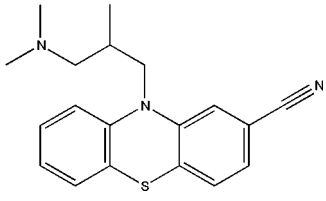
Chemical Name: 10-[3-(Dimethylamino)-2-methylpropyl]-10H-phenothiazine-2-carbonitrile

Common Name: Cyamepromazine

Chemical Abstracts Registry No.: 3546-03-0

Trade Name	Manufacturer	Country	Year Introduced
Terckian	Theraplix	France	1972

Structural Formula:



Raw Materials

3-Chlorophenthiazine
Copper cyanide
Sodium amide
1-Dimethylamino-2-methyl-3-chloropropane

Manufacturing Process

The 3-cyanophenthiazine used as starting material can be prepared by the action of cupric cyanide on 3-chlorophenthiazine in boiling quinoline. It has a first melting point of about 185°C and a second of about 203° to 205°C.

A solution of 3-cyanophenthiazine (10 g) in anhydrous xylene (75 cc) is heated under reflux and treated with 95% sodium amide (2.15 g). The heating is continued for 1 hour and then a solution of 1-dimethylamino-2-methyl-3-chloropropane (7.05 g) in xylene (70 cc) is added over 15 minutes. The mixture is heated under reflux for 20 hours and then cooled. The reaction mixture is treated with water (40 cc) and N methane-sulfonic acid (75 cc). The xylene phase is removed and the aqueous phase is made alkaline with sodium hydroxide. The free base obtained is extracted with ether and the ethereal extracts are dried over anhydrous potassium carbonate and concentrated to dryness. The residue is distilled in vacuo. 3-Cyano-10-(3-dimethylamino-2-methylpropyl)phenthiazine (8.5 g), BP 180° to 205°C/0.9 mm Hg, is thus obtained. The acid maleate prepared in and recrystallized from ethanol melts at 204° to 205°C.

References

Merck Index 2678
Kleeman and Engel p. 252
DOT 8 (6) 216 (1972)
I.N. p. 271
Jacob, R.M. and Robert, J.G.; US Patent 2,877,224; March 10, 1959; assigned to Societe des Usines Chimiques Rhone-Poulenc, France

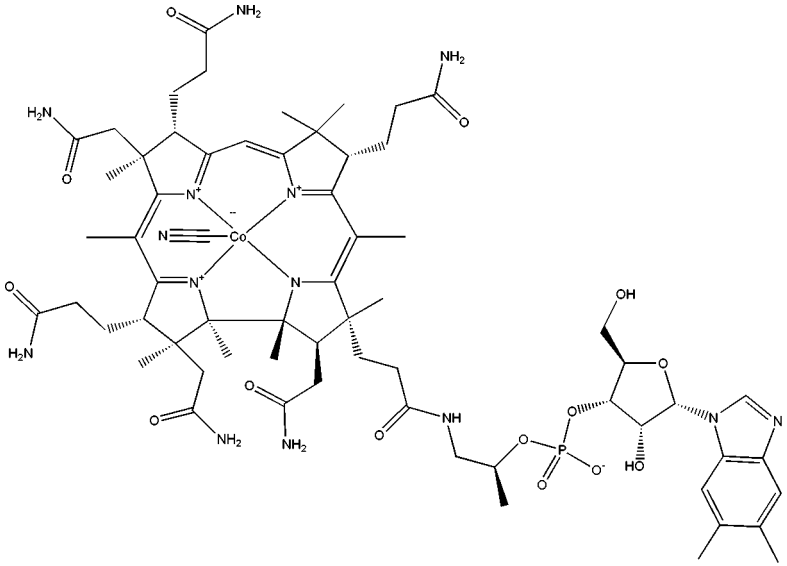
CYANOCOBALAMIN

Therapeutic Function: Hematinic

Chemical Name: 5,6-Dimethylbenzimidazocyl cyanocobamide

Common Name: Vitamin B_{12}

Structural Formula:



Chemical Abstracts Registry No.: 68-19-9

Trade Name	Manufacturer	Country	Year Introduced
Berubigen	Upjohn	US	1949
Rubramin	Squibb	US	1949
Bevidox	Abbott	US	1949
Betalin	Lilly	US	1949
Cobione	MSD	US	1949
Docibin	National	US	1950
Ducobee	Breon	US	1950
Dodex	Organon	US	1950
Be-Dodec	Schieffelin	US	1950
B-Twelvora	Sherman	US	1950
Crystamin	Armour	US	1951
Bexil	Conal	US	1951
Redisol	MSD	US	1951
Bevatine	Dorsey	US	1953
Vibalt	Roerig	US	1954
Bedoce	Lincoln	US	1957

Trade Name	Manufacturer	Country	Year Introduced
Vi-Twel	Cooper	US	1960
Cyano-Gel	Maurry	US	1961
Clarex	Minn. Pharm.	US	1962
Cyredin	Merrell National	US	1967
Feryl	Central	US	1968
Dicopac	Kaken	Japan	1969
Anacobin	Allen and Hanburys	UK	-
Actamin	Yashima	Japan	-
Apavit B12	Locatelli	Italy	-
Antipernicin	Galenika	Yugoslavia	-
Arcavit B12	Arcana	Austria	-
Arcored	Arco	Switz.	-
Arphos	Fournier	France	-
Bedocefarm	Wolner	Spain	-
Bedodeka	Teva	Israel	-
Beduzin	Dincel	Turkey	-
Behepan	Kabi Vitrum	Sweden	-
Berubi	Redel	W. Germany	-
Betolvex	Dumex	Denmark	-
Bexibee	N. American	US	-
Bidocit	Ausonia	Italy	-
B12 Mille	Delagrange	France	-
B12 Vicotrat	Heyl	W. Germany	-
Cabadon M	Raid-Provident	US	-
Cincomil Bedoce	Andromaco	Spain	-
Cobalomin	S. Pacific	Australia	-
Cobalparen	Saarstickstoff-Fatol	W. Germany	-
Cobavite	Lemmon	US	-
Cocavitan	Coca	Spain	-
Copharvit	Cophar	Switz.	-
Cyanabin	Stickley	Canada	-
Cyanovit	Adrian-Marinier	France	-
Cykobemin	Kabi Vitrum	Sweden	-
Cytakon	Glaxo	UK	-
Cytamen	Glaxo	UK	-
Cytobion	Merck	W. Germany	-
Dobetin	Angelini	Italy	-
Docetasan	Santos	Spain	-
Docivit	Robisch	W. Germany	-
Dodecabee	Miller	US	-
Dodecavite	U.S.V.	US	-

Trade Name	Manufacturer	Country	Year Introduced
Dodevitina	C.T.	Italy	-
Eocill B12	Nessa	Spain	-
Erftamin	Erfto-Chemie	W. Germany	-
Eritron	Manetti-Roberts	Italy	-
Eritrovit B12	Lisapharma	Italy	-
Erycytol	Sanabo	Austria	-
Fiviton B12	Alfar	Spain	-
Hemomin	Kirk	US	-
Hemosalus	Totalpharm	Italy	-
Hepacon B12	Consolidated	UK	-
Hepcovite	Endo	US	-
Juvabe	Dolder	Switz.	-
Lifaton B12	Lifasa	Spain	-
Lophakornb B12	Lornapharm	W. Germany	-
Milbedoc	Andromaco	Spain	-
Millevit	Nordmark	W. Germany	-
Neo-Cytamen	Bilim	Turkey	-
Neurobaltina	Sidus	Italy	-
Neuro Liser B12	Perga	Spain	-
Nova-Rubi	Novo	Canada	-
Noventabedoce	Andromaco	Spain	-
Omeogen	UCB-Smit	Italy	-
Optovite B 12	Normon	Spain	-
Permicipur	Mulli	W. Germany	-
Plentasal	Lopez-Brea	Spain	-
Primabalt	Primedics	US	-
Rectocenga	Biotherax	France	-
Redamin	Washington	Italy	-
Reedvit	Celtia	Argentina	-
Retidec B12	Dexter	Spain	-
Rubesol	Central	US	-
Rubraluy	Miluy	Spain	-
Ruvite	Savage	US	-
Sancoba	Santen	Japan	-
Sorbevit B12	Casen	Spain	-
Sorbigen B12	Gentili	Italy	-
Surgevit	Maipe	Spain	-
Twel-Be	Pitman-Moore	US	-
Vicapanbiz	Merckle	W. Germany	-
Viemin 12	Valeas	Italy	-
Vitarubin	Streuli	Switz.	-

Raw Materials

Potassium cyanide	Milorganite (activated sewage sludge)
Sodium nitrite	Hydrochloric acid

Manufacturing Process

The following is taken from US Patent 3,057,851. Milorganite was extracted with water to obtain an aqueous extract containing vitamin B_{12} active substances. This aqueous extract was purified by treatment with an ion exchange resin according to the following method. An aqueous extract of milorganite, 100 ml containing 300 μg of vitamin B_{12} active substances and 4.5 grams of total solids, was combined with 0.5 gram of sodium nitrite and 0.4 gram of potassium cyanide. The resulting solution was adjusted to pH 4.0 with hydrochloric acid and heated to boiling. The boiled solution was filtered through a Super-Cel filter surface, and the filter was then washed with water. The filtrate was obtained in a total volume of 130 ml including the washings.

Amerlite XE-97, an ion exchange resin of the carboxyl type (Rohm and Haas), was classified to an average wet particle size of 100 to 150 mesh. The classified resin was utilized in the hydrogen form, and was not buffered during the ion exchange fractionation. The classified resin, in the amount of 35 ml, was packed into a glass column having a diameter of 25 mm and a height of 250 mm. The cyanide-treated aqueous extract of milorganite was infused gravitationally into the ion exchange bed at a rate of 3 ml per minute.

The effluent was discarded and the resin bed was then washed with the following solutions in the specified sequence: (1) 120 ml of an aqueous 0.1 N hydrochloric acid solution; (2) 75 ml of an aqueous 85% acetone solution; and (3) 70 ml of an aqueous 0.1 N hydrochloric acid solution. After washing, the resin bed was eluted with an aqueous 60% dioxane solution containing 0.1 N of hydrochloric acid. In this elution, 8 ml of colored eluate was collected. This portion of the eluate was found to contain 295 μg of cyanocobalamin and 9 mg of total solids.

References

Merck Index 9822
Kleeman and Engel p. 252
PDR pp. 655, 785, 872, 905, 916, 966, 1083, 1603, 1989
I.N. p. 272
REM pp. 1020, 1022
Rickes, E.L. and Wood, T.R.; US Patents 2,703,302 and 2,703,303; both dated March 1, 1955; both assigned to Merck and Co., Inc.
Speedie, J.D. and Hull, G.W.; US Patent 2,951,017; August 30, 1960; assigned to The Distillers Company Limited, Scotland
McDaniel, L.E.; US Patent 3,000,793; September 19, 1961; assigned to Merck and Co., Inc.
Long, R.A.; US Patent 3,018,225; January 23, 1962; assigned to Merck and Co., Inc.
Van Melle, P.J.; US Patent 3,057,851; October 9, 1962; assigned to Armour-Pharmaceutical Bernhauer, K., Friedrich, W. and Zeller, P.; US Patent 3,120,509; February 4, 1964; assigned to Hoffmann-La Roche Inc.

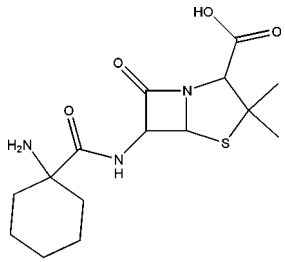
CYCLACILLIN

Therapeutic Function: Antibacterial

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

Common Name: 6-(1-Aminocyclohexanecarboxamido)penicillanic acid; 1-Aminocyclohexylpenicillin; Ciclacillin

Structural Formula:



Chemical Abstracts Registry No.: 3485-14-1

Trade Name	Manufacturer	Country	Year Introduced
Ultracillin	Gruenenthal	W. Germany	1972
Wybital	Wyeth	Japan	1972
Vastollin	Takeda	Japan	1972
Ultracillin	Gruenenthal	Switz.	1973
Cyclapen	Wyeth	US	1979
Calthor	Ayerst	UK	1980
Bionacillin-C	Takata	Japan	-
Citocilina	Medinsa	Spain	-
Citosarin	Toyo Jozo	Japan	-
Orfilina	Orfi	Spain	-
Peamezin	Sawai	Japan	-
Syngacillin	Wyeth	-	-
Vasticillin	Takeda	Japan	-
Vipicil	Wyeth	-	-

Raw Materials

6-Aminopenicillanic acid
1-Amino-1-cyclohexane carboxylic acid chloride

Manufacturing Process

To 21.6 g (0.10 mol) of 6-aminopenicillanic acid (6-APA) and 213 ml of methylene chloride in a dry 500 ml 3-neck flask fitted with stirrer, thermometer, nitrogen inlet and reflux condenser with drying tube, 25.3 g (0.25 mol) of triethylamine and 13.4 g (0.11 mol) of N,N-dimethylaniline were added. After stirring at reflux for one hour, the mixture was cooled and 21.7 g (0.20 mol) of trimethylchlorosilane was added dropwise at 12° to 15°C

The mixture was refluxed for 45 minutes, cooled under nitrogen, and 19.8 g (0.10 mol) of 1-amino-1-cyclohexane-carboxylic acid chloride HCl was added portionwise at -10°C over 20 minutes. The mixture was stirred for an additional hour while the temperature rose to 20°C. The reaction mixture was poured into 200 ml of cold water with stirring and the two-phase mixture clarified by filtration. Dilute sodium hydroxide solution was added to the filtrate at 5° to 10°C to pH 5.4.

After stirring overnight at room temperature, the crystalline product was collected by filtration, washed with water and finally with acetone, and then dried at 45°C; yield of dihydrate, 29.9 g or 79% of theory based on 6-APA; iodometric assay, 922 mcg per mg; bioassay, 921 mcg per mg, as described in US Patent 3,478,018.

References

Merck Index 2693
Kleeman and Engel p. 205
PDR p. 1945
OCDS Vol. 2 p. 439 (1980)
DOT 8 (5) 168 (1972)
I.N. p.230
REM p. 1200
Alburn, H.E., Grant, N.H. and Fletcher, H. III; US Patent 3,194,802; assigned to American Home Products Corporation
Robinson, C.A. and Nescio, J.J.; US Patent 3,478,018; November 11, 1969; assigned to American Home Products Corporation

CYCLAMATE CALCIUM

Therapeutic Function: Pharmaceutic aid

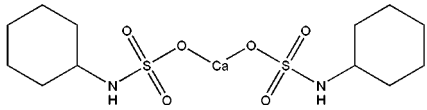
Chemical Name: Cyclohexylsulfamic acid calcium salt

Common Name: -

Chemical Abstracts Registry No.: 139-06-0

Trade Name	Manufacturer	Country	Year Introduced
Sucaryl Calcium	Abbott	US	1953
Sucaryl Calcium	Abbott	France	1966

Structural Formula:



Raw Materials

Cyclohexylamine
Ammonium sulfamate
Calcium hydroxide

Manufacturing Process

220 parts by weight, 2.22 mols, of cyclohexylamine and 57 parts by weight, 0,50 mol, of ammonium sulfamate were mixed at room temperature and heated with agitation. At the end of one-half hour of heating the temperature had reached 110°C and approximately one-half mol of ammonia had been evolved. Heating was continued under reflux at 133°C for 22 additional hours. A second half-mol of ammonia was liberated. The ammonia yield was 100%.

The reaction mixture was cooled to 100°C. To the mixture was added a water slurry containing 20.3 parts by weight, 0.55 equivalent, of calcium hydroxide and 700 parts by weight of water. Cyclohexylamine was then removed by azeotropic distillation with water.

The amine which was recovered can be reused after drying.

The residue from the distillation was evaporated to dryness in a vacuum oven at 50°C and the resulting product analyzed. The product weighing 105.5 parts by weight, 0.488 equivalent, was obtained which is a 98% yield of the technical calcium cyclohexylsulfamate dihydrate.

References

Merck Index 1636
I.N.p.273
Cummins, E.W. and Johnson, R.S.; US Patent 2,799,700; July 16, 1957; assigned to E.I. du Pont de Nemours and Co.
McQuaid, H.S.; US Patent 2,804,477; August 27, 1957; assigned to E.I. du Pont de Nemours and Co.
Freifelder, M.; US Patent 3,082,247; March 19, 1963; assigned to Abbott Laboratories
Birsten, O.G. and Rosin, J.; US Patents 3,361,798; January 2, 1968; and 3,366,670; January 30, 1968; both assigned to Baldwin-Montrose Chemical Co., Inc.

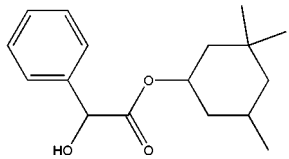
CYCLANDELATE

Therapeutic Function: Spasmolytic

Chemical Name: α-Hydroxybenzeneacetic acid 3,3,5-trimethylcyclohexyl ester

Common Name: 3,3,5-Trimethylcyclohexyl mandelate

Structural Formula:



Chemical Abstracts Registry No.: 456-59-7

Trade Name	Manufacturer	Country	Year Introduced
Cyclospasmol	Ives	US	1958
Cyclospasmol	Beytout	France	1972
Acyclin	Arcana	Austria	-
Anaspat	I.C.I.	Italy	-
Anticen	Nippon Kayaku, Co.	Japan	-
Aposelebin	Hokuriku	Japan	-
Capilan	Takeda	Japan	-
Capistar	Kowa	Japan	-
Ceaclan	Mohan	Japan	-
Cepidan	Meiji	Japan	-
Circle-one	Funai	Japan	-
Circulat	Kozani	Japan	-
Cyclan	Ohta	Japan	-
Cyclan-Cap	Nichiiko	Japan	-
Cyclansato	S.S. Pharm	Japan	-
Cycleat Cap	Hishiyama	Japan	-
Cyclobral	Norgine	UK	-
Cyclolyt	Taro	Israel	-
Hacosan	Sankyo	Japan	-
Hi-Cyclane Cap	Tyama	Japan	-
Lisospasm	Chibi	Italy	-
Mandelic	Seiko	Japan	-
Marucyclan	Maruko	Japan	-
Mitalon	Toyo	Japan	-
Newcellan	Kowa	Japan	-

Trade Name	Manufacturer	Country	Year Introduced
Perebral	Biopharma	France	-
Saiclate	Morishita	Japan	-
Sancyclan	Santen	Japan	-
Sepyron	Sankyo	Japan	-
Spadelate	Zeria	Japan	-
Spasmione	Ravizza	Italy	-
Spasmocyclon	Kettelhack Riker	W. Germany	-
Syklandal	Orion	Finland	-
Vasodyl	Morrith	Spain	-
Vasosyklan	Farmos	Finland	-
Venala	Mochida	Japan	-
Zirkulat	Nippon Shoji	Japan	-

Raw Materials

dl-Mandelic acid
3,3,5-Trimethylcyclohexanol

Manufacturing Process

50 g of dl-mandelic acid are heated for 6 hours at approximately 100°C with 50 g of 3,3,5-trimethylcyclohexanol (mixture of cis and trans isomers), while passing dry hydrochloric acid gas as a catalyst through the mixture. The reaction product is subsequently poured out into water. After neutralization with potassium bicarbonate the ester is extracted with ether. The ether extract is dried with sodium sulfate, the ether is distilled off and the residue is distilled in vacuo. The fraction, which has a boiling point of 192° to 194°C at 14 mm, consists of the 3,3,5-trimethylcyclohexyl ester of mandelic acid, which is obtained in a yield of about 70%. The liquid solidifies to a colorless solid substance having a melting point of 50° to 53°C, according to US Patent 2,707,193.

It has been found that crude cyclandelate may be purified by the following procedure. Crude cyclandelate is dissolved in a solvent chosen for convenience from the class of saturated hydrocarbons. The crude cyclandelate solution is stirred for a suitable interval, typically 1 to 5 hours, with an aqueous solution of sodium borohydride ($NaBH_4$) at temperatures ranging from 25° to 65°C. The preferred temperature range is 40° to 50°C. The pH of the solution may be adjusted to any desired level in the range between 2.5 to 11.5. The preferred pH range is 8.0 to 11.0 because at lower pH levels borohydride is unstable and decomposes rapidly. The amount of sodium borohydride used ranges from about 0.5 to 2.0 wt % of the amount of cyclandelate present.

At the end of the stirring period cyclandelate is recovered by well-known procedures. For instance, the aqueous organic layers may be separated gravimetrically and the product organic layer washed with an appropriate solvent and then distilled, according to US Patent 3,663,597.

References

Merck Index 2695
Kleeman and Engel p. 254
PDR pp. 1606, 1947, 1999
OCDS Vol. 1 p. 94 (1977)
I.N. p. 273
REM p.852
Flitter, D.; US Patent 3,663,597; May 16, 1972; assigned to American Home Products Corporation
Nauta, W.T.; US Patent 2,707,193; April 26, 1955; assigned to N.V. Koninklijke Pharmaceutische Fabrieken Voorbeen Brocades-Stheeman and Pharmacia, Netherlands

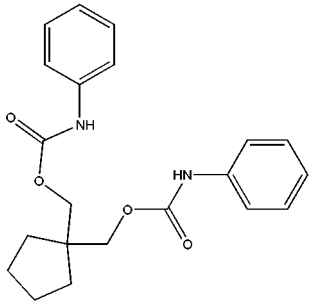
CYCLARBAMATE

Therapeutic Function: Spasmolytic

Chemical Name: 1,1-Dimethylolcyclopentane N,N'-diphenyl-dicarbamate

Common Name: Cyclopentaphene

Structural Formula:



Chemical Abstracts Registry No.: 5779-54-4

Trade Name	Manufacturer	Country	Year Introduced
Casmalon	Cassenne	France	1961

Raw Materials

1,1-Dimethylol cyclopentane
Phenyl isocyanate

Manufacturing Process

This compound is obtained by heating a mixture of 1,1-dimethylol cyclopentane and phenyl isocyanate at a temperature of 85°C to 90°C for one-half hour. The resultant product is washed with petroleum ether, recrystallized from methanol, dissolved in acetone (impurities are filtered off) and recrystallized from acetone.

The compound appears in the form of a white powder or of needle-shaped crystals (MP = 147°C to 149°C), which are tasteless and odorless.

References

Merck Index 2696
I.N. p.274
Rosenberg, E.E.; US Patent 3,067,240; December 4, 1962; assigned to Laboratoires Cassenne (France)

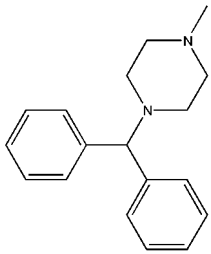
CYCLIZINE

Therapeutic Function: Antinauseant

Chemical Name: 1-Diphenylmethyl-4-methylpiperazine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 82-92-8; 303-25-3 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Marezine	Burroughs-Wellcome	US	1953
Marzine	Wellcome	France	1965
Bon Voyage	Cupal	UK	-
Cleamine	Kodama	Japan	-
Echnatol	Gerot	Austria	-

Trade Name	Manufacturer	Country	Year Introduced
Fortravel	Chemofux	Austria	-
Happy Trip	Mepros	Netherlands	-
Maremal	Gayoso Wellcome	Spain	-
Migwell	Wellcome	France	-
Motozina	Biomedica Foscama	Italy	-
Reis-Fit	A.P.F.	Netherlands	-
Valoid	Burroughs-Wellcome	UK	-

Raw Materials

Benzhydryl chloride
N-Methylpiperazine

Manufacturing Process

One-tenth mol (20 g) of benzhydryl chloride was mixed with 0.19 mol (19 g) of N-methylpiperazine and about 10 cc of benzene and the whole was heated on the steam bath four hours. The contents of the flask was partitioned between ether and water, and the ethereal layer was washed with water until the washings were neutral. The base was then extracted from the ethereal layer by N hydrochloric acid and the extract, made acid to Congo red paper, was evaporated under vacuum. 29.5 g of the pure dihydrochloride of N-methyl-N'-benzhydryl piperazine was recovered from the residue by recrystallization from 95% alcohol melting above 250°C with decomposition.

The addition of alkali to an aqueous solution of the dihydrochloride liberated the base which was recovered by recrystallization from petroleum ether melting at 105.5° to 107.5°C.

References

Merck Index 2703
Kleeman and Engel p. 254
PDR p. 754
OCDS Vol. 1 p. 58 (1977)
I .N. p. 274
REM p. 807
Baltzly, R. and Castillo, J.C.; US Patent 2,630,435; March 3, 1953; assigned to Burroughs Wellcome and Co. (U.S.A.) Inc.

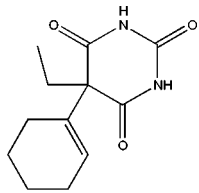
CYCLOBARBITAL

Therapeutic Function: Hypnotic

Chemical Name: 2,4,6-(1H,3H,5H)-Pyrimidinetrione, 5-(1-cyclohexen-1-yl)-5-ethyl-

Common Name: Ciclobarbital; Cyclobarbital; Cyclobarbitone; Tetrahydrophenobarbital

Structural Formula:



Chemical Abstracts Registry No.: 52-31-3

Trade Name	Manufacturer	Country	Year Introduced
Cyclobarbital	Bayer	-	-
Cyklonal	Leo	-	-
Dorminal	Star	-	-
Prodorm	Nyco	-	-

Raw Materials

δ-1,2-Cyclohexenylcyanacetic acid ethyl ester
Ethyl iodide
Sulfuric acid
Sodium
Alcohol
Quanidine sulfate

Manufacturing Process

772.0 g of δ-1,2-cyclohexenylcyanacetic acid ethyl ester are introduced into a stirred and ice cooled solution of 92.0 g of sodium in 1500 ml of absolute alcohol. The sodium δ-1,2-cyclohexenylcyanacetic acid ester formed is then gradually treated without ice cooling with 750.0 g of ethyl iodide. The reaction mixture become warm, sodium iodide separates out and the whole is neutral after a short time. The sodium iodide is filtered off, the filtrate freed from alcohol by distillation, the residues taken up in water, siphoned off, dried over calcium chloride and distilled in vacuum, yields δ-1,2-cyclohexenylethylcyanacetic acid ethyl ester, boil point 125°C. 72.0 g of sodium are dissolved in 1086.0 g of absolute alcohol and boiled for 3.75 h with 285.0 g of guanidine sulfate, then 221.0 g of δ-1,2-cyclohexenylethylcyanacetic acid ester are added and boiling is continued for a further 12 h. The residue remaining after distilling off the alcohol is boiled with 10 times its weight of dilute sulfuric acid and then δ-1,2-cyclohexenylethylbarbituric acid which separates out is recrystallized from hot water, melting point 170°C.

References

DB Patent No. 231,150; March 21,1924; Assigned: Farbeenfabriken vorm. Friedr. Bayer and Co., Germany

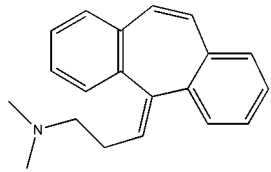
CYCLOBENZAPRINE

Therapeutic Function: Muscle relaxant

Chemical Name: 5-(3-Dimethylaminopropylidene)-dibenzo[a,e] cycloheptatriene

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 303-53-7; 6202-23-9 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Flexeril	Merck Sharp and Dohme	US	1977

Raw Materials

Dibenzo[a,d]cycloheptene-5-one
Magnesium
3-Dimethylaminopropyl chloride
Hydrogen chloride

Manufacturing Process

In an initial step, dibenzo [a,d]cyclohepten-5-one is reacted with the Grignard reagent of 3-dimethylaminopropyl chloride and hydrolyzed to give 5-(3-dimethylaminopropyl)-dibenzo[a,d][1,4]cycloheptatriene-5-ol. Then 13 g of that material, 40 ml of hydrochloric acid, and 135 ml of glacial acetic acid is refluxed for 3½ hours. The solution is then evaporated to dryness in vacuo and added to ice water which is then rendered basic by addition of ammonium hydroxide solution. Extraction of the basic solution with chloroform and removal of the solvent from the dried chloroform extracts yields the crude product which when distilled in vacuo yields essentially pure 5-(3-dimethylaminopropylidene)-dibenzo[a,d][1,4]cycloheptatriene, BP 173°C to 177°C at 1.0 mm.

References

Merck Index 2706
DFU 2 (5) 299 (1977)
Kleeman and Engel p. 255
PDR p. 1178

OCDS Vol. 3 p. 77 (1984)
DOT 14 (12) 467 (1978)
I.N. p. 275
REM p. 926
Villani, F.J.; US Patent 3,409,640; November 5, 1968; assigned to Schering Corporation

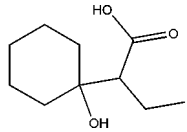
CYCLOBUTYROL

Therapeutic Function: Choleretic

Chemical Name: α-(Hydroxy-1-cyclohexyl)butyric acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 512-16-3

Trade Name	Manufacturer	Country	Year Introduced
Hebucol	Logeais	France	1957
Bas-Bil	Isola-Ibi	Italy	-
Citoliver	Bayropharm	Italy	-
Cytinium	Roques	France	-
Dibilene	Logeais	France	-
Epo-Bon	Sierochimica	Italy	-
Juvallax	Pierrel	Italy	-
Lipotrin	Eisai	Japan	-
Riphole N	Nichiiko	Japan	-
Secrobil	Medital	Italy	-
Tribil	Biol. Italia	Italy	-
Tribilina	Farge	Italy	-
Trommogallol	Trommsdorff	W. Germany	-

Raw Materials

Cyclohexanone
Barium hydroxide
Sulfuric acid
Ethyl α-bromobutyrate
Zinc

Manufacturing Process

Into a balloon flask with two lateral necks furnished with an efficient mechanical agitator and protected from moisture by a calcium chloride guard, there are introduced 12 g (0.185 mol) of pure powdered zinc and 20 ml of a solution of 16.6 g (0.17 mol) of anhydrous cyclohexanone and 31.5 g (0.16 mol) of ethyl α-bromobutyrate in 25 ml of anhydrous benzene. With vigorous stirring in a manner to put the zinc into suspension, the balloon flask is gradually heated in an oil bath to 100°C to 105°C. After a few minutes, a reaction starts, causing violent boiling which is maintained while adding the balance of the reactants. Boiling is then continued for one hour. After cooling, the reaction mixture is turned into a beaker containing 30 ml of sulfuric acid to half (by volume) with ice. After agitation, the mixture is decanted into a container for separation. The aqueous phase is reextracted with benzene. The pooled benzene solutions are washed with dilute (10%) cold sulfuric acid, then with cold sodium carbonate (5%) and then with ice water, and dried over anhydrous sodium sulfate. The benzene is evaporated and the ester, which is ethyl α(hydroxy-1-cyclohexyl) butyrate, is distilled off under reduced pressure. The yield obtained was 17 to 19 g or 49% to 55%.

The ester was saponified with baryta in aqueous methanol as follows:

21.5 g (0.1 mol) of the above ethyl ester is saponified by boiling under reflux for 4 hours, while agitating, with 30 g (0.095 mol) of barium oxide hydrated to $8H_2O$ in 250 ml of a mixture of equal volumes of methanol and water. After concentration to one-half its volume under reduced pressure and filtration, the aqueous solution is washed with ether and then acidified at 0°C with 10% hydrochloric acid. The acid liberated in oily form is extracted with ether. The ether is washed with water, dried and evaporated. The yield is 75-80% (14-15 g of crude acid) which crystallizes spontaneously little by little. It can be crystallized in a mixture of ether and petroleum ether (1:10) or, with better yield, in light gasoline or oil (solubility of the pure acid ranges from 0.3% at 0°C to 100% at the boiling point). The yield of crystals is 75-80%. The α(hydroxy-1-cyclohexyl) butyric acid thus obtained is a colorless crystalline product with a melting point of 81°C to 82°C.

References

Merck Index 2709
Kleeman and Engel p. 256
I.N.p.275
Maillard, J.G.A.E., Morin, R.M. and Benard, M.M.M.; US Patent 3,065,134; November 20, 1962; assigned to Societe d'Exploitation des Laboratoires Jacques Logeals (S.A.R.L.) (France)

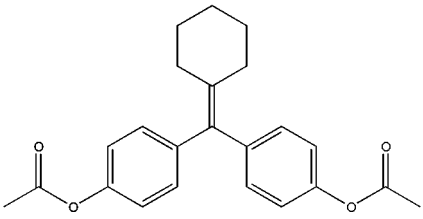
CYCLOFENIL

Therapeutic Function: Ovulation stimulant

Chemical Name: 4-[[4-(Acetyloxy)phenyl]cyclohexylidenemethyl]phenol acetate

Common Name: p,p'-Diacetoxybenzhydrilidenecyclohexane

Structural Formula:



Chemical Abstracts Registry No.: 2624-43-3

Trade Name	Manufacturer	Country	Year Introduced
Ondogyne	Roussel	France	1970
Sexovid	Teikoku Hormon	Japan	1972
Fertodur	Schering	W. Germany	1972
Ondonvid	Roussel	UK	1972
Fertodur	Schering	Italy	1974
Klofenil	Yurtoglu	Turkey	-
Neoclym	Poli	Italy	-
Sexovid	Ferrosan	Sweden	-

Raw Materials

p-Bromoanisole
Potassium hydroxide
Magnesium
p-Hydroxyphenyl cyclohexyl ketone
Ammonium chloride
Acetic anhydride

Manufacturing Process

(A) Preparation of p-Hydroxy-p'-Methoxybenzhydrylidenecyclohexane: To a Grignard solution prepared from 110 g of magnesium (4.5 mols) and 840 g of p-bromoanisole (4.5 mols) in one liter of anhydrous ether, there was added dropwise with vigorous agitation 307 g of p-hydroxyphenyl cyclohexyl ketone (1.5 mols) dissolved in one liter of anhydrous ether. Upon completion of the addition the reaction mixture was refluxed for 2.5 hours with agitation, and was then cooled. Thereupon 15 mols of ammonium chloride dissolved in 3 liters of water were added. The ethereal layer was separated, washed with water, dried over anhydrous sodium sulfate and distilled. Yield: 370 g. BP 180° to 190°C at 0.1 mm. The substance was recrystallized from a mixture of carbon tetrachloride and petroleum ether. MP 145° to 146°C.

(B)Preparation of p,p'-Dihydroxybenzhydrylidenecyclohexane: A mixture of 118 g of p-hydroxy-p'-methoxybenzhydrylidenecyclohexane (0.4 mol), 120 g of potassium hydroxide pellets and 500 ml of triethylene glycol was stirred 4 hours at 220°C. When the reaction mixture was poured into water the substance crystallized, and the crystals were filtered off and washed with

water. The substance was then recrystallized from a mixture of ethanol and petroleum ether. Yield: 104 g. MP 235° to 236°C.

(C) Preparation of p,p'-Diacetoxybenzhydrylidenecyclohexane: 56 g of p,p'-dihydroxybenzhydrylidenecyclohexane (0.2 mol) was mixed with 250 ml of acetic anhydride and 500 ml of pyridine. The mixture was refluxed for 2 hours and was then poured into water, the substance crystallizing out. The crystals were filtered off and washed with water. Finally the substance was recrystallized from ethanol. Yield: 62 g. MP 135° to 136°C.

References

Merck Index 2714
Kleeman and Engel p. 256
DOT 7 (1) 11 (1971)
I.N. p. 275
Olsson, K.G., Wahlstam, H.E.A., Sundbeck, B., Barany, E.H. and Miquel, J.F.; US Patent 3,287,397; November 22, 1966

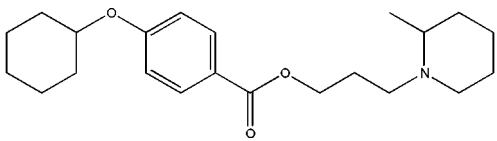
CYCLOMETHYCAINE

Therapeutic Function: Local anesthetic

Chemical Name: 4-(Cyclohexyloxy)benzoic acid 3-(2-methyl-1-piperidinyl) propyl ester

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 139-62-8

Trade Name	Manufacturer	Country	Year Introduced
Surfacaine	Lilly	US	1948
Topocaine	Lilly	-	-

Raw Materials

Ethyl-p-hydroxybenzoate
Sodium
Sodium hydroxide
Cyclohexyl bromide
3-(2'-Methylpiperidino)propyl chloride

Manufacturing Process

7.4 g of sodium are dissolved in 250 cc of isoamyl alcohol, 53 g of ethyl p-hydroxybenzoate are added and the mixture is heated to refluxing temperature for about 15 minutes. To the cooled mixture, 65 g of cyclohexyl bromide are added and the mixture is refluxed for about 3 hours. The isoamyl alcohol is removed by evaporation in vacuo and the residue is extracted with 10% aqueous sodium hydroxide solution to remove the unreacted ethyl p-hydroxybenzoate.

The alkali-insoluble residue comprising ethyl p-cyclohexyloxybenzoate is hydrolyzed by refluxing with 10% sodium hydroxide solution for about 3 hours. The alkaline reaction mixture is acidified with hydrochloric acid whereupon p-cyclohexyloxybenzoic acid precipitates. The precipitate is separated by filtration, washed with water and dried. It melts at about 178° to 180°C. Yield: about 7%.

62 g of p-cyclohexyloxybenozic acid and 49.5g of 3-(2'-methylpiperidino)-propyl chloride are dissolved in 300 cc of dry isopropanol and the mixture refluxed for about 12 hours. About half of the isopropanol is then distilled off and the residual solution cooled to about 0°C. 3(2'-methylpiperidino)-propyl p-cyclohexyloxybenzoate hydrochloride precipitates as a white crystalline compound. It is filtered off, washed once with ether and recrystallized from isopropanol.

3(2'-Methylpiperidino)-propyl p-cyclohexyloxybenzoate hydrochloride thus prepared melted at about 178° to 180°C. Analysis showed the presence of 8.88% chlorine as compared with the calculated value of 8.96%.

References

Merck Index 2729
Kleeman and Engel p. 257
OCDS Vol. 1 p. 14 (1977)
I.N. p.276
REM p. 1055
McElvain, S.M. and Carney,T.P.; US Patent 2,439,818; April 20, 1948

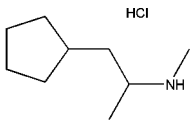
CYCLOPENTAMINE HYDROCHLORIDE

Therapeutic Function: Vasoconstrictor

Chemical Name: N-α-Dimethylcyclopentaneethaneamine hydrochloride

Common Name: Cyclopentadrine

Structural Formula:



Chemical Abstracts Registry No.: 102-45-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Clopane	Lilly	US	1951
Cyclonaranol	Hepatrol	France	-
Nazett	A.L.	Norway	-

Raw Materials

Cyclopentanone
Cyanoacetic acid
Ammonium acetate
Hydrogen
Magnesium
Methyl iodide
Methylamine
Hydrogen chloride

Manufacturing Process

A mixture of 126 g (1.5 mols) of cyclopentanone, 128 g (1.5 mols) cyanoacetic acid, 31 g (0.5 mol) of ammonium acetate and 200 cc of dry benzene is heated under a refluxing condenser and a water trap. The mixture is refluxed for about 12 hours after which time no more water collects in the trap, and the formation of cyclopentylideneacetonitrile is complete. The reaction mixture comprising a mixture of cyclopentylideneacetonitrile and cyclopentylideneacetic acid is washed with about one liter of 2% hydrochloric acid and the benzene layer is separated and the mixture is distilled to cause decarboxylation of the cyclopentylideneacetic acid present. The distillate comprising cyclopentylideneacetonitrile which boils at 172° to 175°C is purified by distillation.

A mixture of 53.5 g (0.5 mol) of cyclopentylideneacetonitrile dissolved in 50 cc of absolute ethanol and 0.5 g of a palladium-carbon catalyst is hydrogenated with hydrogen at a pressure of about 40 lb for about 3 hours. An additional amount of 0.8 g of palladium-carbon catalyst is then added and the hydrogenation continued for about 4 hours during which time the reduction is substantially completed and the cyclopentylideneacetonitrile is converted to cyclopentylacetonitrile. The reaction mixture is filtered to remove the catalyst and the alcohol is evaporated in vacuo.

The residue comprising chiefly cyclopentylacetonitrile is washed with dilute hydrochloric acid to remove any amine which may have been formed during the hydrogenation process, and the organic residue comprising cyclopentylacetonitrile is dissolved in ether, the ether solution dried over anhydrous magnesium sulfate and distilled. The cyclopentylacetonitrile boils at 185° to 187°C and has a refractive index of n_D^{25} = 1.4456.

To an ethereal solution of methyl magnesium iodide prepared from 26.7 g (1.1 mols) of magnesium and 160 g (1.13 mols) of methyl iodide in 200 cc of dry ether, is added a solution of 79 g (0.72 mol) of cyclopentylacetonitrile in 100 cc of dry ether. The reaction mixture is refluxed for 4 hours. The reaction mixture is then decomposed with ice in the usual way, and the ether layer

containing the cyclopentylacetone is separated, is dried over anhydrous magnesium sulfate and the ether removed by evaporation. The residue comprising cyclopentylacetone is purified by distillation in vacuo. The cyclopentylacetone boils at 82° to 84°C at about 32 mm pressure.

A mixture of 75 g (0.6 mol) of cyclopentylacetone, 75 g (2.4 mols) of methylamine, and 10 g of Raney nickel catalyst is placed in a high pressure bomb previously cooled to a temperature below -6°C, and hydrogen is admitted under an initial pressure of about 2,000 psi. The bomb is then heated to about 135° to 150°C for about 2 hours, during which time reductive amination takes place and 1-cyclopentyl-2-methylaminopropane is produced. During the period of heating the reaction mixture is agitated by rocking the bomb. The bomb is then cooled and opened thus permitting the escape of hydrogen and most of the excess methylamine. The reaction mixture is filtered to remove the nickel catalyst and the filtrate comprising 1-cyclopentyl-2-methylaminopropane is purified by distillation under reduced pressure. 1-Cyclopentyl-2-methylaminopropane boils at 83° to 86°C at about 30 mm pressure.

1-Cyclopentyl-2-methylaminopropane thus produced is a colorless liquid of slightly ammoniacal odor. It has a refractive of n_D^{25} = 1.4500. Analysis showed the presence of 9.79% N as compared with a calculated value of 9.99% N.

141 g (1 mol) of 1-cyclopentyl-2-methylaminopropane are dissolved in 500 cc of dry ether, and dry hydrogen chloride is passed into the solution until the weight of the mixture and container has increased by 36 g. During the addition of the hydrogen chloride, the hydrochloric acid addition salt of 1-cyclopentyl-2-methylaminopropane precipitates as a white powder. The salt is filtered off and washed with dry ether. 1-Cyclopentyl-2-methylaminopropane hydrochloride thus prepared melts at about 113° to 115°C. The yield is practically quantitative.

References

Merck Index 2733
Kleeman and Engel p. 258
I.N.p.277
Rohrmann, E.; US Patent 2,520,015; August 22, 1950; assigned to Eli Lilly and Company

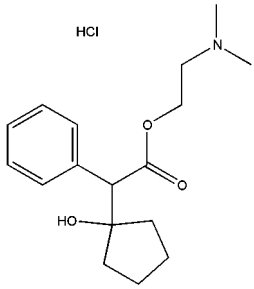
CYCLOPENTOLATE HYDROCHLORIDE

Therapeutic Function: Anticholinergic (ophthalmic)

Chemical Name: α-(1-Hydroxycyclopentyl)benzene-acetic acid 2-(dimethylamino)ethyl ester hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 5870-29-1; 512-15-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Cyclogyl	Schieffelin	US	1953
Cyplegin	Santen	Japan	1972
Skiacol	P.O.S.	France	1976
Pentolair	Pharmafair	US	1983
Ciclolux	Tubi Lux Pharma	Italy	-
Cicloplegic	Frumtost	Spain	-
Colircusi Ciclopejico	Cusi	Spain	-
Cyclomydrin	Alcon	US	-
Cyclopen	Irving	Australia	-
Cyclopentol	Cusi	Belgium	-
Mydplegic	Cooper Vision	Puerto Rico	-
Mydrilate	W.B. Pharm.	UK	-
Oftan-Syklo	Star	Finland	-
Zykolate	Mann	W. Germany	-

Raw Materials

Sodium phenyl acetate
β-Chloroethyl dimethylamine
Cyclopentanone
Isopropyl bromide
Magnesium

Manufacturing Process

To a well stirred suspension of 9 g of sodium phenyl acetate and 2.4 g of magnesium turnings in 25 cc of anhydrous ether, a solution of 9.4 cc of isopropyl bromide in 50 cc of anhydrous ether are added. The mixture is refluxed for one hour (during which time propane is evolved) and then 5 cc of cyclopentanone in 25 cc of anhydrous ether are added dropwise. The mixture is then refluxed for one hour and poured over ice water containing some hydrochloric acid. The ether solution is separated and extracted with 200 cc of 5% sodium hydroxide. The alkaline solution on acidification gives the free acid

which is filtered off, dried in a desiccator and recrystallized from a mixture of ethylene dichloride and petroleum ether.

The product is 2-phenyl-2-(1-hydroxycyclopentyl)ethanoic acid, melting at 95° to 97°C. Of this product, 4.5 g in 30 cc of dry isopropyl alcohol are refluxed for 16 hours with 2.5 g of β-chloroethyl dimethyl amine. The solution is cooled and filtered clear from the solid by-product. The solvent is removed under reduced pressure on the steam bath and the residue is washed with anhydrous ether. It is dissolved in ethyl acetate from which it crystallizes. It is the hydrochloride of β-(dimethylamino)ethyl ester of 2-phenyl-2-(1-hydroxycyclopentyl) ethanoic acid, melting at 134° to 136°C.

References

Merck Index 2740
Kleeman and Engel p. 259
OCDS Vol. 1 p.92 (1977)
I.N. p. 277
REM p.914
Treves, G.R.; US Patent 2,554,511; May 29, 1951; assigned to Schieffelin and Co.

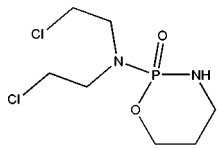
CYCLOPHOSPHAMIDE

Therapeutic Function: Antineoplastic

Chemical Name: N,N-Bis(2-chloroethyl)tetrahydro-2H-1,3,2-oxazaphosphorin-2-amine-2-oxide

Common Name: Cyclophosphane; Cytophosphane

Structural Formula:



Chemical Abstracts Registry No.: 50-18-0

Trade Name	Manufacturer	Country	Year Introduced
Cytoxan	Mead Johnson	US	1959
Endoxan	Lucien	France	1960
Neosar	Adria	US	1982
Carloxan	Laake	Finland	-
Cicloblastina	Montedison	W. Germany	-

Trade Name	Manufacturer	Country	Year Introduced
Cyclostin	Farm. Carlo Erba	Italy	-
Cytophosphan	Taro	Israel	-
Edoxana	Asta	W. Germany	-
Edoxana	W.B. Pharm.	UK	-
Genoxal	Funk	Spain	-
Procytox	Horner	Canada	-
Sendoxan	Pharmacia	Sweden	-

Raw Materials

N,N-Bis(β-chloroethyl)phosphoric acid amide dichloride
Triethylamine
1.3-Propanolamine

Manufacturing Process

A solution of 7.5 g (0.1 mol) of 1,3-propanolamine and 20.2 g of triethylamine in 100 cc of absolute dioxane is added dropwise at 25°C to 30°C while stirring well to a solution of 25.9 g (0.1 mol) of N,N-bis-(β-chloroethyl)-phosphoric acid amide dichloride in 100 cc of absolute dioxane. After the reaction is complete, the product is separated from the precipitated triethylamine hydrochloride and the filtrate is concentrated by evaporation in waterjet vacuum at 35°C. The residue is dissolved in a large amount of ether and mixed to saturation with water. The N,N-bis-(β-chloroethyl)-N,O-propylene phosphoric acid diamide crystallizes out of the ethereal solution, after it has stood for some time in a refrigerator, in the form of colorless water-soluble crystals. MP 48°C to 49°C. Yield: 65% to 70% of the theoretical.

References

Merck Index 2741
Kleeman and Engel p. 259
PDR pp.569, 719
OCDS Vol. 3 p. 161 (1984)
DOT 16 (5) 169 (1980)
I.N. p.278
REM p. 1146
Arnold, H., Brock, N. and Bourseaux, F.; US Patent 3,018,302; January 23, 1962;assigned to Asta-Werke A.G. Chemische Fabrik (W. Germany)

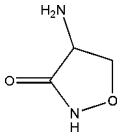
CYCLOSERINE

Therapeutic Function: Antitubercular

Chemical Name: D-4-Amino-3-isoxazolidinone

Common Name: Orientomycin

Structural Formula:



Chemical Abstracts Registry No.: 68-41-7

Trade Name	Manufacturer	Country	Year Introduced
Oxamycin	Merck Sharp and Dohme	US	1956
Seromycin	Lilly	US	1956
Aristoserina	Aristochimica	Italy	-
Ciclovalidin	Bracco	Italy	-
Cyclomycin	Shionogi	Japan	-
Cycloserine	Lilly	US	-
D-Cycloserin	Roche	W. Germany	-
Farmiserina	Farm. Carlo Erba	Italy	-
Micoserina	Beolet	Italy	-
Miroseryn	Morgan	Italy	-
Orientmycin	Kayaru-Kaken Yaku	Japan	-
Setavax	I.C.N.	-	-
Tisomycin	Lilly	-	-

Raw Materials

β-Aminoxyalanine ethyl ester
Bacterium Streptomyces lavendulae
Soybean meal
Potassium hydroxide

Manufacturing Process

Cycloserine may be made by a fermentation process or by direct synthesis. The fermentation process is described in US Patent 2,773,878. A fermentation medium containing the following proportions of ingredients was prepared:

	Parts by Weight
Soybean meal	30.0
Cornstarch	5.0
Corn steep liquor	3.0
Sodium nitrate	3.0

This material was made up with distilled water to provide 41 g per liter, and the mixture was adjusted to pH 7.0 with potassium hydroxide solution. To the mixture were added per liter 5.0 g of calcium carbonate and 7.5 ml of soybean oil. 2,000 ml portions of this medium were then added to fermentation vessels, equipped with stirrers and aeration spargers, and sterilized at 121°C for 60 minutes. After cooling the flasks were inoculated with a suspension of strain No. ATCC 11924 of Streptomyces lavendulae,

obtained from the surface of agar slants. The flasks were stirred for 4 days at 28°C at approximately 1,700 rpm. At the end of this period the broth was found to contain cycloserine in the amount of about 250 C.D.U./ml of broth. The mycelium was separated from the broth by filtration. The broth had a pH of about 7.5. Tests showed it to be highly active against a variety of microorganisms.

The direct synthetic process is described in US Patent 2,772,280. A solution of 73.3 g (0.332 mol) of β-aminoxyalanine ethyl ester dihydrochloride in 100 ml of water was stirred in a 500 ml 3-necked round-bottomed flask cooled in an ice-bath. To the above solution was added over a 30-minute period 65.6 g (1.17 mols) of potassium hydroxide dissolved in 100 ml of water, While the pH of the reaction mixture was 7 to 10.5, a red color appeared which disappeared when the pH reached 11 to 11.5. The light yellow solution was allowed to stand at room temperature for ½ hour and then added to 1,800 ml of 1:1 ethanol-isopropanol. The reaction flask was washed twice with 10 ml portions of water and the washings added to the alcohol solution. The precipitated salts were filtered out of the alcohol solution and the filtrate cooled to 5°C in a 5 liter 3-necked round-bottomed flask. To the cold, well-stirred solution was added dropwise over a 35-minute period sufficient glacial acetic acid to bring the pH of the alcohol solution to 6.0. When the pH of the solution had reached 7 to 7.5, the solution was seeded and no further acetic acid added until crystallization of the oil already precipitated had definitely begun. The crystalline precipitate was collected on a filter, washed twice with 1:1 ethanol-isopropanol and twice with ether. The yield of 4-amino-3-isoxazolidone was 22.7 g.

References

Merck Index 2747
Kleeman and Engel p. 260
PDR p. 1069
OCDS Vol. 3 p. 14 (1984)
I.N.p.278
REM p. 1210
Fermentation Process:
Shull, G.M., Routien, J.B. and Finlay, A.C.; US Patent 2,773,878; December 11, 1956; assigned to Chas. Pfizer and Co., Inc.
Harned, R.L.; US Patents 2,789,983; April 23, 1957; and 3,124,590; March 10, 1964; both assigned to Commercial Solvents Corporation
Howe, E.E.; US Patent 2,845,433; July 29, 1958; assigned to Merck and Co.,Inc.
Synthetic Process:
Peck, R.L.; US Patent 2,772,280; November 27, 1956; assigned to Merck and Co., Inc.
Holly, F.W. and Stammer, C.H.; US Patent 2,840,565; June 24, 1958; assigned to Merck and o., Inc.

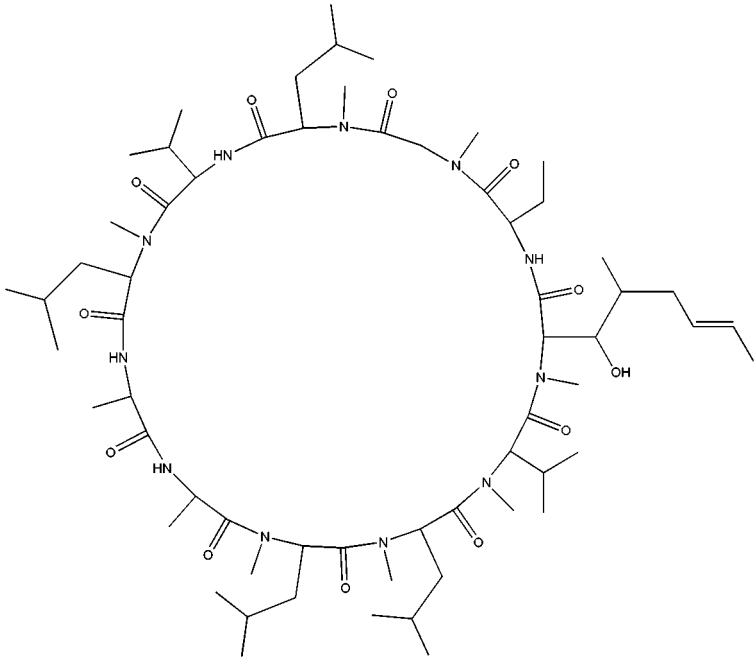
CYCLOSPORIN

Therapeutic Function: Immunosuppressive

Chemical Name: Cyclic oligopeptide

Common Name: Ciclosporin

Structural Formula:



Chemical Abstracts Registry No.: 59865-13-3

Trade Name	Manufacturer	Country	Year Introduced
Sandimmune	Sandoz	US	1983
Sandimmun	Sandoz	UK	1983
Sandimmun	Sandoz	W. Germany	1983
Sandimmune	Sandoz	Switz.	1983

Raw Materials

Sucrose
Corn steep liquor
Fungus Cylindrocarpon Lucidum (NRRL 5760)

Manufacturing Process

10 liters of a nutrient solution (of which each liter contains 30 g of sucrose, 10 g of corn steep, 3 g of $NaNO_3$, 1 g of K_2HPO_4, 0.5 g of $MgSO_4 \cdot 7H_2O$, 0.5 g of KCl and 0.01 g of $FeSO_4 \cdot 7H_2O$) are inoculated with 100 cc of a conidia and

mycelium suspension of the strain NRRL 5760, and incubation is effected in 700 cc penicillin flasks at 27°C for 11 days.

The mycelium, which has been separated from the culture liquid, is extracted in a Turrax apparatus by crushing and stirring with 3.5 liters of 90% methanol, and the crushed mycelium, which is separated from the solvent by filtering with suction, is again treated twice in the same manner with 90% methanol. The combined filtrates are concentrated by evaporation in a vacuum at a bath temperature of 40°C to such an extent that the vapor mainly consists of water alone. The resulting mixture is extracted six times with the same volume of ethylene chloride by shaking, whereupon the combined ethylene chloride solutions are purified by extraction with water and are concentrated by evaporation in a vacuum at a bath temperature of 40°C. The resulting residue is chromatographed on 250 g of silica gel (silica gel 60 Merck, grain size 0.063-0.200 mm), using chloroform containing 2% of methanol as eluant, and is collected in 200 cc fractions. The fractions which are antibiotically active against Aspergillus niger in the plate diffusion test are combined, evaporated to dryness as described above, and after dissolving in methanol are chromatographed on 110 g of Sephadex LH20 with the same solvent, whereupon those 20 cc fractions showing an antibiotic effect against Aspergillus niger in the test indicated above, are combined. A test in the thin layer chromatogram, e.g., with silica gel on Polygram foils and hexane/acetone (1:1) as eluant, indicates that the residue of the methanol solution evaporated as described above mainly consists of the two new antibiotics S 7481/F-1 and S 7481/F-2. These are separated and simultaneously purified by a further chromatography of the mixture thereof, using a 1,000-fold amount of silica gel on the above indicated quality and chloroform contains 2% of methanol. A testing of the eluate fractions having a volume in milliliters which is half as large as the weight of the silica gel in grams, in the thin layer chromatogram, indicates that the antibiotic S 7481/F-1 appears first in the eluate, followed by a mixture of the two antibiotics and finally by homogeneous S748l/F-2.

Further amounts of the two antibiotics may be obtained from the mixture by repeating chromatography under the same conditions.

References

Merck Index 2748
DFU 4 (8) 567 (1979)
PDR p. 1592
DOT 19 (7) 413 and (12) 665 (1983)
I.N. p. 231
REM p. 1147
Harri, E. and Ruegger, A.; US Patent 4,117,118; September 26, 1978; assigned to Sandoz, Ltd. (Switz.)

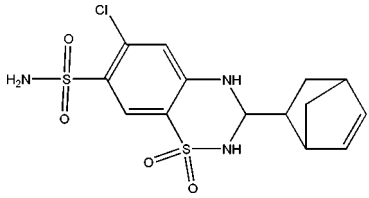
CYCLOTHIAZIDE

Therapeutic Function: Diuretic, Antihypertensive

Chemical Name: 3-Bicyclo[2.2.1]hept-5-en-2-yl-6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 2259-96-3

Trade Name	Manufacturer	Country	Year Introduced
Anhydron	Lilly	US	1963
Fluidil	Adria	US	1980
Baronorm	Roussel	France	-
Cycloteriam	Roussel	France	-
Dimapres	Dieckmann	W. Germany	-
Doburil	Pharmacia	Sweden	-
Doburil	Boehringer Ingelheim	-	-
Tensodiural	Rafa	Israel	-
Valmiran	Boehringer Tanabe	Japan	-

Raw Materials

6-Chloro-4-aminobenzene-1,3-disulfonamide
2,5-Endomethylene-δ(3)-tetrahydrobenzaldehyde

Manufacturing Process

A mixture of 8.5 g (0.03 mol) of 6-chloro-4-amino-benzene-1,3-disulfonamide, 4.0 g (0.033 mol) of 2,5-endomethylene-δ^3-tetrahydrobenzaldehyde and 25 cc of diethyleneglycol-dimethyl ether was heated for 2 hours at 100°C. During this time the major portion of the initially undissolved crystals went into solution; thereafter, the reaction mixture was allowed to stand for 14 hours at room temperature, during which the remaining undissolved crystals also went into solution. The reddish, clear solution thus obtained was admixed with 50 cc of chloroform. The greyish-white precipitate formed thereby was separated by vacuum filtration, washed with a small amount of chloroform, dried and recrystallized from aqueous methanol. 7.5 g of white crystalline needles having a melting point of 229° to 230°C were obtained.

References

Merck Index 2749
Kleeman and Engel p. 261
OCDS Vol. 1 p. 358 (1977)
I.N .p. 278
REM p. 939
Muller, E. and Hasspacher, K.; US Patent 3,275,625; September 27, 1966; assigned to Boehringer Ingelheim GmbH, Germany

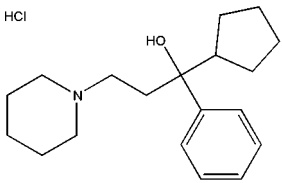
CYCRIMINE HYDROCHLORIDE

Therapeutic Function: Muscle relaxant, Antiparkinsonian

Chemical Name: α-Cyclopentyl-α-phenyl-1-piperidinepropanol hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 126-02-3; 77-39-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Pagitane	Lilly	US	1953
Pagitane	Lilly	Italy	-

Raw Materials

Bromobenzene
Magnesium
Cyclopentyl-β-(N-piperidyl)ethyl ketone
Hydrogen chloride

Manufacturing Process

The manufacture of the cyclohexyl analog is as follows. Phenyl magnesium bromide was prepared from 48.5 g (0.308 mol) of bromobenzene, 7 g (0.29 mol) of magnesium, and 125 ml of dry ether. To it was added at 5°C over a period of ½ hour 40 g (0.18 mol) of cyclohexyl β-(N-piperidyl)-ethyl ketone (BP 115° to 117°C/1 mm) in 125 ml of dry ether. The mixture was allowed slowly to come to room temperature, refluxed for one hour, and then poured into ice containing 80 ml of concentrated hydrochloric acid. Ammonium

chloride (100 g) and 200 ml of concentrated ammonium hydroxide were added and the organic layer was separated. After drying and removing the solvent, the residue was distilled under reduced pressure. The base distilled at 158° to 170°C (1 mm) and solidified. Upon recrystallization from methanol it melted at 112° to 113°C.

References

Merck index 2752
Kleeman and Engel p. 262
OCDS Vol. 1 p. 47 (1977)
I.N. p.279
REM p.932
Ruddy, A.W. and Becker, T.J.; US Patent 2,680,115; June 1, 1954; assigned to Winthrop-Stearns Inc.

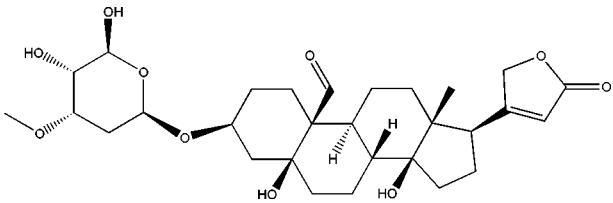
CYMARIN

Therapeutic Function: Cardiotonic

Chemical Name: 5β-Card-20(22)-enolide, 3β-3-((2,6-dideoxy-3-O-methyl-β-D-ribo-hexopyranosyl)oxy)-5,14-dihydroxy-19-oxo-

Common Name: Cimarinum; Cymarin; h-Strophanthin; k-Strophanthin-β; Tsimarin

Structural Formula:



Chemical Abstracts Registry No.: 508-77-0

Trade Name	Manufacturer	Country	Year Introduced
Alvonal	Goumldecke	-	-

Raw Materials

Seeds of Castilloa elastica
Column of alumina

Manufacturing Process

Finely ground seeds of Castilloa elastica (3550 g) are percolated with sufficient light petroleum (boiling point 60°-80°C) to ensure removal of all the fat. The mart is dried with a current of air and percolated with chloroform until no further color is obtained with alkaline m-dinitrobenzene. The percolate is evaporated under reduced pressure, the residue triturated with dry ether (750 ml) and filtered. The residue (69.75 g) is washed with dry ether, dried, and some of the washed residue (20 g) is dissolved in a benzene-chloroform mixture (50 ml), comprising one part benzene to two parts chloroform by volume, and is absorbed on to a column of alumina (7x32 cm), previously deactivated with 10% acetic acid [hereinafter referred to as Column (I)] and eluted with the same solvent mixture.

The compositions of the following fractions (collected from Column (I)) are identified by paper chromatography using Whatman No. 1 paper [Registered Trade Mark] and the aforementioned benzene-chloroform mixture.

Column (I). Fraction: (a) a pigment; (b) a substance of R_f 0.66; (c) a small quantity of a substance of R_f 0.66 and a substance of R_f 0.45; (d) a substance of R_f 0.45.

Fraction (c) is obtained from the column and concentrated. The solid residue is dissolved in the aforementioned benzene-chloroform mixture (15 ml) and fractionated further on a second deactivated alumina column (4x30cm). From this column [hereinafter referred to as Column (II)] the following fractions are collected and identified using the same chromatographic system as was used for identifying the fractions of Column (I).

Column (II). Fraction: (a) a substance of R_f 0.66; (b) a trace of a substance of R_f 0.66; (c) a substance of R_f 0.45.

The fractions (d) of Column (I) and (c) of Column (II) are combined and evaporated and the residue (80 g) crystallized from methanol and ether followed by further re-crystallization from dilute alcohol. On heating to 120°C under a pressure of 0.01 mm/Hg, the crystals lost water to give a compound, cymarin, which has an $[\alpha]_d^{22} = +39.0°$. The $[\alpha]_d^{20}$ of cymarin (obtained from another source) in methanol is + 39.3°.

Alternatively, fractional crystallization may be used in place of adsorption chromatography.

Cumarin may be also prepared from seeds of Strophantus Kombe.

References

Wilinson S.; G.B. Patent No. 972,917; April 21, 1961; Assigned to Wellcome Foundation Limited a company incorporated in England, London

Stoll A., Renz J.; D.R. Patent No. 721,001; May 21, 1942; Assigned to Sandoz A.G. in Basel, Schweiz.

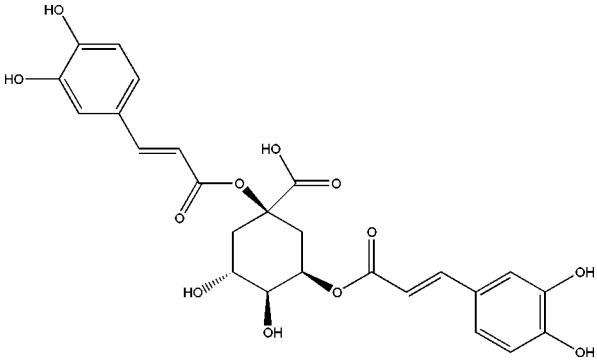
CYNARINE

Therapeutic Function: Choleretic, Antihyperlipidemic

Chemical Name: Cyclohexanecarboxylic acid, 1,3-bis((3-(3,4-dihydroxyphenyl)-1-oxo-2-propenyl)oxy)-4,5-dihydroxy-, (1R-(1α,3α,4α,5β))-

Common Name: Cinarina; Cynarex; Cynarine

Structural Formula:



Chemical Abstracts Registry No.: 30964-13-7

Trade Name	Manufacturer	Country	Year Introduced
Anghirol	Biofarm	-	-
Angirol	Biofarm-Romferchim	-	-
Listrocol	Farmitalia	-	-
Plemocil	Farmitalia	-	-
Hepar SL 50	Serturner Arzneimittel	-	-

Raw Materials

Caffeic acid
Sodium bicarbonate
Phosphorus pentachloride
Hydrochloric acid
Quinide
Ligroin

Manufacturing Process

18.0 g of caffeic acid, suspended in 500 ml of water, are dissolved by adding

sodium bicarbonate and stirring. The solution is cooled to 2°-3°C and then, while stirring continuously, 20.0 g of phosgene dissolved in 200 ml of chloroform are added in 4 to 5 portions. After acidifying by cautiously adding iced hydrochloric acid (1:1), the solution is filtered and the collected precipitate is washed with water. Upon crystallization from glacial acetic acid, the carbonylcaffeic acid thus obtained melts at 238°-240°C (dec.).

5.0 g of carbonylcaffeic acid are suspended in 70 ml of ligroin (b. p. 120°-140°C). After adding 6.0 g of phosphorus pentachloride and avoiding access of moisture while frequently stirring, the suspension is refluxed by boiling slowly and gently until everything is dissolved except a small amount of reddish, resinous materials that adhere to the bottom. Then solution is rapidly decanted into another flask containing 1.0 g of phosphorus pentachloride and the whole is refluxed gently for about 15-30 min, after which time evolution of hydrochloric acid ceases. This solution is left to cool on air for 1-2 h, and then, the obtained carbonylcaffeic acid chloride rapidly is filtered, washed with low-boiling ligroin and dried under vacuum at room temperature for about 1-1.5 h. Melting point 118°-120°C.

5.0 g of carbonylcaffeic acid chloride are thoroughly mixed with 12.8 g of dry, powdered quinide in a flask immersed in an oil bath. The flask is put under vacuum and is heated to 120°C and then, slowly, to about 160°C, maintaining this temperature for about 20-30 min. The molten mass is left to cool under vacuum and then it is crushed in a mortar in the presence of water. This material is washed with water several times. The residue is dissolved in dioxin. 400 ml of cold, 3% barium hydroxide solution are added and cooled with ice water and stirring vigorously in nitrogen atmosphere. The solution is left standing insulated from contact with air for 20 h, whereupon the content is rapidly acidified and concentrated in vacuum, on a water bath, to a volume of about 80-100 ml. After cooling and standing, well protected from contact with air, the brown material is filtered off and purified by crystallization from 50% acetic acid. 1,4-Dicaffeylquinic acid is obtained, melting point 226°-228°C.

References

Rome L. P., Vercellone A.; US Patent No. 3,100,224; August 6, 1963; Assigned: Societa Farmaceutici Italia, Milan, Italy

CYPROHEPTADINE

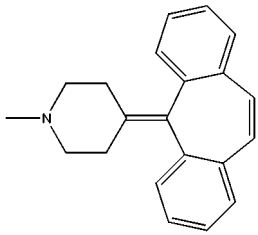
Therapeutic Function: Antipruritic, Antihistaminic, Appetite stimulant

Chemical Name: 4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-methylpiperidine

Common Name: -

Chemical Abstracts Registry No.: 129-03-3; 969-33-5 (Hydrochloride salt)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Periactin	Merck Sharp and Dohme	US	1961
Nuran	Merck Sharp and Dohme	W. Germany	1961
Periactin	Chibret	Switz.	1961
Periactin	MSD	UK	1961
Periactin	MSD	Italy	1961
Periactine	MSD-Chibret	France	1962
Anarexol	MSD	-	-
Antegan	Frosst	Australia	-
Cipractin	Andromaco	Spain	-
Cipro	Beta	Argentina	-
Cypromin	Sawai	Japan	-
Ifrasarl	Showa	Japan	-
Oractine	Teva	Israel	-
Periactol	Sharp and Dohme	W. Germany	-
Peritol	EGYT	Hungary	-
Sigloton	Miluy	Spain	-
Sipraktin	Kimya Evi	Turkey	-
Siprodin	Saba	Turkey	-
Vimicon	Merck-Frosst	Canada	-

Raw Materials

Ethyl bromide
Hydrogen chloride
Magnesium
Sodium hydroxide
4-Chloro-1-methylpiperidine
Dibenzo[a,e]cycloheptatrien-5-one
Acetic anhydride

Manufacturing Process

(A) Preparation of 1-Methyl-4-Piperidyl-Magnesium Chloride: Magnesium turnings (5.45 g, 0.22 g-atom) were placed in a 500 ml 3-necked flask provided with a condenser, Hershberg stirrer and dropping funnel and protected with a drying tube. An atmosphere of dry nitrogen was maintained in the apparatus throughout the reaction. The magnesium was covered with

20 ml of dry tetrahydrofuran. A crystal of iodine and 1.2 g of ethyl bromide were added and after the reaction had subsided (formation of ethylmagnesium bromide) a solution of 29.4 g (0.22 mol) of 4-chloro-1-methyl-piperidine in dry tetrahydrofuran (total volume, 103 ml) was added dropwise at such a rate that gentle reflux was maintained.

The solution of 4-chloro-1-methylpiperidine in tetrahydrofuran was dried over calcium hydride at ice-bath temperature prior to use. When the addition of the halide was complete the reaction mixture was refluxed with stirring for one hour. In some subsequent experiments this period of refluxing was omitted with no deleterious result.

(B) Preparation of 1-Methyl-4-(5-Hydroxy-5-Dibenzo[a,e]Cycloheptatrienyl)-Piperidine: The solution of the Grignard reagent prepared in (A) was cooled to 5° to 10°C and stirred while 22.7 g (0.11 mol) of dibenzo[a,e] cycloheptatrien-5-one was added in portions. After stirring for 1 hour during which time the reaction mixture was allowed to warm up to room temperature, the bulk of the tetrahydrofuran was distilled at 40° to 50°C under reduced pressure. Benzene, 150 ml, was added and the reaction mixture stirred and cooled in an ice-bath while water, 100 ml, was added gradually. The benzene layer was separated by decantation and the gelatinous residue extracted three times with 75 ml portions of boiling benzene.

The solvent was evaporated from the combined benzene extracts to give 33.4 g of a clear light brown resin. Crystallization from an alcohol-water mixture gave 19.5 g of 1-methyl-4-(5-hydroxy-5-dibenzo[a,e]cycloheptatrienyl)-piperidine, MP 156° to 157°C. Two recrystallizations from alcohol-water mixtures followed by two recrystallizations from benzene-hexane mixtures gave analytically pure product, MP 166.7° to 167.7°C.

(C) Preparation of 1-Methyl-4-(5-Dibenzo[a,e]Cycloheptatrienylidene)-Piperidine Hydrochloride: 1-Methyl-4-(5-hydroxy-5-dibenzo[a,e] cycloheptatrienyl)-piperidine (3.05 g, 0.01 mol) was dissolved in glacial acetic acid, 15 ml. The solution was saturated with dry hydrogen chloride with external cooling. A white solid separated. Acetic anhydride (3.07 g, 0.03 mol) was added and the mixture heated on the steam bath for one hour. The solid dissolved in the first 5 minutes of the heating period.

The reaction mixture was poured into 25 ml of water and the mixture made strongly basic with 10N sodium hydroxide solution. The mixture was extracted 3 times with 50 ml portions of benzene, the combined extracts washed with water and concentrated to a volume of approximately 50 ml. The solution was saturated with dry hydrogen chloride and the white crystalline product collected and dried. The yield of product, MP 251.6° to 252.6°C (dec.) was 2.5 g. Recrystallization from a mixture of absolute alcohol and absolute ether gave a product, MP 252.6° to 253.6°C. A sample was analyzed after drying for 7 hours at 110°C over phosphorus pentoxide in vacuo.

(D) Preparation of 1-Methyl-4-(5-Dibenzo[a,e]Cycloheptatrienylidene)-Piperidine: The hydrochloride salt, 4.3 g, was suspended in 100 ml of warm water and the mixture made strongly alkaline by the addition of 15 ml of 5% sodium hydroxide. The mixture was extracted with four 50 ml portions of benzene and the extracts dried over sodium sulfate. Evaporation of the benzene on the steam-bath at reduced pressure left 3.7 g (97%) of the base,

MP 110.3° to 111.3°C. Recrystallization from a mixture of alcohol and water gave product, MP 112.3° to 113.3°C.

References

Merck Index 2766
Kleeman and Engel p. 263
PDR pp.830, 1208, 1606, 1999
OCDS Vol. 1 p. 151 (1977)
I.N. p. 280
REM p. 1132
Engelhardt, E.L.; US Patent 3,014,911; December 26, 1961; assigned to Merck and Co., Inc.

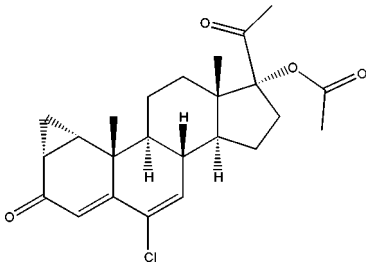
CYPROTERONE ACETATE

Therapeutic Function: Antiandrogen

Chemical Name: 6-Chloro-1β,2β-dihydro-17-hydroxy-3'H-cyclopropa[1,2] pregna-1,4,6-triene-3,20-dione acetate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 2098-66-01

Trade Name	Manufacturer	Country	Year Introduced
Androcur	Schering	W. Germany	1973
Androcur	Schering	Switz.	1973
Androcur	Schering	UK	1974
Androcur	Schering	Italy	1975
Androcur	Schering	Japan	1982
Cyprostat	Schering	-	-
Diane	Schering	W. Germany	-

Raw Materials

1,2α-Methylene-δ(4,6)-pregnadiene-17α-ol-3,20-dione-17-acetate
Perbenzoic acid
Acetic acid

Manufacturing Process

2.34 g of 1,2α-methylene-$\delta^{4,6}$-pregnadiene-17α-ol-3,20-dione-17-acetate are dissolved in 18.25 cc of ethylene chloride which contains 844 rng of perbenzoic acid. The solution is stored for 16 hours at +5°C and 7 hours at room temperature. It is then diluted with methylene chloride and, with aqueous ferrous sulfate solution, sodium bicarbonate solution and with water washed until neutral.

The organic phase is dried over sodium sulfate and then concentrated to dryness. 1.62 g of the thus obtained crude 1,2α-methylene-6,7α-oxido-δ^4-pregnene-17α-ol-3,20-dione-17-acetate are dissolved in 109 cc of glacial acetic acid. This solution is then saturated at room temperature with hydrogen chloride gas and stored for 20 hours, It is then diluted with methylene chloride and washed with water until neutral.

The organic phase is dried over sodium sulfate and then concentrated to dryness. The thus obtained crude 6-chloro-1α-chloromethyl-$\delta^{4,6}$-pregnadiene-17α-ol-3,20-dione-17-acetate is heated to boiling in 20 cc of collidine for 20 minutes under nitrogen. After dilution with ether it is washed with 4 N hydrochloric acid and washed with water until neutral.

After drying over sodium sulfate and concentration to vacuum the remaining residue is subjected to chromatography over silica gel. Using a benzene-ethyl acetate mixture (19:1) there is eluated 900 mg of 6-chloro-1,2α-methylene-$\delta^{4,6}$-pregnadiene-17α-ol-3,20-dione-17-acetate, which upon recrystallization from isopropyl ether melts at 200° to 201°C.

References

Merck Index 2769
Kleeman and Engel p. 263
OCDS Vol. 2 p. 166 (1980)
DOT 10 (1) 12 (1974)
I.N.p.280
Wiechert, R.; US Patent 3,234,093; February 8, 1966; assigned to Schering AG, Germany

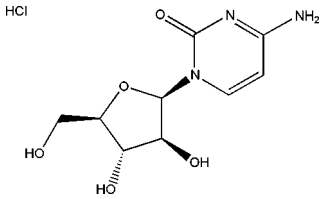
CYTARABINE HYDROCHLORIDE

Therapeutic Function: Cancer chemotherapy

Chemical Name: 4-Amino-1β-D-arabinofuranosyl-2(1H)-pyrimidinone hydrochloride

Common Name: β-Cytosine arabinoside

Structural Formula:



Chemical Abstracts Registry No.: 69-74-9; 147-94-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Cytosar	Upjohn	US	1969
Cytosar	Upjohn	UK	1970
Alexan	Mack	W. Germany	1971
Kilocyde	Nippon Shinyaku	Japan	1971
Cytosar	Diethelm	Switz.	1971
Aracytine	Upjohn	France	1972
Aracytin	Upjohn	Italy	1972
Arabitin	Sankyo	Japan	-
Cyclocide	Nippon Kayaku, Co.	Japan	-
Erpalfa	Intes	Italy	-
Iretin	Torii	Japan	-
Udicil	Upjohn	W. Germany	-

Raw Materials

1-(2,3,5-Tri-O-acetyl-β-arabinofuranosyl)uracil
Phosphorus pentasulfide
Ammonia

Manufacturing Process

(A) Preparation of 1- (2,3,5-Tri-O-Acetyl-β-D-Arabinofuranosyl)-4-Thiouracil: A mixture of 1.85 g (5.0 mmol) of 1-(2,3,5-tri-O-acetyl-β-arabinofuranosyl) uracil, 1.23 g (5.55 mmol) of phosphorus pentasulfide, and 30 ml of pyridine was heated under gentle reflux for 2.5 hours with exclusion of moisture. The reaction mixture was cooled, and the supernatant solution was transferred by means of a pipette into a mixture of crushed ice and water. The reaction flask was washed twice with pyridine, and these washings were added to the ice-water mixture. This mixture was kept at about 25°C until the ice had melted, and was then stored at 0°C for one hour. A pale yellow precipitate that formed was collected on a filter, washed with ice-water, and dried in air.

This material was triturated with chloroform, and the chloroform mixture was filtered. A small amount of undissolved material collected on the filter and it

was washed with chloroform. The chloroform solution (filtrate plus washings) was washed three times with ice-water, twice with ice-cold 3 N sulfuric acid, twice with ice-cold saturated aqueous sodium bicarbonate solution, twice with ice-water, and then dried over anhydrous sodium sulfate. The chloroform was removed under reduced pressure at a bath temperature of about 40°C, leaving a yellow, somewhat gummy residue. This yellow residue was dissolved in absolute methanol which was then evaporated at reduced pressure at about 40°C, and the residue was then held for 2 hours at 0.5 to 2.0 mm pressure and a bath temperature of about 50°C. There was thus obtained 1.69 g of 1-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)-4-thiouracil.

(B) Preparation of 1-β-D-Arabinofuranosylcytosine: In a glass liner, a mixture of 1.16 g (3.0 mmol) of 1-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)-4-thiouracil prepared in (A) and about 60 ml of absolute methanol which had been saturated with anhydrous ammonia at 0°C was heated in a steel bomb at 98° to 105°C for 35 hours. After cooling to about 25°C and venting the bomb, the dark solution was filtered into a round-bottom flask. The methanol and excess ammonia were then removed under reduced pressure at about 25°C. The residual syrup was dissolved in absolute methanol, and the methanol was removed under reduced pressure at a bath temperature of about 40°C. This procedure of dissolving in absolute methanol and removing the solvent was repeated, and the residue was held under reduced pressure at a bath temperature of 45°C for 12 hours.

The resulting semisolid was triturated thoroughly with absolute methanol, and the resulting suspension was chilled at 0°C. A pale tan solid that separated was collected on a filter and washed repeatedly with methanol. After washing with anhydrous ether, there was obtained 430 mg of 1-β-D-arabinofuranosylcytosine.

(C) Preparation of 1-β-D-Arabinofuranosylcytosine Hydrochloride: The absolute methanolic filtrate obtained after triturating and filtering the 1-β-D-arabinofuranosylcytosine in (B) above was warmed and stirred with decolorizing charcoal. The mixture was filtered through a bed of filter aid, and the filter bed was washed repeatedly with absolute methanol. The combined filtrate and washings were pale yellow. The solution was diluted to faint cloudiness with anhydrous ether, and an excess of anhydrous hydrogen chloride was introduced. Crystallization began at about 25°C and further crystallization was induced by chilling at 0°C for 14 hours. The crystalline product was collected on a filter, washed with anhydrous ether, and dried in air. There was thus obtained 180 mg of pale yellow 1-β-D-arabinofuranosylcytosine hydrochloride melting at 186° to 189°C.

The pale yellow product was dissolved in warm, absolute methanol, and the solution after mixing with decolorizing charcoal was filtered through a bed of filter aid. The filter bed was washed with warm absolute methanol, and the combined methanolic filtrate and washings were warmed and diluted with anhydrous ether to incipient crystallization. The methanol-ether mixture was kept at about 25°C for about 1 hour and then chilled, first at 0°C, and then at -20°C. The resulting colorless needles were collected on a filter, washed with anhydrous ether, and dried at 85°C, yielding 100 mg of 1-β-D-arabinofuranosylcytosine hydrochloride having a melting point of 186° to 188°C.

References

Merck Index 2778
Kleeman and. Engel p. 264
PDR p. 1833
DOT 13 (11) 477 (1977)
I.N. p.281
REM p. 1147
Hunter, J.H.; US Patent 3,116,282; December 31, 1963; assigned to The Upjohn Company