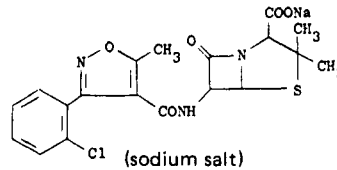
CLOXACILLIN

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:



(sodium salt)

Chemical Abstracts Registry No.: 61-72-3; 642-78-4 (Sodium Salt)

Trade Name	Manufacturer	Country	Year Introduced
Orbenin	Beecham	U.K.	1962
Cloxypen	Allard	France	1964
Orbenin	Beecham	W. Germany	1964
Tegopen	Bristol	U.S.	1965
Cloxapen	Beecham	U.S.	1976
Acucillin	Fuji	Japan	–
Ampiclox	Beecham	W. Germany	–
Austrastaph	C.S.L.	Australia	–
Bactopen	Beecham	–	–
Benicil	Ibsa	Switz.	–
Ellecid	Pharmax	Italy	–
Ekvacilline	Astra	–	–
Gelstaph	Beecham	–	–
Kloxerate	Duphar	U.K.	–
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-methylisoxazole-4-carbonyl chloride (7.66 g) gave the sodium salt of 3-o-chlorophenyl-5-methyl-4-isoxazolyl-penicillin (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 & 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.; U.S. Patent 2,996,501; August 15, 1961

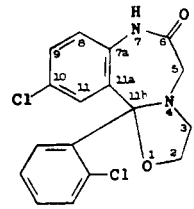
CLOXAZOLAM

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 U.S. 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 & 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.; U.S. Patents 3,696,094; October 3, 1972; and 3,772,371; November 13, 1973; both assigned to Sankyo Company Limited, Japan

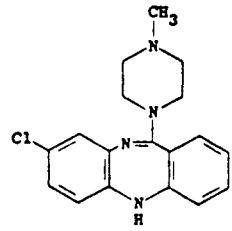
CLOZAPINE

Therapeutic Function: Tranquilizer

Chemical Name: 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e] [1,4] diazepine

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 5786-21-0

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 & Engel p. 240
OCDS Vol. 2 p. 425 (1980)
DOT 9 (1) 17 & (6) 232 (1973)
I.N. p. 255
Schmutz, J. and Hunziker, F.; U.S. Patent 3,539,573; November 10, 1970

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	U.S.	1977
Colestid	Upjohn	U.K.	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.; U.S. Patent 3,803,237; April 9, 1974; assigned to The Upjohn Co.

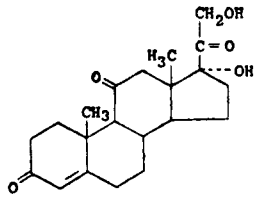
CORTISONE ACETATE

Therapeutic Function: Glucocorticoid

Chemical Name: 17α,21-dihydroxy-4-pregnene-3,11,20-trione-21-acetate

Common Name: —

Structural Formula:



(base)

Chemical Abstracts Registry No.: 50-04-4; 53-06-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Cortone Acetate	MSD	U.S.	1950
Acetisone	Farmigea	Italy	—

Raw Materials

3(α)-Hydroxy-21-acetoxy-11,20-diketopregnane
Potassium cyanide
Acetic acid
Chromic acid
Phosphorus oxychloride
Osmium tetroxide

Manufacturing Process

The following technique is described in U.S. 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-keto-pregnane 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 3,11,20-triketo-17(α)-21-dihydroxy-pregnane; MP 227° to 229°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 & Engel p. 246
OCDS Vol. 1 pp. 188, 190 (1977)
I.N. p. 265
REM p. 964
Reichstein, T.; U.S. Patent 2,403,683; July 9, 1946
Gallagher, T.F.; U.S. Patent 2,447,325; August 17, 1948; assigned to Research Corporation
Sarett, L.H.; U.S. Patent 2,541,104; February 13, 1951; assigned to Merck & Co., Inc.

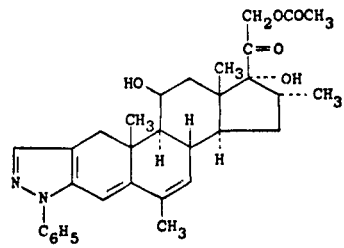
CORTIVAZOL

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	—

Trade Name	Manufacturer	Country	Year Introduced
Idaltim	Roussel	–	–
Dilaster	Roussel	–	–

Raw Materials

11β,17α,21-Trihydroxy-6,16α-dimethyl-4,6-pregnadiene-3,20-dione
Formaldehyde
Hydrogen chloride
Ethyl formate
Phenyl hydrazine
Formic acid
Acetic anhydride

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°, IR 5.81 and 8.37 μ. 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 2 N 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 U.S. Patent 3,300,483.

References

Merck Index 2513
Kleeman & 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.; U.S. Patents 3,067,194; December 4, 1962; and 3,300,483; January 24, 1967; both assigned to Merck & Co., Inc.

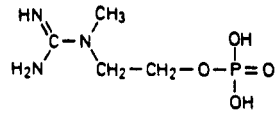
CREATINOLFOSFATE

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

Trade Name	Manufacturer	Country	Year Introduced
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 & Engel p. 249
I.N. p. 268
Allievi, E.; U.S. Patent 4,012,467; March 15, 1977

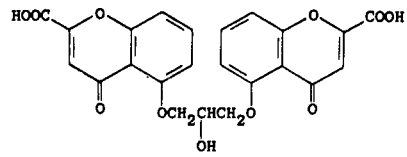
CROMOLYN SODIUM

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

Structural Formula:



Chemical Abstracts Registry No.: 15826-37-6; 16110-51-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Intal	Fisons	U.K.	1969
Intal	Fisons	W. Germany	1970
Lomudal	Fisons	Switz.	1970
Intal	Fujisawa	Japan	1971
Frenasma	Italseber	Italy	1971

Trade Name	Manufacturer	Country	Year Introduced
Lomudal	Fisons	France	1972
Intal	Fisons	U.S.	1973
Aarane	Fisons	U.S.	1973
Nalcrom	Fisons	Italy	1983
Aarane	Syntex	U.S.	—
Alercrom	Osiris	Argentina	—
Colimone	Fisons	W. Germany	—
Cromo-Asma	Aldo	Spain	—
Cusicrom	Cusi	Spain	—
Frenal	I.S.F.	Italy	—
Gastrofrenal	I.S.F.	Italy	—
Kromolin	Iltas	Turkey	—
Lomupren	Fisons	W. Germany	—
Nalcrom	Fisons	U.K.	—
Nasmil	Lusofarmaco	Spain	—
Nebulasma	Septa	Spain	—
Opticron	Fisons	France	—
Rynacrom	Fisons	U.K.	—

Raw Materials

2,6-Dihydroxyacetophenone
Diethyl oxalate
Epichlorohydrin
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)-2-hydroxypropane.

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 & Engel p. 250
PDR p. 876
OCDS Vol. 3 pp. 66, 235 (1984)
DOT 10 (7) 246 (1974) & 14 (7) 283 (1978)
I.N. p. 19
REM p. 1131
Fitzmaurice, C. and Lee, T.B.; U.S. Patent 3,419,578; December 31, 1968; assigned to Fisons Pharmaceuticals Limited, England

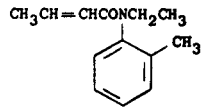
CROTAMITON

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	U.S.	1949
Crotan	Owen	U.S.	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, while 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 & Engel p. 251
I.N. p. 269
REM p. 1239
British Patent 615,137; January 3, 1949; assigned to J.R. Geigy AG, 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.: —

Trade Name	Manufacturer	Country	Year Introduced
Unitensen	Neisler	U.S.	1954

Raw Materials

Veratrum viride
Triethylamine
Tannic acid
Benzene
Hydrogen chloride

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; λ maximum 255 mμ, λ minimum 240 mμ. 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.; U.S. Patent 2,789,977; April 23, 1957; assigned to Irwin, Neisler and Company

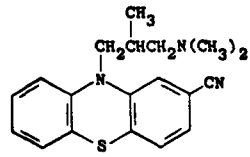
CYAMEMAZINE

Therapeutic Function: Tranquilizer

Chemical Name: 10-[3-(dimethylamino)-2-methylpropyl]-10H-phenothiazine-2-carbonitrile

Common Name: Cyamepromazine

Structural Formula:



Chemical Abstracts Registry No.: 3546-03-0

Trade Name	Manufacturer	Country	Year Introduced
Terckian	Theraplix	France	1972

Raw Materials

3-Chlorophenthiazine
Cupric 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% sodamide (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 & Engel p. 252
DOT 8 (6) 216 (1972)
I.N. p. 271
Jacob, R.M. and Robert, J.G.; U.S. Patent 2,877,224; March 10, 1959; assigned to Societe des Usines Chimiques Rhone-Poulenc, France

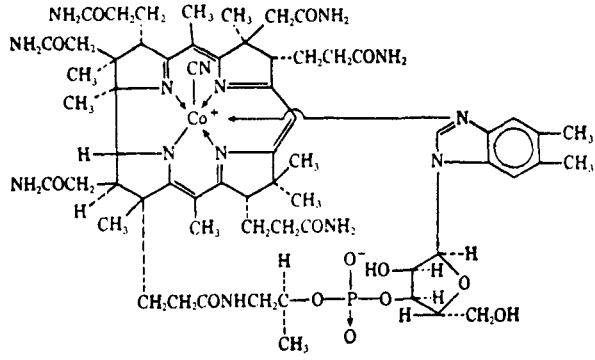
CYANOCOBALAMIN

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	U.S.	1949
Rubramin	Squibb	U.S.	1949
Bevidox	Abbott	U.S.	1949
Betalin	Lilly	U.S.	1949
Cobione	MSD	U.S.	1949
Docibin	National	U.S.	1950
Ducobee	Breon	U.S.	1950
Dodex	Organon	U.S.	1950
Be-Dodec	Schieffelin	U.S.	1950

Trade Name	Manufacturer	Country	Year Introduced
B-Twelvora	Sherman	U.S.	1950
Crystamin	Armour	U.S.	1951
Bexil	Conal	U.S.	1951
Redisol	MSD	U.S.	1951
Bevatine	Dorsey	U.S.	1953
Vibalt	Roerig	U.S.	1954
Bedoce	Lincoln	U.S.	1957
Vi-Twel	Cooper	U.S.	1960
Cyano-Gel	Maurry	U.S.	1961
Clarex	Minn. Pharm.	U.S.	1962
Cyredin	Merrell Nat	U.S.	1967
Feryl	Central	U.S.	1978
Dicopac	Kaken	Japan	1979
Anacobin	Allen & Hanburys	U.K.	–
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	U.S.	–
Bidocit	Ausonia	Italy	–
B12 Mille	Delagrange	France	–
B12 Vicotrat	Heyl	W. Germany	–
Cabadon M	Reid-Provident	U.S.	–
Cincomil Bedoce	Andromaco	Spain	–
Cobalomin	S. Pacific	Australia	–
Cobalparen	Saarstickstoff-Fatoo	W. Germany	–
Cobavite	Lemmon	U.S.	–
Cocavitan	Coca	Spain	–
Copharvit	Cophar	Switz.	–
Cyanabin	Stickley	Canada	–
Cyanovit	Adrian-Marinier	France	–
Cykobemin	Kabi-Vitrum	Sweden	–
Cytakon	Glaxo	U.K.	–
Cytamen	Glaxo	U.K.	–
Cytobion	Merck	W. Germany	–
Dobetin	Angelini	Italy	–
Docetasan	Santos	Spain	–
Docivit	Robisch	W. Germany	–
Dodecabee	Miller	U.S.	–
Dodecavite	U.S.V.	U.S.	–
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	U.S.	–
Hemosalus	Totalfarm	Italy	–
Hepacon B12	Consolidated	U.K.	–

Trade Name	Manufacturer	Country	Year Introduced
Hepcovite	Endo	U.S.	—
Juvabe	Dolder	Switz.	—
Lifaton B12	Lifasa	Spain	—
Lophakomb B12	Lomapharm	W. Germany	—
Milbedoc	Andromaco	Spain	—
Millevit	Nordmark	W. Germany	—
Neo-Cytamen	Bilim	Turkey	—
Neurobaltina	Sidus	Italy	—
Neuro Liser B12	Perga	Spain	—
Nova-Rubi	Nova	Canada	—
Noventabedoce	Andromaco	Spain	—
Omeogen	UCB-Smit	Italy	—
Optovite B12	Normon	Spain	—
Permicipur	Mulli	W. Germany	—
Plentasal	Lopez-Brea	Spain	—
Primabalt	Primedics	U.S.	—
Rectocenga	Biotherax	France	—
Redamin	Washington	Italy	—
Reedvit	Celtia	Argentina	—
Retidex B12	Dexter	Spain	—
Rubesol	Central	U.S.	—
Rubraluy	Miluy	Spain	—
Ruvite	Savage	U.S.	—
Sancoba	Santen	Japan	—
Sorbevit B12	Casen	Spain	—
Sorbigen B12	Gentili	Italy	—
Surgevit	Maipe	Spain	—
Twel-Be	Pitman-Moore	U.S.	—
Vicapanbiz	Merckle	W. Germany	—
Viemin 12	Valeas	Italy	—
Vitarubin	Streuli	Switz.	—

Raw Materials

Milorganite (activated sewage sludge)
Potassium cyanide
Sodium nitrite
Hydrochloric acid

Manufacturing Process

The following is taken from U.S. 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 & 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.; U.S. Patents 2,703,302 and 2,703,303; both dated March 1, 1955; both assigned to Merck & Co., Inc.
Speedie, J.D. and Hull, G.W.; U.S. Patent 2,951,017; August 30, 1960; assigned to The Distillers Company Limited, Scotland
McDaniel, L.E.; U.S. Patent 3,000,793; September 19, 1961; assigned to Merck & Co., Inc.
Long, R.A.; U.S. Patent 3,018,225; January 23, 1962; assigned to Merck & Co., Inc.
Van Melle, P.J.; U.S. Patent 3,057,851; October 9, 1962; assigned to Armour-Pharmaceutical
Bernhauer, K., Friedrich, W. and Zeller, P.; U.S. Patent 3,120,509; February 4, 1964; assigned to Hoffmann-La Roche Inc.

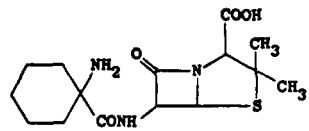
CYCLACILLIN

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	U.S.	1979
Calthor	Ayerst	U.K.	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 U.S. Patent 3,478,018.

References

Merck Index 2693
Kleeman & 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; U.S. Patent 3,194,802; assigned to American Home Products Corporation
Robinson, C.A. and Nescio, J.J.; U.S. Patent 3,478,018; November 11, 1969; assigned to American Home Products Corporation

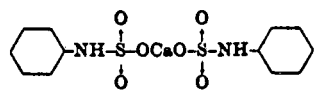
CYCLAMATE CALCIUM

Therapeutic Function: Nonnutritive sweetener

Chemical Name: Cyclohexylsulfamic acid calcium salt

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 139-06-0

Trade Name	Manufacturer	Country	Year Introduced
Sucaryl Calcium	Abbott	U.S.	1953
Sucaryl Calcium	Abbott	France	1966

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.; U.S. Patent 2,799,700; July 16, 1957; assigned to E.I. du Pont de Nemours & Co.
McQuaid, H.S.; U.S. Patent 2,804,477; August 27, 1957; assigned to E.I. du Pont de Nemours & Co.
Freifelder, M.; U.S. Patent 3,082,247; March 19, 1963; assigned to Abbott Laboratories
Birsten, O.G. and Rosin, J.; U.S. Patents 3,361,798; January 2, 1968; and 3,366,670; January 30, 1968; both assigned to Baldwin-Montrose Chemical Co., Inc.

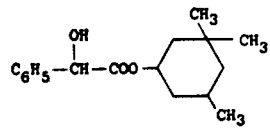
CYCLANDELATE

Therapeutic Function: Antispasmodic

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	U.S.	1958
Cyclospasmol	Beytout	France	1972
Acyclin	Arcana	Austria	—

Trade Name	Manufacturer	Country	Year Introduced
Anaspat	I.C.I.	Italy	–
Anticen	Nippon Kayaku	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	U.K.	–
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	–
Perebral	Biopharma	France	–
Salclate	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 U.S. 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 U.S. Patent 3,663,597.

References

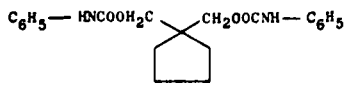
Merck Index 2695
Kleeman & Engel p. 254
PDR pp. 1606, 1947, 1999
OCDS Vol. 1 p. 94 (1977)
I.N. p. 273
REM p. 852
Flitter, D.; U.S. Patent 3,663,597; May 16, 1972; assigned to American Home Products Corporation
Nauta, W.T.; U.S. Patent 2,707,193; April 26, 1955; assigned to N.V. Koninklijke Pharmaceutische Fabrieken Voorbeen Brocades-Stheeman & Pharmacia, Netherlands

CYCLARBAMATE

Chemical Name: 1,1-Dimethylol cyclopentane 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.; U.S. Patent 3,067,240; December 4, 1962; assigned to Laboratoires Cassenne (France)

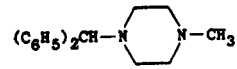
CYCLIZINE

Therapeutic Function: Antinauseant

Chemical Name: 1-diphenylmethyl-4-methylpiperazine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 82-92-8; 303-25-3 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Marezine	Burroughs-Wellcome	U.S.	1953
Marzine	Wellcome	France	1965
Bon Voyage	Cupal	U.K.	–
Cleamine	Kodama	Japan	–
Echnatol	Gerot	Austria	–
Fortravel	Chemofux	Austria	–
Happy Trip	Mepros	Neth.	–
Maremal	Gayoso Wellcome	Spain	–
Migwell	Wellcome	France	–
Motozina	Biomedica Foscama	Italy	–
Reis-Fit	A.P.F.	Neth.	–
Valoid	Burroughs-Wellcome	U.K.	–

Raw Materials

Benzhydryl chloride
N-Methyl piperazine

Manufacturing Process

One-tenth mol (20 g) of benzhydryl chloride was mixed with 0.19 mol (19 g) of N-methyl-piperazine 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 & 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.; U.S. Patent 2,630,435; March 3, 1953; assigned to Burroughs Wellcome & Co. (U.S.A.) Inc.

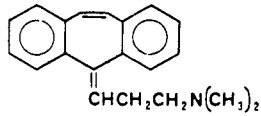
CYCLOBENZAPRINE

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)

Trade Name	Manufacturer	Country	Year Introduced
Flexeril	Merck Sharp & Dohme	U.S.	1977

Raw Materials

Dibenzo[a,d]cycloheptene-5-one
3-Dimethylaminopropyl chloride
Magnesium
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 & 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.; U.S. Patent 3,409,640; November 5, 1968; assigned to Schering Corporation

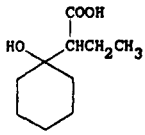
CYCLOBUTYROL

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	Nichiko	Japan	—
Secrobil	Medital	Italy	—
Tribil	Biol. Italia	Italy	—
Tribilina	Farge	Italy	—
Trommogallol	Trommsdorf	W. Germany	—

Raw Materials

Cyclohexanone
Ethyl α-bromobutyrate
Barium hydroxide
Zinc
Sulfuric acid

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 & Engel p. 256
I.N. p. 275
Maillard, J.G.A.E., Morin, R.M. and Benard, M.M.M.; U.S. Patent 3,065,134; November 20, 1962; assigned to Societe d'Exploitation des Laboratoires Jacques Logeais (S.A.R.L.) (France)

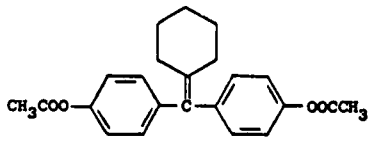
CYCLOFENIL

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	U.K.	1972
Fertodur	Schering	Italy	1974
Klofenil	Yurtoglu	Turkey	—
Neoclym	Poli	Italy	—
Sexovid	Ferrosan	Sweden	—

Raw Materials

p-Bromoanisole
p-Hydroxyphenyl cyclohexyl ketone
Potassium hydroxide
Ammonium chloride
Magnesium
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 & 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.; U.S. Patent 3,287,397; November 22, 1966

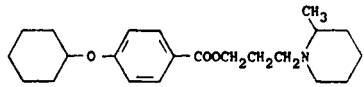
CYCLOMETHYCAINE

Therapeutic Function: Topical 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	U.S.	1948
Topocaine	Lilly	–	–

Raw Materials

Ethyl-p-hydroxybenzoate
Cyclohexyl bromide
3-(2'-Methylpiperidino)propyl chloride
Sodium
Sodium hydroxide

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 49.5 g 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 & Engel p. 257
OCDS Vol. 1 p. 14 (1977)
I.N. p. 276
REM p. 1055
McElvain, S.M. and Carney, T.P.; U.S. Patent 2,439,818; April 20, 1948

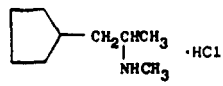
CYCLOPENTAMINE HYDROCHLORIDE

Therapeutic Function: Vasoconstrictor

Chemical Name: N-α-dimethylcyclopentaneethaneamine hydrochloride

Common Name: Cyclopentadrine

Structural Formula:



(base)

Chemical Abstracts Registry No.: 102-45-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Clopane	Lilly	U.S.	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 & Engel p. 258
I.N. p. 277
Rohrmann, E.; U.S. Patent 2,520,015; August 22, 1950; assigned to Eli Lilly and Company

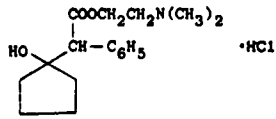
CYCLOPENTOLATE HYDROCHLORIDE

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	U.S.	1953
Cyplegin	Santen	Japan	1972
Skiacol	P.O.S.	France	1976
Pentolair	Pharmafair	U.S.	1983
Ciclolux	Tubi Lux Pharma	Italy	–
Ciclоplegic	Frumtost	Spain	–
Colircusi Ciclopejico	Cusi	Spain	–
Cyclomydrin	Alcon	U.S.	–
Cyclopen	Irving	Australia	–
Cyclopentol	Cusi	Belgium	–
Mydplegic	Cooper Vision	Puerto Rico	–
Mydrilate	W.B. Pharm.	U.K.	–
Oftan-Syklo	Star	Finland	–
Zykolate	Mann	W. Germany	–

Raw Materials

Sodium phenyl acetate
Isopropyl bromide
β-Chloroethyl dimethylamine
Magnesium
Cyclopentanone

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 & Engel p. 259
OCDS Vol. 1 p. 92 (1977)
I.N. p. 277
REM p. 914
Treves, G.R.; U.S. Patent 2,554,511; May 29, 1951; assigned to Schieffelin & Co.

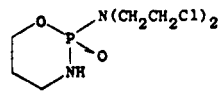
CYCLOPHOSPHAMIDE

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	U.S.	1959
Endoxan	Lucien	France	1960
Neosar	Adria	U.S.	1982
Carloxan	Laake	Finland	–
Cicloblastina	Montedison	W. Germany	–
Cyclostin	Farm. Carlo Erba	Italy	–
Cytophosphan	Taro	Israel	–
Edoxana	Asta	W. Germany	–
Edoxana	W.B. Pharm.	U.K.	–
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 (1/10 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 (1/10 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 & 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.; U.S. Patent 3,018,302; January 23, 1962; assigned to Asta-Werke A.G. Chemische Fabrik (W. Germany)

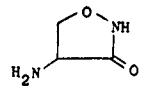
CYCLOSERINE

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 Sharpe & Dohme	U.S.	1956
Seromycin	Lilly	U.S.	1956
Aristoserina	Aristochimica	Italy	–
Ciclovalidin	Bracco	Italy	–
Cyclomycin	Shionogi	Japan	–
Cycloserine	Lilly	U.S.	–
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 U.S. 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 U.S. 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 & 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.; U.S. Patent 2,773,878; December 11, 1956; assigned to Chas. Pfizer & Co., Inc.
Harned, R.L.; U.S. Patents 2,789,983; April 23, 1957; and 3,124,590; March 10, 1964; both assigned to Commercial Solvents Corporation
Howe, E.E.; U.S. Patent 2,845,433; July 29, 1958; assigned to Merck & Co., Inc.
Synthetic Process:
Peck, R.L.; U.S. Patent 2,772,280; November 27, 1956; assigned to Merck & Co., Inc.
Holly, F.W. and Stammer, C.H.; U.S. Patent 2,840,565; June 24, 1958; assigned to Merck & Co., Inc.

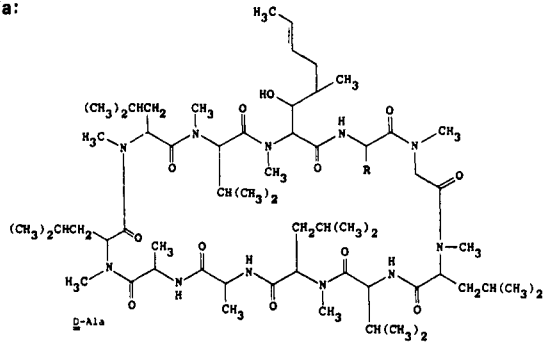
CYCLOSPORIN

Therapeutic Function: Immunosuppressive

Chemical Name: Cyclic oligopeptide (See Structural Formula)

Common Name: Ciclosporin

Structural Formula:



Chemical Abstracts Registry No.: —

Trade Name	Manufacturer	Country	Year Introduced
Sandimmune	Sandoz	U.S.	1983
Sandimmun	Sandoz	U.K.	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 S 7481/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 & (12) 665 (1983)
I.N. p. 231
REM p. 1147
Harri, E. and Ruegger, A.; U.S. Patent 4,117,118; September 26, 1978; assigned to Sandoz, Ltd. (Switz.)

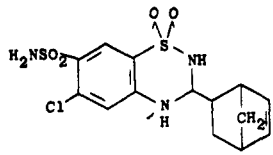
CYCLOTHIAZIDE

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	U.S.	1963
Fluidil	Adria	U.S.	1980
Baronorm	Roussel	France	—
Cycloteriam	Roussel	France	—
Dimapres	Dieckmann	W. Germany	—
Doburil	Pharmacia	Sweden	—
Doburil	Boehr/Ingel.	—	—
Tensodiural	Rafa	Israel	—
Valmiran	Boehr/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 & Engel p. 261
OCDS Vol. 1 p. 358 (1977)
I.N. p. 278
REM p. 939
Müller, E. and Hasspacher, K.; U.S. Patent 3,275,625; September 27, 1966; assigned to Boehringer Ingelheim GmbH, Germany

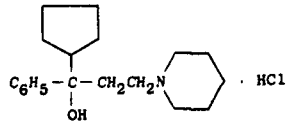
CYCRIMINE HYDROCHLORIDE

Therapeutic Function: Muscle relaxant; Antiparkinsonism

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	U.S.	1953
Pagitane	Lilly	Italy	–

Raw Materials

Bromobenzene
Cyclopentyl-β-(N-piperidyl)ethyl ketone
Magnesium
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 & Engel p. 262

OCDS Vol. 1 p. 47 (1977)
I.N. p. 279
REM p. 932
Ruddy, A.W. and Becker, T.J.; U.S. Patent 2,680,115; June 1, 1954; assigned to Winthrop-Stearns Inc.

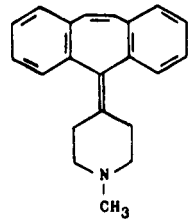
CYPROHEPTADINE

Therapeutic Function: Antipruritic, Antihistaminic, Appetite stimulant

Chemical Name: 4-(5H-dibenzo[a,d] cyclohepten-5-ylidene)-1-methylpiperidine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 129-03-3; 969-33-5 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Periactin	Merck Sharp & Dohme	U.S.	1961
Nuran	Merck Sharp & Dohme	W. Germany	1961
Periactin	Chibret	Switz.	1961
Periactin	MSD	U.K.	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 & Dohme	W. Germany	–
Peritol	Egyt	Hungary	–
Sigloton	Miluy	Spain	–
Sipraktin	Kimya Evi	Turkey	–
Siprodin	Saba	Turkey	–
Vimicon	Merck-Frosst	Canada	–

Raw Materials

Ethyl Bromide
4-Chloro-1-methyl piperidine
Dibenzo[a,e] cycloheptatrien-5-one
Hydrogen chloride
Magnesium
Acetic anhydride
Sodium hydroxide

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 10 N 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 & 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.; U.S. Patent 3,014,911; December 26, 1961; assigned to Merck & Co., Inc.

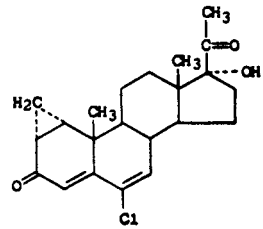
CYPROTERONE ACETATE

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:



(base)

Chemical Abstracts Registry No.: 2098-66-01

Trade Name	Manufacturer	Country	Year Introduced
Androcur	Schering	W. Germany	1973
Androcur	Schering	Switz.	1973
Androcur	Schering	U.K.	1974
Androcur	Schering	Italy	1975
Androcur	Schering	Japan	1982
Cyprostat	Schering	—	—
Diane	Schering	W. Germany	—

Raw Materials

1,2α-Methylene-$\Delta^{4,6}$-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 mg 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 & Engel p. 263
OCDS Vol. 2 p. 166 (1980)
DOT 10 (1) 12 (1974)
I.N. p. 280
Wiechert, R.; U.S. Patent 3,234,093; February 8, 1966; assigned to Schering AG, Germany

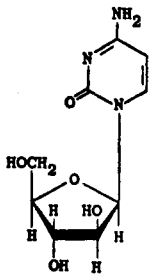
CYTARABINE HYDROCHLORIDE

Therapeutic Function: Cancer chemotherapy

Chemical Name: 4-amino-1β-D-arabinofuranosyl-2(1H)-pyrimidinone hydrochloride

Common Name: β-cytosine arabinoside

Structural Formula:



(base)

Chemical Abstracts Registry No.: 69-74-9; 147-94-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Cytosar	Upjohn	U.S.	1969
Cytosar	Upjohn	U.K.	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	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 & Engel p. 264
PDR p. 1833
DOT 13 (11) 477 (1977)
I.N. p. 281
REM p. 1147
Hunter, J.H.; U.S. Patent 3,116,282; December 31, 1963; assigned to The Upjohn Company