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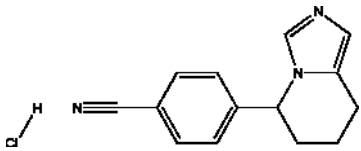
FADROZOLE HYDROCHLORIDE

Therapeutic Function: Antineoplastic

Chemical Name: Benzonitrile, 4-(5,6,7,8-tetrahydroimidazo[1,5-a]pyridin-5-yl)-, monohydrochloride

Common Name: Fadrozole hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 131833-46-6 (Base); 102676-96-0

Trade Name	Manufacturer	Country	Year Introduced
Arensin	Ciba-Geigy	-	-

Raw Materials

Butyl lithium
Sodium hydride
Sodium bicarbonate
Thionyl chloride
Ammonium chloride
4-(3-Ethoxycarbonylpropyl)-1H-imidazole
Trimethylsilyl chloride
Diisobutylaluminum hydride
p-t-Butylaminocarbonylbromobenzene

Manufacturing Process

5-p-Cyanophenyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine hydrochloride:

A solution of 2.0 g of 4-(4-chloro-4-p-cyanophenyl-n-butyl)-1H-imidazole in 50 ml of chloroform is refluxed for 4 hours under nitrogen, cooled and evaporated to yield the 5-p-cyanophenyl-5,6,7,8-tetrahydroimidazo[1,5-a]

pyridine hydrochloride; melting point 231-233°C (from 2-propanol).

Preparation of the starting materials:

(a) 4-(3-Formyl-n-propyl)-1-trimethylsilylimidazole:

A solution of 1.82 g of 4-(3-ethoxycarbonylpropyl)-1H-imidazole in 30 ml of tetrahydrofuran under nitrogen is treated with 0.5 g of sodium hydride (50% oil dispersion) at 0°C for 30 min and 1.45 ml of trimethylsilyl chloride at 0°C for 3 hours. The reaction mixture is washed with cold 0.5 N sodium bicarbonate solution, dried over sodium sulfate and evaporated to dryness. The oil is redissolved in 100 ml of methylene chloride at -78°C under nitrogen and 12.82 ml of diisobutylaluminum hydride (1.56 M) is added dropwise. The reaction mixture is stirred for 5 min at -78°C, quenched with 1 ml of methanol followed by 10 ml of water and filtered through Celite®. The organic phase is separated, dried over sodium sulfate and evaporated to yield the title compound (a).

(b) 4-(4-p-t-Butylaminocarbonylphenyl-4-hydroxy-n-butyl)-1-trimethylsilylim idazole:

6.95 g of p-tert-butylaminocarbonylbromobenzene is dissolved in 175 ml of tetrahydrofuran at -70°C under nitrogen and 20.1 ml of a solution of n-butyl lithium (2.7 m) in hexane is added dropwise. After reacting 30 min, a solution of 5.69 g of 4-(3-formyl-n-propyl)-1-trimethylsilyl imidazole in 10 ml of tetrahydrofuran is added slowly. The reaction mixture is allowed to warm slowly to room temperature and 20 ml of ammonium chloride is added. The organic layer is separated, dried over sodium sulfate and evaporated to yield the title compound (b).

(c) 4-(4-Chloro-4-p-cyanophenyl-n-butyl)-1H-imidazole:

A solution of 4.5 g of 4-(4-p-t-butylaminocarbonylphenyl-4-hydroxy-n-butyl)-1-trimethylsilylimidazole in 50 ml of thionyl chloride is refluxed for 1 hour, cooled and evaporated. The residue is partitioned between methylene chloride and aqueous sodium bicarbonate solution. The organic phase is separated, dried over sodium sulfate and evaporated to yield the title compound (c).

5-p-Cyanophenyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine:

A solution of 2.0 g of 4-(4-chloro-4-p-cyanophenyl-n-butyl)-1H-imidazole in 50 ml of chloroform is refluxed for 4 hours under nitrogen, cooled and evaporated to yield the 5-p-cyanophenyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine.

References

Browne L.J.; US Patent No. 4,617,307; October 14, 1986; Assigned to Ciba-Geigy Corporation (Ardsley, NY)

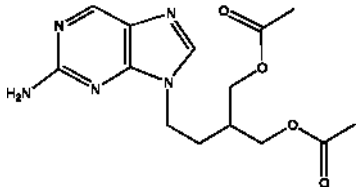
FAMCICLOVIR

Therapeutic Function: Antiviral

Chemical Name: 1,3-Propanediol, 2-(2-(2-amino-9H-purin-9-yl)ethyl)-, diacetate (ester)

Common Name: Famciclovir

Structural Formula:



Chemical Abstracts Registry No.: 104227-87-4

Trade Name	Manufacturer	Country	Year Introduced
Famciclovir	GlaxoSmithKline	-	-
Famtrex	Cipla Limited	India	-
Famvir	SmithKline Beecham Pharmaceuticals	UK	-

Raw Materials

Acetic acid 2-acetoxymethyl-4-hydroxybutyl ester
2-Amino-6-chloropurine
Palladium on charcoal
Ammonium formate

Manufacturing Process

A suspension 1.0 mmol of 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-chloropurine (was synthesized from 2-amino-6-chloropurine and acetic acid 2-acetoxymethyl-4-hydroxybutyl ester) and 400 mmol 10% palladium-on-charcoal in methanol containing ammonium formate was heated under reflux for 30 min. The mixture was allowed to cool, filtered and the solvent removed. The residue was taken up in water and solution extracted twice with chloroform. The organic layers were combined, dried (magnesium sulfate) and the solvent removed to afford 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-purine, yield 90%, m.p. 102-104°C.

References

Hanson J.Ch.; US Patent No. 6,093,819; 07.25.2000; Assigned to SimthKline plc.

Hamden M.R. et al.; EP 0,182,024; 09.09.1986; Assignee to Beecham Group Plc.

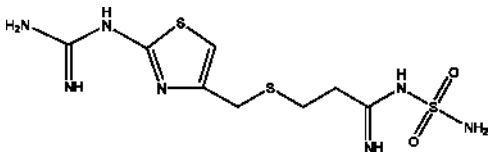
FAMOTIDINE

Therapeutic Function: Antiulcer

Chemical Name: Propanimidamide, 3-(((2-((aminoiminomethyl)amino)-4-thiazolyl)methyl)thio)-N-(aminosulfonyl)-

Common Name: Amifatidine; Famotidine

Structural Formula:



Chemical Abstracts Registry No.: 76824-35-6

Trade Name	Manufacturer	Country	Year Introduced
Acredin	Sarabhai Chemicals	-	-
Apo-Famotidine	Apotex Inc.	Canada	-
Blokacid	IPCA laboratories Ltd.	India	-
Famocid	Sun Pharmaceuticals Industries Ltd.	India	-
Famonit	Cadila Healthcare	India	-
Famonite	Zydus Alidac	India	-
Famorila	Glenmark Pharmaceuticals Ltd.	India	-
Famosan	Alkaloid	Macedonia	-
Famosan	Pro. Med. CS Praha a.s.	Czech Republic	-
Famotidin	Hemofarm	Serbia and Montenegro	-
Famotidin	Serena Pharma Pvt. Ltd.	India	-
Famotidin	Chemo Iberica	Spain	-
Famotidin	SMS Pharmaceuticals	India	-
Famotidin	JAKA-80	Macedonia	-
Famotidin	Tai Yuan Pharmaceutical Factory	China	-
Famotidine	Novopharm	-	-
Famowal	Wallace Pharmaceuticals Ltd.	India	-

Trade Name	Manufacturer	Country	Year Introduced
Gastrosidin	Eczacibasi Ilac Sanayi	Turkey	-
Lecedil	Zdravle	Yugoslavia	-
Pepdin	Overseas Health Care Pvt Ltd.	India	-
Quamatel	Gedeon Richter	Hungary	-
Topcid	Torrent Pharmaceuticals Ltd.	India	-
Ulceran	Medochemie Ltd.	Cyprus	-
Ulfamid	Krka	Slovenia	-

Raw Materials

Dichloroacetone
Tiourea
Sodium hydroxide
Sulfamide
Amidinothiourea
beta-Chloropropionitrile
Hydrogen chloride

Manufacturing Process

60.0 kg of dichloroacetone is dissolved in 550 ml of acetone. After cooling the solution to -5°C, 55.8 kg of amidinothiourea is added to the solution under cooling portionwise at one hour intervals in a 10 kg amount of amidinothiourea. The mixture is stirred continuously for 5 days below 0°C. The 111.6 kg resultant precipitates of N"-[4-(chloromethyl)-4,5-dihydro-4-hydroxy-2-thiazolyl]-guanidine hydrochloride are collected, and washed with 50 L of acetone. In 500 ml of water are dissolved 111.6 kg of N"-[4-(chloromethyl)-4,5-dihydro-4-hydroxy-2-thiazolyl]-guanidine hydrochloride and 32.9 kg of thiourea. The solution is stirred for one hour at 50°C. N'-[4-[[(Aminoiminomethyl)thio]methyl]-2-thiazolyl]-guanidine dihydrochloride is formed in the reaction mixture, and this reaction mixture containing this compound is directly used for the next process without isolation of the formed compound.

The reaction mixture obtained is cooled below 10°C, and to the solution are added 45.6 kg of beta-chloropropionitrile and 200 L of isopropanol. A solution of 69.1 kg of sodium hydroxide in 280 L of water is added dropwise to the solution under nitrogen stream followed by stirring for 2 hours at 0°C. The crystals precipitated are collected by filtration, and washed with cold water and dried to provide 91.7 kg of the N"-[4-[[(2-cyanoethyl)thio]methyl]-2-thiazolyl]-guanidine, melting point 125-126.5°C.

In 60 L of anhydrous dimethylformamide is dissolved 34.3 kg of the N"-[4-[[(2-cyanoethyl)thio]methyl]-2-thiazolyl]-guanidine. After adding 60 L of anhydrous methanol to the solution, 61.9 kg of hydrogen chloride gas is passed through the solution below 5°C. After stirring the reaction mixture for 2 days at 0°C, the reaction mixture is poured into a mixture of 350 L of water, 250 kg of potassium carbonate, 30 L of ethyl acetate and ice while stirring below 5°C for 2 hours. The resultant precipitates are collected by filtration. After stirring a mixture of the precipitates and 400 L of water for 0.5 hour at 0°, the resultant precipitates are collected by filtration, washed with 40 L of water and 10 L of cooled acetone respectively, and dried at reduced pressure

to provide 30.6 kg of the methyl 3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]propionimidate showing a melting point of 125.7°C.

In 340 L of methanol is dissolved 88.4 kg of sulfamide under heating, and the solution is cooled to 30°C. To the solution, 114.2 kg of the methyl 3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]propionimidate are added portionwise three times while stirring at 20-30°C. (The second addition is added 8 hours after the first addition, and the third addition is added 24 hours after the first addition). After stirring the reaction mixture for a further 2 days, the crystals formed are collected by filtration, washed with 200 L of cooled methanol, and air-dried at room temperature to provide 87.5 kg of the 3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]-N-sulfamoylpropionamidine (generic name: famotidine) showing a melting point of 157.6°C. Some of the obtained product is recrystallized from dimethylformamide-water, and is dissolved in an equivalent molar amount of aqueous acetic acid (%). To the solution is added an equivalent molar amount of a dilute sodium hydroxide solution in water to separate crystals showing a melting point of 163-164°C.

References

Hirata Y., Yanagisawa I.; US Patent No. 4,609,737; Sep. 2, 1986; Assigned to Yamanouchi Pharmaceutical Co.

Bekhazi M., Oren J.; US Patent No. 5,068,405; Assigned to As, Delmar Chemicals Inc.

Bod P. et al.; US Patent No. 4,731,479; March 15, 1988; Assigned to Richter Gedeon Vegyeszeti Gyar Rt.

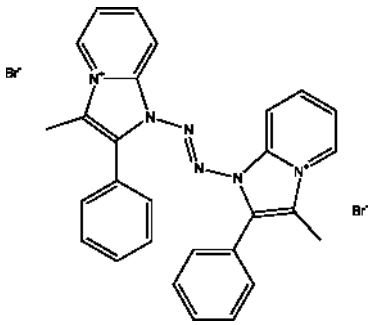
FAZIDINIUM BROMIDE

Therapeutic Function: Muscle relaxant

Chemical Name: 1,1'-Azobis[3-methyl-2-phenylimidazo[1,2-a]pyridinium] dibromide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 49564-56-9

Trade Name	Manufacturer	Country	Year Introduced
Fazadon	Duncan Flockhart	UK	1976
Fazadon	Glaxo	Italy	1981

Raw Materials

2-(2-Acetylhydrazino)pyridine
Hydrogen bromide
2-Bromopropiophenone
Bromine

Manufacturing Process

(a) 1-Acetamido-3-methyl-2-phenylimidazo[1,2-a]pyridinium bromide - A mixture of 2-(2-acetylhydrazino)pyridine (2 g) and 2-bromopropiophenone (2.84 g), in ethanol (10 ml) was heated in an open flask in a bath at 160°C to 170°C until the ethanol had evaporated; the residual melt was then heated for a further 0.25 hour. After cooling, the residual gum was triturated with acetone and the resulting solid (2.8 g) recrystallized from ethanol-ether giving the bromide as colorless prisms, MP 232°C to 234°C.

(b) 1-Amino-3-methyl-2-phenylimidazo[1,2-a]pyridinium bromide - A solution of the acetamido compound (2.78 g) in 24% hydrobromic acid (12 ml) was boiled under reflux for 1 hour. The solution was then evaporated under reduced pressure and the residue dissolved in methanol. Addition of ether precipitated the bromide which crystallized from ethanol as colorless prisms, MP 243°C to 244°C (1.7 g).

(c) 1,1'-Azobis[3-methyl-2-phenyl-1H-imidazo[1,2-a]pyridinium]dibromide - A warm (50°C) solution of the N-amino compound (0.6 g) in water (10 ml) was treated with saturated bromine water (70 ml) and the precipitated orange solid filtered off and washed with water. The orange solid was sucked dry and then boiled with acetone (30 ml) until the suspended solid became yellow. Absolute acetone (10 ml) was then added and the solution filtered giving the dibromide (0.57 g) which crystallized from water as the yellow dihydrate, MP 215°C to 219°C (softened at 196°C).

References

Merck Index 3878
DFU 1 (10) 466 (1976)
DOT 13 (3) 98 (1977)
I.N. p. 413
Jack, D. and Glover, E.E.; US Patents 3,773,746; November 20, 1973 and 3,849,557; November 19, 1974; both assigned to Allen & Hansburys Ltd.

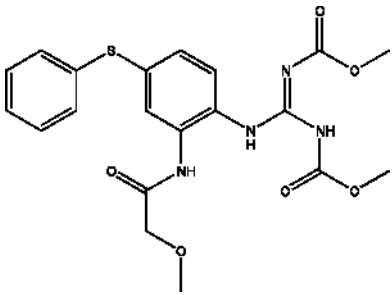
FEBANTEL

Therapeutic Function: Anthelmintic

Chemical Name: Dimethyl[[2-(2-methoxyacetamido)-4-phenylthiophenyl]-imidacarbonyl]dicarbamate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 58306-30-2

Trade Name	Manufacturer	Country	Year Introduced
Rintal	Bayer	W. Germany	1979

Raw Materials

2-Amino-5-phenylthiomethoxyacetanilide
N,N'-Bis-methoxycarbonylisothiourea-S-methyl ether

Manufacturing Process

2-Amino-5-phenylthiornethoxyacetanilide in methanol solution is heated with N,N'-bis-methoxycarbonyl-isothiourea-S-methyl ether with the addition of a catalytic amount of p-toluenesulfonic acid for three hours with stirring under reflux. The mixture is then filtered hot and after cooling the febantel product crystallizes out. It is filtered off, rinsed with ether and dried under high vacuum to give the final product, melting at 129°C to 130°C.

References

Merck Index 3879
DFU 3 (5) 377 (1978)
I.N. p. 413
Kolling, H., Thomas, H., Widdig, A. and Wollweber, H.; US Patent 4,088,780; May 9, 1978; assigned to Bayer AG

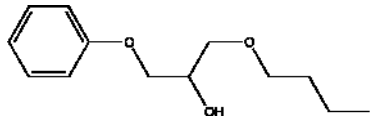
FEBUPROL

Therapeutic Function: Choleretic

Chemical Name: 3-n-Butoxy-1-phenoxy-2-propanol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 3102-00-9

Trade Name	Manufacturer	Country	Year Introduced
Valbil	Rohm Pharma	W. Germany	1981
Valbil	Klinge	W. Germany	-

Raw Materials

n-Butylglycidyl ether
Phenol
Potassium hydroxide

Manufacturing Process

Initially, 4.5 g (0.08 mol) pulverized potassium hydroxide was dissolved in 300 ml isopropanol in a 500 ml four-neck flask equipped with stirrer, intensive cooler, dropping funnel and feed pipe for the gas treatment with nitrogen.

Then, 52.0 g (0.4 mol) n-butylglycidyl ether and 41.4 g (0.44 mol) phenol was added thereto, whereafter the material was heated to boiling under nitrogen. The material was stirred, about 8.5 hours, until no glycidyl ether could be determined, e.g., by gas chromatography.

After the suspension was cooled under nitrogen, the solvent was distilled off under vacuum. The residue was taken up in 200 ml water and the milky emulsion extracted exhaustively with ether. From the organic phase, the excess butylglycidyl ether was extracted with diluted potassium hydroxide solution. The ether phase was washed neutral with water and the solvent removed after drying with sodium sulfate. The remaining oily residue was distilled under vacuum; there was obtained a colorless liquid of BP 123.5°C/0.07 mm. Yield: 81.8 g (91.1% of the theory).

References

Merck Index 3882

DFU 3 (3) 191 (1978)
DOT 19 (12) 683 (1983)
I.N. p. 413
Hoffmann, H., Wagner, J., Hofrichter, G. and Grill, H.; US Patent 3,839,587; October 1, 1974; assigned to Chemisch-Pharmazeutische Fabrik Adolf Klinge and Co.

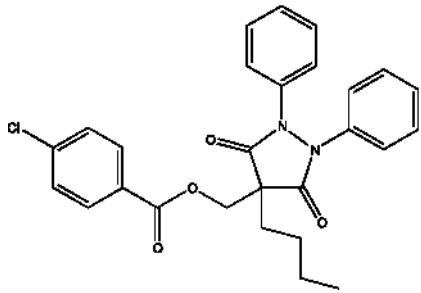
FECLOBUZONE

Therapeutic Function: Antiinflammatory, Analgesic

Chemical Name: p-Chlorobenzoic acid ester with 4-butyl-4-(hydroxymethyl)-1,2-diphenyl-3,5-pyrazolidinedione

Common Name: Feclobuzone

Structural Formula:



Chemical Abstracts Registry No.: 23111-34-4

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

Raw Materials

1,2-Diphenyl-4-n-butyl-3,5-dioxo-pyrazolidine
Formaldehyde
p-Chlorobenzyl chloride

Manufacturing Process

a) Preparation of 1,2-diphenyl-4-n-butyl-3-hydroxy-methyl-3,5-dioxopyrazolidine:

308 g (1 mole) of 1,2-diphenyl-4-n-butyl-3,5-dioxo-pyrazolidine are refluxed during 2 hours in a mixture of 900 ml absolute ethanol and 100 ml of a solution of formaldehyde 40% in water. The mixture is allowed to cool overnight in a refrigerator and after filtration, washing with alcohol and drying; crystals (305 g) are obtained. Melting point: 146-147°, yield 90%.

b) Preparation of para-chlorobenzoic ester of 1,2-di-phenyl-4-n-butyl-4-hydroxymethyl-3,5-dioxopyrazolidine:

In a 2 liter 3-necked flask fitted with mechanical stirrer, dropping funnel and entry for nitrogen circulation, 338 g (1 mole) of the 1,2-diphenyl-4-n-butyl-3-hydroxy-methyl-3,5-dioxopyrazolidine are added. The resultant mixture is dissolved in a mixture of 200 ml pyridine and 600 ml dimethylformamide. When the temperature reaches 0°C, 175 g (1 mole) of p-chlorobenzyl chloride previously subjected to a mild nitrogen flow are added dropwise under stirring. Once the addition of all the amount of the acid chloride is completed, the material is maintained under stirring during one hour and is then allowed to stand during 24 hours in a refrigerator and finally 24 hours at room temperature. The temperature is then raised to 30-40°C to dissolve the precipitate which occurred. The mixture is then cooled and poured in ice-water containing hydrogen chloride (1:1). Stand 24 hours, filter and wash several times with water and once with cold alcohol. Following two recrystallisazions from alcohol, there are obtained 380 g of perfect prismatic crystals melting at 90-91°C. Esterification yield: 80%.

References

Esteve A.; US Patent No. 3,755,576; Assigned to Laboratorios Del Dr.

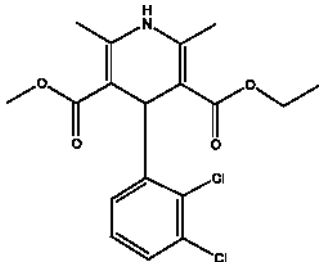
FELODIPINE

Therapeutic Function: Antihypertensive

Chemical Name: 3,5-Pyridinedicarboxylic acid, 1,4-dihydro-4-(2,3-dichlorophenyl)-2,6-dimethyl-, ethyl methyl ester

Common Name: Felodipine

Structural Formula:



Chemical Abstracts Registry No.: 72509-76-3

Trade Name	Manufacturer	Country	Year Introduced
Felodip	Galena a.s.	Czech Republic	-
Munobal	Astra	Germany	-
Plendil	AstraZeneca	-	-
Felogard	Cipla Limited	India	-
Plendil	AstraZeneca	India	-

Raw Materials

2,3-Dichlorobenzaldehyde
Methyl acetoacetate
Ethyl-3-aminocrotonate
Hydrochloric acid

Manufacturing Process

Preparation of 2,3-dichlorobenzylideneacetylacetic acid-methylester.

2,3-Dichlorobenzaldehyde is reacted with methyl acetoacetate in a suitable solvent in the presence of a catalytic amount of acetic acid and piperidine. Water is azeotropically separated off during the reaction. The reaction mixture is extracted in order to remove the catalysts. The solvent is evaporated and methanol is added. The product is crystallized by cooling the solution, isolated by filtration and finally washed with methanol.

A stirred mixture of 81 g of 2,3-dichlorobenzylideneacetylacetic acid methylester and 46.67 g ethyl-3-aminocrotonate in 75 mL of ethanol (anhydrous) under an argon atmosphere was heated to reflux rapidly and maintained at reflux for 1 hour. The heating mantle was removed and the stirred reaction mixture cooled in air to a pot temperature of 75°C. An ethanolic aqueous hydrochloric acid solution (22.5 mL of 12.1 N HCl + 22.5 mL of water + 45 mL of ethanol) was added to the hot solution over 5 minutes time. The reaction mixture was allowed to cool to 41°C and crystallization began. The mixture was then cooled to room temperature; cooled in an ice bath and then refrigerated over the weekend. The solids were filtered cold and washed in portions with 300 mL of 1:1 v/v ethanol/water solution at -10°-15°C. The pH of the filtrate at the end of washing was about pH 5. The solid was suction dried under a nitrogen stream then dried under high vacuum at 40°C overnight to provide 94.3 g of Felodipine (HPLC 98.9% pure) 83.3% yield. Diethyl ester impurity 0.33% by HPLC.

References

Auerbach J.; US Patent No. 5,310,917; 05.10.1994; Assignede to Merck and | Co., Inc.
Gustavsson A., Kallsttom A., Palmer S.; US Patent No. 5,942,624; 08.24.1999; Assigned to Astra Aktiebolag

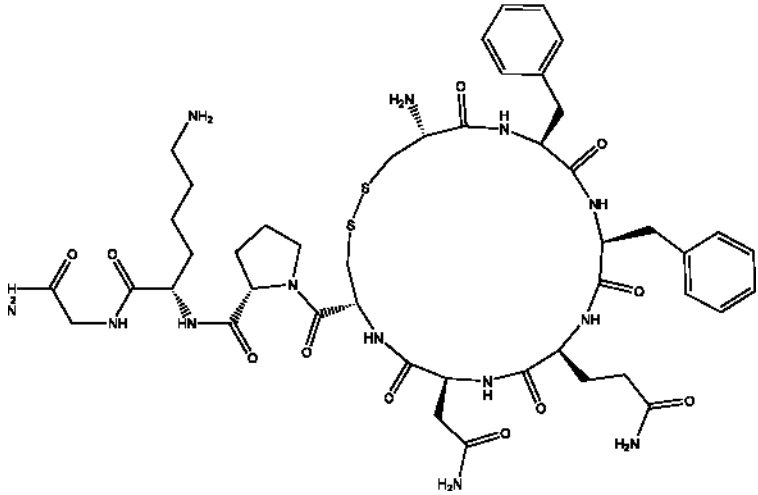
FELYPRESSIN

Therapeutic Function: Vasoconstrictor

Chemical Name: Vasopressin 2-(L-phenylalanine)-8-L-lysine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 56-59-7

Trade Name	Manufacturer	Country	Year Introduced
Octapressin	Sandoz	W. Germany	1967
Octapressin	Sandoz	Japan	1971
Colupressine	Joullie	France	-

Raw Materials

Oxygen
Ammonia
Acetic acid
Hydrogen bromide
N-Carbobenzoxy-L-prolyl-ε-N-p-toluenesulfonyl-L-lysyl-glycinamide
N-Carbobenzoxy-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-azide
N-Carbobenzoxy-S-benzyl-L-cysteinyl-L-phenylalanyl azide

Manufacturing Process

Preparation of N-Carbobenzoxy-L-Glutaminyl-L.Asparaginyl-S-Benzyl-L-

Cysteinyl-L-Prolyl-ε-N-p-Toluenesulfonyl-L-Lysylglycinamide: 200 parts by weight of N-carbobenzoxy-L-prolyl-ε-N-p-toluenesulfonyl-L-lysyl-glycinamide are dissolved in 1,000 parts by volume of anhydrous acetic acid which has been saturated with HBr, the mixture allowed to stand for 1 hour at 20°C and then evaporated under reduced pressure at below 40°C. The residue from this evaporation is carefully washed with diethyl ether and then added to a solution of 185 parts by weight of N-carbobenzoxy-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-azide and 48 parts by volume of triethylamine in 1,500 parts by volume of dimethylformamide. The mixture is allowed to stand overnight at 20°C and the mixture is then poured into twice its volume of acetone. The precipitate which settles out is filtered off, washed with water, and recrystallized from dimethylformamide-acetone. There are thus obtained 190 parts by weight of N-carbobenzoxy-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-ε-N-p-toluenesulfonyl-L-lysyl-glycinamide; MP 165°C (decomposition).

Preparation of N-Carbobenzoxy-S-Benzyl-L-Cysteinyl-L-Phenylalanyl-L-Phenylalanyl-L-Glutaminyl-L-Asparaginyl-S-Benzyl-L-Cysteinyl-L-Prolyl-ε-N-p-Toluenesulfonyl-L-Lysyl-Glycinamide: 50 parts by weight of N-carbobenzoxy-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-ε-N-p-toluenesulfonyl-L-lysyl-glycinamide are dissolved in 400 parts by volume of anhydrous acetic acid which is saturated with HBr, and the mixture allowed to stand for 1 hour at 20°C. After evaporating off the solvent under reduced pressure at a temperature of 35°C (or another temperature below 40°C), the residue is carefully washed with diethyl ester, whereupon a solution of 32 parts by weight of N-carbobenzoxy-S-benzyl-L-cysteinyl-L-phenylalanyl-L-phenylalanyl-azide and 70 parts by volume of triethylamine in 500 parts by volume of dimethylformamide is added.

The mixture is allowed to stand for 2 days at 20°C, after which twice its volume of ethylacetate is added and the resultant precipitate then washed with warm methanol. There are obtained 45 parts by weight of N-carbobenzoxy-S-benzyl-L-cysteinyl-L-phenylalanyl-L-phenylalanyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-ε-N-p-toluenesulfonyl-L-lysyl-glycinamide; MP 222°C.

Preparation of L-Cysteinyl-L-Phenylalanyl-L-Phenylalanyl-L-Glutaminyl-L-Asparaginyl-L-Cysteinyl-L-Prolyl-L-Lysyl-Glycinamide: Metallic potassium is stirred into a solution of 10 parts by weight of N-carbobenzoxy-S-benzyl-L-cysteinyl-L-phenylalanyl-L-phenylalanyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-ε-N-p-toluenesulfonyl-L-lysyl-glycinamide in 2,500 parts of dry liquid ammonia at boiling temperature of the solution, until a stable blue coloration appears. After the addition of 1.8 parts by weight of ammonium chloride, the solution is evaporated to dryness. The residue of this evaporation contains the desired L-cysteinyl-L-phenylalanyl-L-phenylalanyl-L-glutaminyl-L-asparaginyl-L-cysteinyl-L-prolyl-L-lysyl-glycinamide.

Preparation of Felypressin: The aforesaid residue, containing the L-cysteinyl-L-phenylalanyl-L-phenylalanyl-L-glutaminyl-L-asparaginyl-L-cysteinyl-L-prolyl-L-lysyl-glycinamide, is dissolved in 20,000parts by volume of 0.01 normal acetic acid and is then oxidized by passing air into the solution at a pH of 6.5 to 8.0 for 1 hour. The solution, which contains Felypressin, is adjusted to a pH of 4.0 to 5.0, whereupon 100 parts by weight of sodium chloride are added and the mixture evaporated to dryness, yielding a dry powder of good stability. It can

be stored, and yields a clear solution, e.g., in water or other appropriate solvent. The solution may be used directly or, if desired, after dilution with water or a sodium chloride solution.

References

Merck Index 3885
Kleeman & Engel p. 385
I.N. p. 414
Boissonnas, R. and Guttmann, S.; US Patent 3,232,923; February 1, 1966:assigned to Sandoz AG, Switzerland

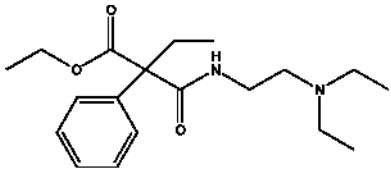
FENALAMIDE

Therapeutic Function: Spasmolytic, Smooth muscle relaxant

Chemical Name: Benzeneacetic acid, α-(((2-(diethylamino)ethyl)amino) carbonyl)-α-ethyl-, ethyl ester

Common Name: Fenalamide; Phemamide

Structural Formula:



Chemical Abstracts Registry No.: 4551-59-1

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

Raw Materials

Phenylethylmalonic acid ethyl ester chloride
Sodium carbonate
N,N-Diethylethylenediamine

Manufacturing Process

To a solution of 25.5 g of phenylethylmalonic acid ethyl ester chloride in 100 ml of anhydrous benzene 5.3 g of anhydrous sodium carbonate are added followed by 11.6 g of N,N-diethylethylenediamine in small portion. After the spontaneous heat evolution has subsided the mixture is refluxed for 2 hours until the evolution of carbon dioxide ceases. After cooling the mixture is

allowed to stand for some hours, the precipitated sodium chloride is removed by filtration. The filtrat is evaporated to dryness in vacuo and the residue distilled at 182-188°C/3 mm Hg.

The phenylethylmalonic acid (diethyl amino) ethylamide ethyl ester (free base) is converted in hydrochloride by bubbling hydrogen chloride into a diethyl ether solution of the free base; melting point 71-74°C.

References

Galiberti P., Garosa V., Melandri M.M.; US Patent No. 3,025,317; Mar. 1962; Assigned to Societa Italiani Prodotti Schering, Milan, Italy

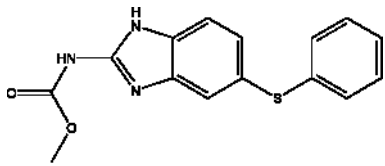
FENBENDAZOLE

Therapeutic Function: Anthelmintic

Chemical Name: 5-Phenylmercapto-benzimidazole-2-methyl-carbamate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 43210-67-9

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

Raw Materials

S-Methyl thiourea
Chloroformic acid methyl ester
3,4-Diamino-diphenyl-thioether

Manufacturing Process

20.9 g of S-methyl-thiourea were dissolved in 27 ml of water with 13.5 ml of chloroformic acid methyl ester. Then, 45.7 ml of 25% sodium hydroxide solution were added dropwise, while stirring, at a temperature of 5°C to 10°C. After having stirred for 20 minutes, the reaction mixture was combined with

27 ml of glacial acetic acid, 100 ml of water and 29 g of 3,4-diamino-diphenyl-thioether. Stirring was continued for 90 minutes at a temperature of 85°C, during which time methyl-mercaptan was separated. After having allowed the whole to cool and stand overnight, the 5-phenylmercapto-benzimidazole-2-methyl-carbamate that had formed was filtered off with suction. After recrystallization from a mixture of glacial acetic acid and methanol, 14 g of 4-phenylmercapto-benzimidazole-2-methyl-carbamate melting at 233°C were obtained.

References

Merck Index 3891
OCDS Vol. 3 p. 176 (1984)
DOT 14 (1) 45 (1978)
I.N. p. 414
Loewe, H., Urbanietz, J., Kirsch, R. and Duwel, D.; US Patent 3,984,561; October 5, 1976; assigned to Hoechst AG
Loewe, H., Urbanietz, J., Kirsch, R. and Duwel, D.; US Patent 3,954,791; May 4, 1976; assigned to Hoechst AG

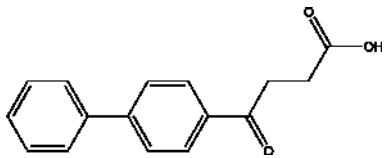
FENBUFEN

Therapeutic Function: Antiinflammatory

Chemical Name: 3-(4-Biphenylylcarbonyl)propionic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 36330-85-5

Trade Name	Manufacturer	Country	Year Introduced
Cinopal	Cyanamid	Italy	1976
Lederfen	Cyanamid	W. Germany	1979
Lederfen	Lederle	UK	1979
Cinopal	Opopharma	Switz.	1979
Napanol	Lederle	Japan	1980
Cinopal	Cyanamid	France	1971
Bufemid	Lederle	-	-

Raw Materials

Biphenyl
Succinic anhydride
Aluminum chloride

Manufacturing Process

135 g of aluminum chloride is dissolved in 500 ml of nitrobenzene, the solution being held below 10°C by external cooling. A finely ground mixture of 50 g of succinic anhydride and 75 g of biphenyl is added to the stirred solution, the temperature being held below 10°C. It is then held at room temperature for four days. After pouring the reaction mixture into a solution of 150 ml of concentrated hydrochloric acid in 1 liter of ice water, the nitrobenzene is removed by steam distillation. The solid is collected, dissolved in 4 liters of 3% hot sodium carbonate solution, clarified, and reprecipitated by the addition of excess 6N sulfuric acid solution. The crude product is collected, dried, and recrystallized from ethanol to give the pure subject compound, MP 185°C to 187°C.

References

Merck Index 3893
DFU 1 (1) 26 (1976)
Kleeman & Engel p. 386
OCDS Vol. 2 p. 126 (1980)
DOT 13 (4) pp. 133, 136 (1977)
I.N. p. 416
Tomcufcik, A.S., Child, R.G. and Sloboda, A.E.; US Patent 3,784,701; January 8, 1974; assigned to American Cyanamid Co.

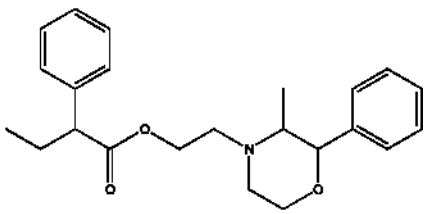
FENBUTRAZATE

Therapeutic Function: Anorexic, Central stimulant

Chemical Name: Benzeneacetic acid, α-ethyl-, 2-(3-methyl-2-phenyl-4-morpholinyl)ethyl ester

Common Name: Fenbutrazate; Phenbutrazate

Structural Formula:



Chemical Abstracts Registry No.: 4378-36-3

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

Raw Materials

4-(2-Hydroxyethyl)-3-methyl-2-phenylmorphotine
2-Ethyl-2-phenyl-acetylchloride

Manufacturing Process

1105 g of 2-phenyl-3-methyl-4-(α-hydroxyethyl)-tetrahydro-1,4-oxazine-(4-(2-hydroxyethyl)-3-methyl-2-phenylmorphotine) are dissolved in 4000 ml of anhydrous toluene. 910 g of α-phenyl-α-ethyl acetic acid chloride (2-ethyl-2-phenyl-acetylchloride) are dissolved in 400 ml of anhydrous toluene and the resulting solution is slowly added to the heated solution of the tetrahydro-1,4-oxazine compound. The mixture is then heated to boiling for about 5 hours. About 1000 g of ice are added to the cooled reaction mixture, which is then rendered alkaline by the addition of 20% sodium carbonate solution to a pH of 9.0. Thereafter the mixture is vigorously stirred by means of a turbine mixer for one hour and the toluene phase is separated. The toluene solution is washed with 1000 ml of saturated sodium chloride solution and is dried over anhydrous sodium sulfate. The toluene is then evaporated and the residue is subjected to high vacuum distillation. 1650 g of α-phenyl-α-ethylacetic acid (2-phenyl-3-methyltetrahydro-1,4-oxazine)-N-ethyl ester (fenburazate), boiling at 235°-240°C/0.05 mm are obtained thereby in a yield of 90.5% of the theoretical yield.

References

Miescher K. et al.; US Patent No. 2,234,311; March 11, 1941; Assigned to Ciba Pharmaceutical Products, Incorporated, Summit, N.J., a corporation of New Jersey

FENCAMFAMIN

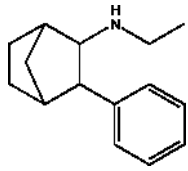
Therapeutic Function: Central stimulant, Anorexic

Chemical Name: 2-Norbornanamine, N-ethyl-3-phenyl-

Common Name: Fencamfamin

Trade Name	Manufacturer	Country	Year Introduced
Fencamfamin	Shanghai Lansheng Corporation	-	-
Euvitol	Allen and Hanburys	-	-
Norcamphane	Emedia Export	-	-

Structural Formula:



Chemical Abstracts Registry No.: 1209-98-9

Raw Materials

2-Phenyl-3-aminobicyclo[2.2.1]heptane
Acetaldehyde
Platinum oxide
Nickel Raney

Manufacturing Process

1) 28.05 g of 2-phenyl-3-aminobicyclo[2.2.1]heptane are mixed with 6.9 g acetaldehyde keeping the mixture cool. The mixture is heated for 20 minutes on the stream bath under reflux, and the reaction product is freed from water in vacuum at 60°C. The crude base is dissolved in 300 ml of methanol and hydrogenated with 2 previously reduced platinum oxide. After it has taken up the calculated quantity of hydrogen, the solvent is distilled off in vacuum, the residue dissolved in dilute hydrochloric acid and the neutral by-products are shaken out with ether. The aqueous solution is made alkaline with caustic soda and extracted with ether. From ethereal solution 13.2 g of the base are obtained with a boiling point at 1 mm of 128°-131°C.

2) 25 g of 2-phenyl-3-aminobicyclo[2.2.1]heptane,15 g Raney nickel and 75 ml absolute alcohol are boiled under a reflux for 15 hours. The filtrate from the catalyst is neutralised with dilute hydrochloric acid and distilled to dryness in vacuum. The hydrochloric residue is purified by recrystallisation from acetone or dioxane-petrol-ether. Yield 21.5 g; MP: 191°C.

References

G.B. Patent No. 913,866; Aug. 1, 1959; Merck Aktiengeselshaft of Francfurter Strasse 250, Darmstadt, Germany, a German Body Corporate

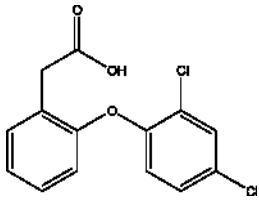
FENCLOFENAC

Therapeutic Function: Antiinflammatory

Chemical Name: Benzeneacetic acid, 2-(2,4-dichlorophenoxy)-

Common Name: Fenclofenac

Structural Formula:



Chemical Abstracts Registry No.: 34645-84-6

Trade Name	Manufacturer	Country	Year Introduced
Flenac	Reckitt and Colman	-	-

Raw Materials

2,4-Dichlorphenol
2-Chloroacetophenone
Sulfur
Morpholine

Manufacturing Process

1-[2-(2,5-Dichloro-phenoxy)-phenyl]-ethanone was prepared from a mixture of 2,4-dichlorphenol, 2-chloroacetophenone and copper catalyst (prepared according to R.Q. Brewster and T. Groening Organic Syntheses, John Wiley and Sons, Inc., New York, 1943, Coll. Vol.11, p.446). 1 mol of the above phenoxy compound was mixed with 3 mol of sulfur and 3.5 mol of morpholine and heated under gentle reflux for 72 hours. The mixture was evaporated, water was added and extracted with ether. The aueous layer was then acidified with concentrated hydrochloric acid and the product was extracted into ether, the ether extract was dried and evaporated. The solid residue was recrystallized from CCl_4 to give [2-(2,4-dichlorophenoxy)-phenyl]acetic acid, Yield 37%; MP: 134°-136°C.

References

Godfrey K.E.; U.S. Patent No. 3,766,263; Oct. 16, 1973; Assigned to Reckitt and Colman Products Limited, Hull, Yorkshire, England

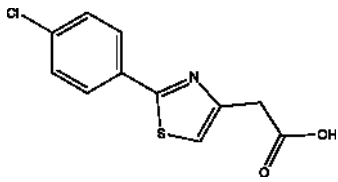
FENCLOZIC ACID

Therapeutic Function: Antiinflammatory, Analgesic, Antipyretic

Chemical Name: 4-Thiazoleacetic acid, 2-(4-chlorophenyl)-

Common Name: Acidum fenclozicum; Fenclozic acid; Fenclozin

Structural Formula:



Chemical Abstracts Registry No.: 17969-20-9

Trade Name	Manufacturer	Country	Year Introduced
Fenclozic Acid	ZYF Pharm Chemical	-	-

Raw Materials

2-(4-Chlorophenyl)-4-cyanomethylthiazole
Hydrochloric acid
Ammonia
Acetic acid

Manufacturing Process

3.7 parts of 2-(4-chlorophenyl)-4-cyanomethylthiazole and 35 parts of 6 N hydrochloric acid are heated under reflux for 2 hours. The solution is cooled by the addition of ice and made alkaline to pH 8 by the addition of 30% aqueous ammonia. The mixture is filtered to remove trace impurities, and an excess of 40% sodium hydroxide solution is then added to the filtrate to cause precipitation of a sodium salt, which is collected by filtration and crystallised from water. There is thus obtained sodium 2-(4-chlorophenyl)thiazol-4-ylacetate, M.P. 13°C (decomposition).

This sodium salt is dissolved in hot water, and the solution is brought to pH 4 by the addition of acetic acid, which causes the precipitation of 2-(4-chlorophenyl)thiazol-4-ylacetic acid. This is collected by filtration, washed with water, and dried in vacuo over phosphorus pentoxide. It has an M.P. 155-156°C (from ethyl acetate).

References

Hepworth W., Gilbert J. S.; US Patent No. 3,538,107; Nov. 3, 1970; Assigned to Imperial Chemical Industries Limited, London, England, a corporation of Great Britain

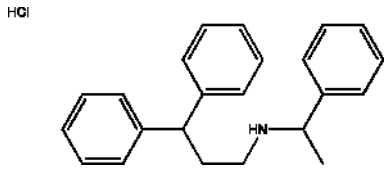
FENDILINE HYDROCHLORIDE

Therapeutic Function: Coronary vasodilator

Chemical Name: γ-Phenyl-N-(1-phenylethyl)benzenepropanamine hydrochloride

Common Name: N-(1-Phenylethyl)-3,3-diphenyl-propylamine

Structural Formula:



Chemical Abstracts Registry No.: 13636-18-5; 13042-18-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Sensit	Thiemann	W. Germany	1974
Sensit F	Ravasini	Italy	1981
Difmecor	UCM-Difme	Italy	-
Fendilar	SPA	Italy	-

Raw Materials

Hydrogen
Acetophenone
γ,γ-Diphenylpropylamine
Hydrogen chloride

Manufacturing Process

21.13 grams of γ,γ-diphenyl-propylamine and 12.01 grams of acetophenone are hydrogenated in 200 ml of methanol at 55°C and a pressure of 10 atmospheres in the presence of palladium charcoal. On filtration of the catalyst the solution is concentrated and the remainder is distilled in vacuo at a pressure of 0.3 Hg mm. The main distillate is collected at 206° to 210°C. 25.38 grams of N-[1'-phenylethyl-(1')]-1,1-diphenyl-propyl-(3)-amine are obtained.

The product is dissolved in 134 ml of 96% ethanol whereupon 26.8 ml of concentrated hydrochloric acid and 201 ml of water are added while cooling with ice-water. The precipitate is filtered off and dried in vacuo at 100°C. 22.98 grams of N-[1'-phenylethyl)-(1')]-1,1-diphenyl-propyl-(3)-amine hydrochloride are obtained. MP 200° to 201°C. On recrystallization from 285 ml of a 2:1 mixture of water and 96% ethanol the melting point remains unchanged.

References

Merck Index 3903
Kleeman & Engel p. 389
DOT 10 (12) 337 (1974)
I.N. p. 417
Harsanyi, K., Korbonits, D., Takats, K., Tardos, L. and Leszkovszky, G.; US Patent 3,262,977; July 26, 1966; assigned to Chinoin Gyogyszer-ek Vegyeszeti Termekek, Hungary

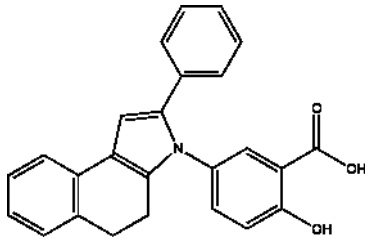
FENDOSAL

Therapeutic Function: Analgesic, Antiinflammatory, Antipyretic

Chemical Name: Benzoic acid, 5-(4,5-dihydro-2-phenyl-3H-benz[e]indol-3-yl)-2-hydroxy-

Common Name: Fendosal

Structural Formula:



Chemical Abstracts Registry No.: 53597-27-6

Trade Name	Manufacturer	Country	Year Introduced
Alnovin	Hoechst	-	-
Fendosal	Shanghai Lansheng Corporation	-	-

Raw Materials

1-(1-Pyrrolidino)-3,4-dihydronaphthalene
Phenacyl bromide
5-Aminosalicyclic acid

Manufacturing Process

To a stirred refluxing solution of 20.2 g (0.1 mole) of 1-(1-pyrrolidino)-3,4-dihydronaphthalene and 50 ml of toluene was added dropwise during 30

minutes under nitrogen a solution of 20.1 g (0.1 mole) of phenacyl bromide in 65 ml of dry toluene. The mixture was heated under reflux for 6 hours, diluted with 50 ml of water, refluxed for 4 hours, and cooled. The layers were separated and the aqueous phase was extracted with benzene. The organic solution was dried over sodium sulfate and concentrated to a semi-solid. Trituration with cold 30°-60° petroleum ether gave 23.6 g (78%) of solid, 2-phenacyl-1-tetralone, MP: 73°-76°C. Recrystallization from 60°-90° petroleum ether raised the melting point to 87°-88°C.

A mixture of 20.0 g (0.076 mole) of 2-phenacyl-1-tetralone, 11.6 g (0.076 mole) of 5-aminosalicyclic acid, and 70 ml of glacial acetic acid was heated under reflux for 4 hours, cooled, diluted with 10 ml of water and filtered. The filter cake was washed with water and dried to provide 15.5 g of solid, 5-(4,5-dihydro-2-phenyl-3H-benz[e]indol-3-yl)-2-hydroxy-benzoic acid. MP: 215°-218°C. Recristallization from benzene-cyclohexane gave 6.5 g (22%) of yellow crystals, MP: 245°-247°C.

References

Allen R. et al.; US Patent No. 3,878,225; Apr. 15, 1975

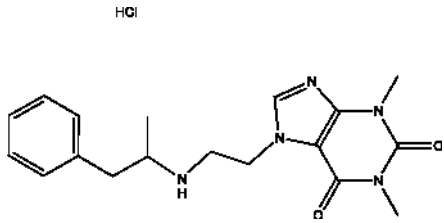
FENETHYLLINE HYDROCHLORIDE

Therapeutic Function: Central stimulant

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

Common Name: Theophyllineethylamphetamine

Structural Formula:



Chemical Abstracts Registry No.: 1892-80-4; 3736-08-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Captagon	Homburg	W. Germany	1961
Gelosedine	Bayer	France	1964
Captagon	Gerda	France	-
Fitton	Teva	Israel	-

Raw Materials

7-(β-Chloroethyl)-theophylline
α-Methyl-β-phenylethylamine
Hydrogen chloride

Manufacturing Process

1 mol of 7-(β-chloroethyl)-theophylline and 2½ mols of α-methyl-β-phenyl ethylamine are heated for 6 hours in an oil bath, if necessary with addition of alcohol or toluene. The reaction mixture is diluted with alcohol and acidified with alcoholic hydrochloric acid. The crystalline mass formed is filtered with suction and extracted by boiling with alcohol. A product having a melting point of 237°C to 239°C is formed. With prolonged extraction by boiling with alcohol, the melting point of the mass falls, preferably due to a change in modification, to 227°C to 229°C. However, analysis shows that both products are the pure condensation product.

Instead of the chloroethyl theophylline, it is also possible to use the corresponding bromine derivative. It was found that in this way the process is facilitated and the yield is improved.

References

Merck Index 3906
Kleeman & Engel p. 390
OCDS Vol. 1 p.425 (1977)
I.N. p. 418
Kohlstaedt, E. and Klingler, K.H.; US Patent 3,029,239; April 10, 1962; assigned to Chemiewerke Homburg

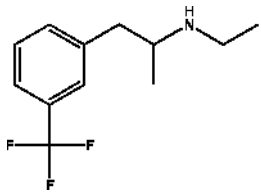
FENFLURAMINE

Therapeutic Function: Anorexic

Chemical Name: Benzeneethanamine, N-ethyl-α-methyl-3-(trifluoromethyl)-

Common Name: Fenfluramine; Phenfluoramine; Trifluethamine

Structural Formula:



Chemical Abstracts Registry No.: 458-24-2

Trade Name	Manufacturer	Country	Year Introduced
Obenon	Neofarma	-	-
Obetrol	Mulda	-	-
Ponderal	Servier	-	-

Raw Materials

(Trifluoromethyl-3'-phenyl)-1-oximino-2-propane
Hydrogen
Nickel Raney

Manufacturing Process

38.5 parts of (trifluoromethyl-3'-phenyl)-1-oximino-2-propane in 550 parts of ethanol (with ammonia) was hydrogenated under pressure of hydrogen 90 kg with a catalyst nickel Reney (20 parts). After a completion of reaction to the reaction mixture was added 1000 parts of water and 300 parts of hydrochloric acid. The mixture was concentrated in vacuo and extracted with 450 parts of ether. To an aqueous phase was added the sodium carbonate and the mixture was extracted with 500 parts of ether. Organic phase was concentrated in vacuo to obtain 29 g of 1-(meta-trifluoromethyl-phenyl)-2-ethylaminopropane. B.P. 96°C at 17 mm.

References

Merck Index, Monograph number: 4015, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Beregl L. et al.; Patent FR-M 1,658; April 4, 1961; Assigned to Science-Union Et Cic Societe, France

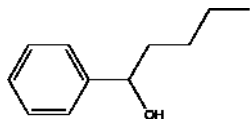
FENIPENTOL

Therapeutic Function: Choleretic

Chemical Name: α-Butylbenzenemethanol

Common Name: Phenylpentanol

Structural Formula:



Chemical Abstracts Registry No.: 583-03-9

Trade Name	Manufacturer	Country	Year Introduced
Pancoral	Eisai	Japan	1973
Euralan	Badrial	France	1974
Billicol	Violani-Farmavigor	Italy	-
Cholipin	Boehringer Ingelheim	Italy	-
Critichol	Angelini	Italy	-
Epatolark	Farm. Milanese	Italy	-
Eprox	Off	Italy	-
Fabil-Valeas	Valeas	Italy	-
Florobil	Scalari	Italy	-
Kol	Mitim	Italy	-
Liverpen	Guidi	Italy	-
Pentabil	Off	Italy	-
Suiclisin	Nikken	Japan	-

Raw Materials

Benzaldehyde
Butyl bromide
Magnesium

Manufacturing Process

The 1-phenylpentanol-(1) may be prepared in any convenient manner. Benzaldehyde may be reacted with n-butyl-magnesium bromide, and after purification 1-phenyl-pentanol-(1) is obtained in the form of a colorless oil at room temperature.

References

Merck Index 3909
Kleeman & Engel p. 391
DOT 10 (6) 203 (1974)
I.N. p. 418
Scheffler, H. and Engelhorn, R.; US Patent 3,084,100; April 2, 1963; assigned to Dr. Karl Thomae G.m.b.H.

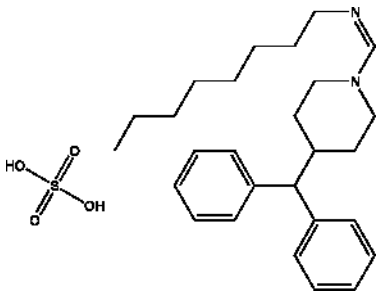
FENOCTIMINE SULFATE

Therapeutic Function: Gastric antisecretory

Chemical Name: Piperidine, 4-(diphenylmethyl)-1-(N-octylformimidoyl)-, sulfate (1:1)

Common Name: Fenoctimine sulfate

Structural Formula:



Chemical Abstracts Registry No.: 69365-65-7 (Base); 69365-66-8

Trade Name	Manufacturer	Country	Year Introduced
Fenoctimine sulfate	ZYF Pharm Chemical	-	-

Raw Materials

Dimethyl sulfate	Dimethyl formamide
n-Otylamine	Dimethylamine
Sodium hydroxide	4-(Diphenylmethyl)piperidine

Manufacturing Process

Dimethyl sulfate (126.1 g, 1.0 mole) was heated to 65°C. The temperature was maintained at 60-70°C while dimethylformamide (73.1 g, 1.0 mole) was added over a period of about 30 minutes. After the addition was complete, the reaction was heated at 70°C for 7 hours, then cooled to below 30°C. n-Octylamine (129.2 g, 1.0 mole) was added over a 20 minute period with external cooling to maintain the temperature at 40°C. The reaction was stirred an additional 3 hours at 40°C after addition was complete. The reaction was cooled to about 10°C and treated with toluene (200 ml), water (200 ml) and finally 27% sodium hydroxide solution (180 g , 2 moles). The organic phase was separated, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to yield 190 g of a light yellow liquid which was fractionally distilled twice to yield 113 g (61%) of the title compound as a water white liquid; b.p. 115.-117°C at 15 mm Hg.

4-(Diphenylmethyl)piperidine (12.5 g, 0.05 mole) and N,N-dimethyl-N'-octylformamidine (11.5 g, 0.06 mole) were placed in a 3-necked flask equipped with magnetic stirrer, heating mantle, thermometer and nitrogen inlet. A moderate stream of nitrogen was blown through the flask while the reaction was heated to 120°C. The reaction was stirred and heated at 120°C for 5 hours, then cooled to 20°C and diluted with toluene (35 ml). The reaction was cooled in an ice bath, stirred, and treated with a mixture of ice (50 g) and sulfuric acid (9 g, 0.088 mole). After stirring for 15 min, the resulting solid was isolated by filtration, and washed sequentially with toluene (10 ml), and 1 N sulfuric acid (2 x 10 ml). The solid was suspended twice in a

mixture of water (100 ml) and 1 N sulfuric acid (20 ml) and stirred for 30 min each time prior to filtration. Finally, the product was washed with water (2x10 ml), and cyclohexane (20 ml). The filter cake was dried under reduced pressure at 30°C to constant weight to yield 21.3 g (85.6%) of the 4-(diphenylmethyl)-1-[(octylimino)methyl]piperidine sulfate (1:1), m.p. 113-115°C. 4-(Diphenylmethyl)-1-[(octylimino)methyl]piperidine may be used as a sulfate.

References

Feth Georg, Mills John E.; US Patent No. 4,499,274; February 12, 1985; Assigned to McNeilab, Inc. (Fort Washington, PA)

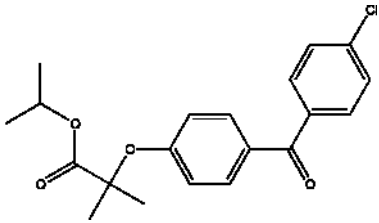
FENOFIBRATE

Therapeutic Function: Antihyperlipoproteinemic

Chemical Name: 2-[4-(4-Chlorobenzoyl)phenoxy]-2-methylpropanoic acid-1-methylethyl ester

Common Name: Procetofen

Structural Formula:



Chemical Abstracts Registry No.: 49562-28-9

Trade Name	Manufacturer	Country	Year Introduced
Lipantyl	Fournier	France	1975
Lipanthyl	Fournier	Switz.	1975
Lipanthyl	Pharma Holz	W. Germany	1978
Lipanthyl	Nativelle	Italy	1979
Lipidax	UCB-Smit	Italy	1979
Ankebin	Volpino	Argentina	-
Elasterin	Phoenix	Argentina	-
Fenobrate	Gerardo Ramon	Argentina	-
Fenolibs	L.I.B.S.	France	-
Lipanthyl	Falorni	Italy	-

Trade Name	Manufacturer	Country	Year Introduced
Lipidil	Ibirn	Italy	-
Lipoclar	Farmacosmici	Italy	-
Lipofene	Selvi	Italy	-
Liposit	S.I.T.	Italy	-
Nolipax	Biomedica Foscama	Italy	-
Procetoken	Bernabo	Argentina	-
Protolipan	Millet	Argentina	-
Sedufen	Microsules	Argentina	-

Raw Materials

Acetone	4-Hydroxy-4'-chlorobenzophenone
Chloroform	Sodium hydroxide
Isopropanol	Thionyl chloride

Manufacturing Process

(a) Preparation of p-(4-chlorobenzoyl)-phenoxyisobutyric acid: 1 mol of 4-hydroxy-4'-chlorobenzophenone is dissolved in anhydrous acetone and then 5 mols of powdered sodium hydroxide is added. The corresponding sodium phenoxide precipitates. Refluxing is effected, and then, 1.5 mols of $CHCl_3$ diluted with anhydrous acetone is added and the resulting mixture is refluxed for 10 hours. After cooling, water is added, the acetone is evaporated, the aqueous phase is washed with ether and acidified and the organic phase is redissolved in ether and extracted into a solution of bicarbonate. The bicarbonate solution is than acidified to obtain the desired acid, having a melting point of 185°C, with a yield of 75%.

(b) Preparation of fenofibrate: 1 mol of the acid obtained is converted into its acid chloride using thionyl chloride (2.5 mols). 1 mol of the acid chloride is then condensed with 1.05 mol of isopropyl alcohol in the presence of 0.98 mol of pyridine in an inert solvent such as benzene.

Since traces of SO_2 (which has a bad smell) may be obtained from the thionyl chloride, it is preferable to avoid this disadvantage by carrying out the esterification directly.

References

Merck Index 3912
Kleeman and Engel p. 392
I.N. p. 419
Mieville, A.; US Patent 3,907,792; September 23, 1975

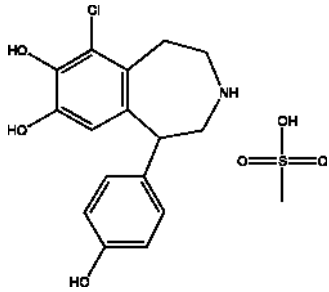
FENOLDOPAM MESYLATE

Therapeutic Function: Antihypertensive

Chemical Name: 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-, monomethanesulphonate (salt)

Common Name: Fenoldopam mesylate

Structural Formula:



Chemical Abstracts Registry No.: 67227-57-0; 67227-56-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Corlopam	Pharmaforce, Inc.	-	-
Corlopam	Abbott Laboratories	USA	-
Corlopam	SmithKline Beecham	-	-

Raw Materials

2-Chloro-3,4-dimethoxyphenethylamine
p-Methoxystyrene oxide
Boron tribromide

Manufacturing Process

2-Chloro-3,4-dimethoxyphenethylamine (1.0 g) was reacted with 0.70 g of p-methoxystyrene oxide to give the hydroxyphenethylamine; m.p. 118.5-121°C. This compound (2.16 g) was stirred at room temperature in 15 ml of trifluoroacetic acid with 4 drops of conc. sulfuric acid. After purification over a silica gel column with chloroform, 10% methanol/chloroform as eluates, was obtained 6-chloro-7,8-dimethoxy-1-p-methoxyphenyl-2,3,4,5-tetrahydro-1H-3-benzazepine (0.78 g), m.p. 143-145°C.

The trimethoxy product (0.87 g, 2.50 mmoles) in 25 ml of dry methylene chloride was cooled in an ice-methanol bath and 12.5 ml (25.0 mmoles) of boron tribromide in methylene chloride was added dropwise. After stirring for 4 hours, the mixture was cooled in an ice bath while methanol was carefully added to give 0.37 g of 6-chloro-7,8-dihydroxy-1-p-hydroxyphenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide, m.p. 215°C.

The base was regenerated from the hydrobromide salt using sodium

carbonate solution in 85% yield. Treating the base with various acids gave the following salts: dl-tartrate, fumarate, hydrochloride, sulfate, and the most water soluble one, the methanesulfonate, m.p. 272°C.

References

Gaitanopoulos D., Weinstock J.; US Patent No. 4,600,714; July 15, 1986; Assigned: SmithKline Beckman Corporation (Philadelphia, PA)
Dewey R.H.; US Patent No. 4,388,240; June 14, 1983; Assigned to SmithKline Beckman Corporation (Philadelphia, PA)
Weinstock J.; US Patent No. 4,197,297; April 8, 1980; Assigned to SmithKline Corporation (Philadelphia, PA)

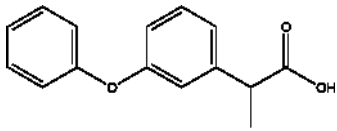
FENOPROFEN

Therapeutic Function: Antiinflammatory

Chemical Name: α-Methyl-3-phenoxybenzeneacetic acid

Common Name: m-Phenoxyhydratropic acid

Structural Formula:



Chemical Abstracts Registry No.: 31879-05-7

Trade Name	Manufacturer	Country	Year Introduced
Fenopron	Dista	UK	1974
Feprona	Lilly	W. Germany	1975
Nalfon	Dista	US	1976
Fepron	Lilly	Italy	1978
Nalgesic	Lilly	France	1979
Fenopron	Yamanouchi	Japan	1982
Fenoprex	Lilly	-	-
Progesic	Lilly	-	-

Raw Materials

Bromobenzene	m-Hydroxyacetophenone
Copper	Potassium carbonate
Sodium cyanide	Sodium borohydride
Sodium hydroxide	Phosphorus tribromide

Manufacturing Process

3-Phenoxyacetophenone: A mixture consisting of 908 grams (6.68 mols) of m-hydroxyacetophenone, 4,500 grams (28.6 mols) of bromobenzene, 996 grams (7.2 mols) of anhydrous potassium carbonate, and 300 grams of copper bronze was heated under reflux with stirring until water evolution was complete, using a Dean-Stark water separator. The mixture was then stirred and refluxed for 24 hours. After cooling to room temperature, the reaction was diluted with an equal volume of $CHCl_3$ and filtered. The filtrate was washed with 5% HCl, then with 5% NaOH, with water, dried over Na_2SO_4 and evaporated in vacuo. The residual oil was distilled through a 15 cm Vigreux column, yielding 918 grams of 3-phenoxy-acetophenone, BP 120° to 121°C (0.09 mm).

α-Methyl-3-Phenoxybenzyl Alcohol: A stirred solution of 700 grams of m-phenoxyacetophenone in 3,000 ml anhydrous methanol was cooled to 0°C in an ice-acetone bath. Sodium borohydride, 136 grams (3.6 mols) was added to this solution in small portions at such a rate that the temperature never rose above 10°C. After borohydride addition was complete, the reaction mixture was allowed to warm to room temperature and stirred for 18 hours. It was then stirred and refluxed for 8 hours. About 400 ml of methanol was distilled out and the remaining solution was evaporated to about one-third its original volume in vacuo and poured into ice water. This mixture was extracted twice with ether, acidified with 6 N HCl, and again extracted with ether. The ether extracts were combined, washed with saturated NaCl solution, dried over anhydrous sodium sulfate, and evaporated in vacuo. The residual oil was distilled through a 15 cm Vigreux column, yielding 666 grams of α-methyl-3-phenoxybenzyl alcohol, BP 132° to 134°C (0.35 mm), n_D^{25} = 1.5809.

α-Methyl-3-Phenoxybenzyl Bromide: A stirred solution of 1,357 grams of α-methyl-3-phenoxybenzyl alcohol in 5,000 ml anhydrous CCl_4 (predriedover molecular sieve) was cooled to 0°C. To this was added 1,760 grams PBr_3,stirring and cooling being maintained at such a rate that the temperature remained at 0° to 5°C, during the addition. The reaction mixture was then allowed to warm to room temperature and was stirred at room temperature overnight (ca 12 hours). The reaction mixture was then poured into ice water and the organic phase separated. The aqueous phase was extracted with CCl_4 and the combined extracts were washed three times with water, dried over anhydrous sodium sulfate and evaporated to dryness in vacuo to yield 1,702 grams of α-methyl-3-phenoxybenzyl bromide as a heavy viscous oil, n_D^{25}=1.5993.

2-(3-Phenoxyphenyl)Propionitrile: A well-stirred suspension of 316 grams of 98% sodium cyanide in 5,000 ml of anhydrous dimethyl sulfoxide (previously dried over molecular sieve) was warmed to 55° to 60°C and maintained at this temperature while 1,702 grams of α-methyl-3-phenoxybenzyl bromide was slowly added. After the bromide addition was completed, the temperature was raised to 75°C and the mixture stirred at this temperature for 1.5 hours. The mixture was then allowed to cool to room temperature and was stirred overnight at room temperature and then poured into ice water. The resulting aqueous suspension was extracted twice with ethyl acetate, and then with ether. The organic extract was washed twice with a sodium chloride solution, once with water, and dried over anhydrous sodium sulfate. Evaporation of the

solvent in vacuo left an oily residue which was distilled through a 15 cm Vigreux column to yield 1,136 grams of 2-(3-phenoxyphenyl)propionitrile, BP 141° to 148°C (0.1 mm), n_D^{25} = 1.5678.

2-(3-Phenoxyphenyl)Propionic Acid: A mixture of 223 grams of 2-(3-phenoxyphenyl)propionitrile and 400 grams of sodium hydroxide in 1,600 ml of 50% ethanol was refluxed with stirring for 72 hours. After cooling to room temperature, the reaction mixture was poured into ice water. The resulting solution was washed with ether, acidifed with concentrated HCl, and extracted with ether. The ether extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness in vacuo. The residual oil was distilled to yield 203.5 grams (84%) of 2-(3-phenoxyphenyl)propionic acid as a viscous oil; BP 168° to 171°C (0.11 mm), n_D^{25} = 1.5742.

References

Merck Index 3913
Kleeman & Engel p. 392
PDR p. 843
OCDS Vol. 2 p. 67 (1980)
DOT 8 (1) 34 (1972) & 9 (9) 373 (1973)
I.N. p. 419
REM p. 1116
Marshall, W.S.; US Patent 3,600,437; August 17, 1971; assigned to Eli Lilly and Company

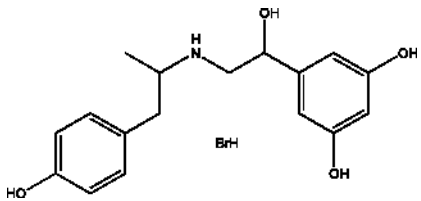
FENOTEROL HYDROBROMIDE

Therapeutic Function: Bronchodilator

Chemical Name: 3,5-Dihydroxy-α-[[(p-hydroxy-α-methylphenethyl)amino] methyl]benzyl alcohol hydrobromide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 1944-12-3; 13392-18-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Berotec	Boehringer Ingelheim	W. Germany	1972
Berotec	W.B. Pharm.	UK	1977
Dosberotec	Boehringer Ingelheim	Italy	1980
Berotec	Boehringer Ingelheim	Switz.	1982
Airum	Promeco	Argentina	-
Berotec	Fher	Spain	-
Partusisten	Boehringer Ingelheim	-	-

Raw Materials

Bromine	3,5-Diacetoxyacetophenone
Hydrogen	Hydrogen chloride
Hydrogen bromide	1-p-Methoxyphenyl-2-benzylamino propane

Manufacturing Process

441 grams (1.4 mols) of 3,5-diacetoxy-α-bromo-acetophenone (MP 66°C), prepared by bromination of 3,5-diacetoxy-acetophenone, were added to a solution of 714 grams (2.8 mols) of 1-p-methoxyphenyl-2-benzylamino-propane in 1,000 cc of benzene, and the resulting solution mixture was refluxed for 1 hour. The molar excess of 1-p-methoxy-phenyl-2-benzylamino-propane precipitated out as its hydrobromide. After separation of the precipitated hydrobromide of the amino component, the hydrochloride of 1-p-methoxy-phenyl-2-(β-3',5'-diacetoxyphenyl-β-oxo)-ethyl-benzylamino-propane was precipitated from the reaction solution by addition of an ethanolic solution of hydrochloric acid. The precipitate was separated and, without further purification, was deacetylated by boiling it in a mixture of 2 liters of aqueous 10% hydrochloric acid and 1.5 liters of methanol.

The resulting solution was filtered through animal charcoal and, after addition of 2 liters of methanol, it was debenzylated by hydrogenation at 60°C over palladinized charcoal as a catalyst. After removal of the catalyst by filtration, the filtrate was concentrated by evaporation, whereupon the hydrochloride of 1-p-methoxyphenyl-2-(β-3',5'-dihydroxyphenyl-β-oxo)-ethylamino-propane (MP 244°C) crystallized out. For the purpose of demethylation, the 350 grams of the hydrochloride thus produced were refluxed for 2 hours with 3.5 liters of aqueous 48% hydrobromic acid. Upon cooling of the reaction solution, 320 grams of 1-p-hydroxyphenyl-2-(β-3',5'-dihydroxyphenyl-β-oxo)-ethylamino-propanehydrobromide (MP 220°C) crystallized out.

220 grams of 1-p-hydroxyphenyl-2-(β-3',5'-dihydroxyphenyl-β-oxo)-ethylamino-propane hydrobromide were dissolved in 1 liter of methanol, the resulting solution was boiled with activated charcoal, the charcoal was filtered off and the filtrate was hydrogenated in the presence of Raney nickel at 60°C and 5 atmospheres gauge. Thereafter, the catalyst was filtered off, the methanolic solution was admixed with a small amount of concentrated hydrobromic acid, and the mixture was evaporated to dryness in vacuo. The residue was stirred with acetone, the mixture was vacuum filtered and the filter cake was recrystallized from a mixture of methanol and ether. The 1-p-hydroxyphenyl-2-(β-3',5'-dihydroxyphenyl-β-hydroxy)-ethylamino-propane hydrobromide thus obtained had a melting point of 222° to 223°C.

References

Merck Index 3914
Kleeman & Engel p. 393
OCDS Vol. 2 p. 38 (1980)
DOT 8 (1) 36 (1972), 9 (1) 21 (1973) & 11 (1) 20 (1975)
I.N. p. 419
Zeile, K., Thoma, O. and Mentrup, A,; US Patent 3,341,593; September 12, 1967; assigned to Boehringer Ingelheim GmbH, Germany

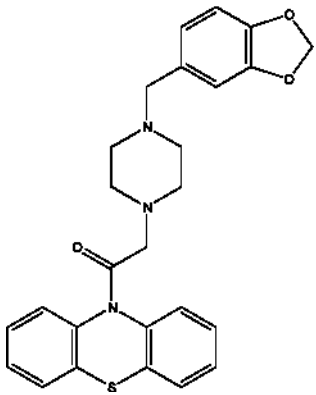
FENOVERINE

Therapeutic Function: Spasmolytic

Chemical Name: 10-((4-Piperonyl-1-piperazinyl)acetyl)phenothiazine

Common Name: Fenoverine

Structural Formula:



Chemical Abstracts Registry No.: 37561-27-6

Trade Name	Manufacturer	Country	Year Introduced
Spasmopriv	Paillusseau	-	-
Spasmopriv	Eurodrug	-	-
Fenoverine	Shanghai Lansheng Corporation	-	-
Fenoverine	CSC	-	-

Raw Materials

Phenothiazine Bromine

Chloroacetyl chloride Piperonyl-1-piperazine
Pyridine

Manufacturing Process

To a hot solution 199.3 g (0.1 mol) of phenothiazine in 2 L of dry benzene was added a little quantity of bromine and then were added dropwise 136 g (0.1 mol) of chloroacetyle chloride. Then a mixture was refluxed for 5 hours. After cooling the mixture was concentrated in vacuo. Product was dissolved at reflux in ethanol absolute and filtered. At room temperature was crystallized chloracetyl-10-phenothiazine with 123°C; yield 242 g.

A mixture of 13.8 g (0.05 mol) of chloracetyl-10-phenothiazine, 11.8 g (0.05 mol) of piperonyl-1-piperazine and 3.9 g (0.05 mol) of pyridine in 200 ml of dry toluene was refluxed for 3 hours. Then the solution was cooled and filtered. The filtrate was concentrated. The crystals of 10-((4-piperonyl-1-piperazinyl)acetyl)phenothiazine was recrystallized from isopropylic ether; M.P. 141-142°C; yield 67%.

References

Merck Index, Monograph number: 4023, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Buzas A., Pierre R.; FR Patent No. 2,092,639; June 3, 1972

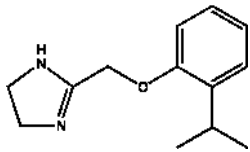
FENOXAZOLINE

Therapeutic Function: Sympathomimetic

Chemical Name: 2-[(2-Isopropylphenoxy)methyl]-2-imidazoline

Common Name: Fenoxazoline; Phenoxazoline

Structural Formula:



Chemical Abstracts Registry No.: 4846-91-7

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

Raw Materials

o-Isopropylphenyloxy acetimino ether hydrochloride
Ethylene diamine

Manufacturing Process

To a solution 257.5 g (1 mol) of o-isopropylphenyloxy-acetimino ether hydrochloride in 500 ml ethanol absolute were added 54 g (0.9 mol) of dry ethylene diamine. A mixture was refluxed for 3 hours. Then the mixture was cooled, filtered and concentrated in vacuo. o-Isopropylphenyloxy-methyl-2-imidazoline obtained was crystallized from acetone; M.P. 174°C; Yield 70%.

References

Merck Index, Monograph number: 4025, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
FR Patent No. 1,365,971; Fev.19, 1963; Assigned to Societe les Laboratoires Dausse et Societe dite: Societe B.M.C., France

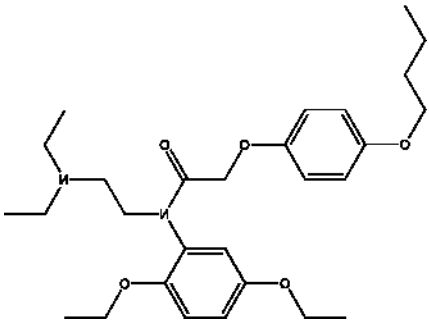
FENOXEDIL

Therapeutic Function: Vasodilator

Chemical Name: 2-(4-Butoxyphenoxy)-N-(2,5-diethoxyphenyl)-N-[2-(diethylamino)ethyl]acetamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 54063-40-4; 27471-60-9 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Suplexedil	Hepatrol	France	1974

Raw Materials

Triethylamine
Sodium amide
2,5-Diethoxyaniline
2-Diethylamino-1-chloroethane
4-Butoxyphenoxy acetyl chloride

Manufacturing Process

420 grams of 2,5-diethoxy aniline are dissolved in 4 liters of dichloroethane and 230 grams of triethylamine are added. The mixture is heated, while stirring, with 845 grams of 4-butoxy phenoxy acetyl chloride. The temperature increases towards 40°C. The mixture is then heated for 2 hours at 80°C. After cooling the product is washed with normal hydrochloric acid, then with water, then with normal sodium carbonate and finally with water.

The organic phase is dried over sodium sulfate, filtered, the dichloroethane is evaporated off and the residue is crystallized from ethyl alcohol (95%). The product is dried in the oven and there is thus obtained about 800 grams (yield 90%) of the N-(2,5-diethoxyphenyl)-4-butoxy phenoxy acetamide, MP 101°C.

A vessel provided with a mechanical agitator, a thermometer and a refrigerant, is charged with 49.2 grams of sodamide (90%) in suspension in 300 ml of anhydrous toluene, and a solution of 465 grams of amide obtained as above in 2 liters of anhydrous toluene. The solution is poured in, little by little during 1.5 hours with slight warming. The mixture is maintained for 1 hour at 80°C during which ammonia is evolved. It is cooled to 45°C, there is added, in a single quantity, 170 grams of 2-diethyl-amino-1-chloroethane and the temperature is raised slowly to 100°C and is maintained there for 10 hours.

The mixture is cooled, the organic phase washed with water and dried over sodium sulfate. The toluene is evaporated and the residue taken up in 2 liters of normal acetic acid, with cooling. It is allowed to crystallize in the cold, filtered to remove the insoluble portion and the base precipitated from the filtrate by the addition of sodium carbonate; this is extracted with dichloroethane and the organic phase dried over sodium sulfate. After evaporation of the solvent an oil is distilled, BP 225° to 230°C/0.1 mm, weight 340 grams, yield 58%. The hydrochloride prepared by the action of gaseous hydrogen chloride on this oil in ethyl ether melts at 140°C.

References

Merck Index 3916
Kleeman & Engel p. 395
DOT 11 (2) 58 (1975)
I.N. p. 420
Thuillier, G. and Geffroy, F.; US Patent 3,818,021; June 18, 1974; assigned to CERPHA (Centre Europeen de Recherches Pharmacologiques), France

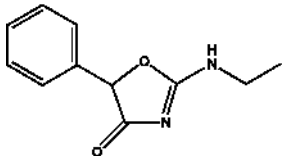
FENOZOLONE

Therapeutic Function: Psychostimulant

Chemical Name: 2-Oxazolin-4-one, 2-ethylamino-5-phenyl-

Common Name: Ethylpemoline; Fenozolone; Phenozolone

Structural Formula:



Chemical Abstracts Registry No.: 15302-16-6

Trade Name	Manufacturer	Country	Year Introduced
Fenozolone	Shanghai Lansheng Corporation	-	-
Ordinator	Synthelabo		-
Ordinator	Dausse	-	-

Raw Materials

Ethyl urea
α-Chlorophenyl acetyl chloride
Sodium

Manufacturing Process

Into a 3-necked spherical flask of 1 L provided with a dropping funnel, a condenser surmounted by a calcium chloride tube and a mechanical stirrer, is introduced a suspension of 17.6 g (0.2 mol) of ethyl urea in 150 ml of anhydrous benzene. There is added through the dropping funnel in 20 minutes a solution of 18.9 g (0.1 mol) α-chlorophenyl-acetyl chloride in 300 ml of benzene. The mixture is left at ambient temperature for 15 minutes and is then heated under reflux on the water bath with stirring for 5 hours. The benzene solution is decanted at elevated temperature in order to separate it from an oil deposited on the bottom of the flask, the benzene is driven off on the water bath, the last traces removed in vacuum, the crystalline residue is triturated in a mortar in about 200 ml of water, and the crystalline solid is separated off and is with water and dried in vacuum over phosphorus pentoxide. There are thus recovered 19.6 g (yield 82%) of 1-(2-chloro-2-phenyl-acetyl)-3-ethyl-urea, which when recrystallized from 80 ml of benzene, takes the form of white crystals soluble in benzene but insoluble in water. The product has melting point 146°C.

To a suspension of 39 g (0.163 mol) of 1-(2-chloro-2-phenyl-acetyl)-3-ethyl-urea in 250 ml of anhydrous ethyl alcohol is added a sodium ethoxide solution containing 3.75 g (0.163 mol) of sodium dissolved in 250 ml of ethyl alcohol. The mixture is heated under reflux for 2 hours and left overnight at ambient temperature. The precipitated sodium chloride is separated off and copiously washed with alcohol. The alcohol is driven off from the filtrate on the water bath, the oily residue is triturated in 20 ml of iced water, and the solid formed is refrigerated for several hours, separated, washed with water and dried in vacuum over phosphorus pentoxide. The 5-phenyl-2-ethylamino-4-oxazolinone (fenozolone) obtained is recrystallized from anhydrous benzene. It then forms a white crystalline compound soluble in benzene and insoluble in water, MP: 148°C.

References

G.B. Patent No. 963,375; Feb. 23, 1962; Assigned: Les Laboratoires Dausse, A French Body Corporate, of 4 rue Aubriot, Paris, France

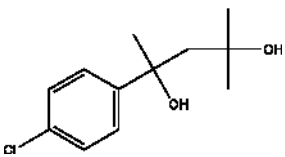
FENPENTADIOL

Therapeutic Function: Antidepressant, Tranquilizer

Chemical Name: 2,4-Pentanediol, 2-(p-chlorophenyl)-4-methyl-

Common Name: Fenpentadiol; Phenpentanediol

Structural Formula:



Chemical Abstracts Registry No.: 15687-18-0

Trade Name	Manufacturer	Country	Year Introduced
Tredum	Heacutepatrol	-	-
Fenpentadiol	Shanghai Lansheng Corporation	-	-

Raw Materials

2-(p-Chlorophenyl)-3-hydroxybytiric acid ethyl ester
Methylmagnesium iodide

Manufacturing Process

2-(p-Chlorophenyl)-4-methylpentane-2,4-diol (M.P. 76.5°C) was synthesized and condensation of 2-(p-chlorophenyl)-3-hydroxybytiric acid ethyl ester with CH_3 MgI in ether.

References

Merck Index, Monograph number: 4029, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Rolland A., Brevet Special de Medicament FP-M1984, Jul. 26, 1962
Arzneimittelforshung 1971; 21: 1-15

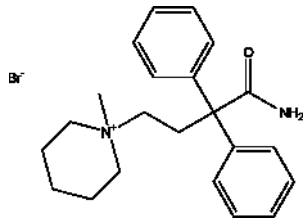
FENPIVERINIUM BROMIDE

Therapeutic Function: Spasmolytic

Chemical Name: Piperidinium, 1-(4-amino-4-oxo-3,3-diphenylbutyl)-1-methyl-, bromide

Common Name: Bulgar amide; Fenpipramide methylbromide; Fenpiverinium bromide

Structural Formula:



Chemical Abstracts Registry No.: 125-60-0

Trade Name	Manufacturer	Country	Year Introduced
Fenpiverinium bromide	R L Fine Chem	-	-

Raw Materials

Diphenylpiperidine ethyl acetonitrile
2-Piperidinoethyl chloride
Methyl bromide

Manufacturing Process

17.5 g diphenylpiperidine ethyl acetonitrile, prepared from sodium amide and 2-piperidinoethyl chloride (D.B. Patent No. 710,227) was heated to reflux with 35 g KOH, 70 ml ethanol and 2 ml water for 6 hours. On cooling rich white crystals dropped. They was filtered off, washed with water to neutral and dried. Then the product was recrystallized from ethanol. Yield of diphenylpiperidine ethyl acetamide 15 g. MP: 186°-187°C.

10 g diphenylpiperidine ethyl acetamide was mixed with 42 g of 17% solution methyl bromide in benzene and 60 ml isopropanol and heated to reflux on a steam bath for 0.5 hour. The solvent was distilled in vacuum to dryness, dissolved in 100 ml of water and the very muddy solution was through a coal filtered. The clear filtrate was distilled off to dryness. Fenpiverinium bromide was light dissolved in water and had neutral reaction.

References

Bockmuhl M. et al.; DB Patent No. 731,560; Feb. 11, 1943; I.G.Farbenindustrie AG. In Frankfurt, Main

Ehrhart G.; DB Patent No. 858,552; Dec. 8, 1952; Farbwerke Hoechst, vormaaals Meister Lucius and Bruning Frankfurt/M.-Hochst

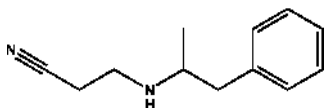
FENPROPOREX

Therapeutic Function: Anorexic

Chemical Name: 3-[(1-Methyl-2-phenylethyl)amino]propanenitrile

Common Name: N-2-Cyanoethylamphetamine

Structural Formula:



Chemical Abstracts Registry No.: 15686-61-0

Trade Name	Manufacturer	Country	Year Introduced
Fenproporex	Chephasaar	W. Germany	1975
Fenproporex	Bottu	France	1977
Desobesi	Luer	Brazil	-
Fenorex	Biosintetica	Brazil	-
Lineal	Roussel	-	-
Lipolin	ICN-Usafarma	Brazil	-
Perphoxene	Bottu	France	-

Trade Name	Manufacturer	Country	Year Introduced
Perphoxene	Siegfried	Switz.	-
Tegisec	Roussel	-	-

Raw Materials

Acrylonitrile
α-Methyl-β-phenylethylamine
Hydrogen chloride

Manufacturing Process

(a) 22 g of acrylonitrile and 27 g of racemic α-methyl-β-phenylethylamine were introduced into a 100 ml round-bottomed flask and left standing for 13 hours at ambient temperature, and then the mixture was boiled under reflux for 12½ hours. The excess acrylonitrile was then evaporated in vacuo and the residue distilled. 27.3 g (yield: 72.6%) of racemic N-(β-cyanoethyl)-α-methyl-β-phenylethylamine were obtained as an oily liquid, BP = 126°C to 127°C/2 mm Hg.

(b) 22 g of the base obtained in (a) were dissolved in 80 ml of anhydrous diethyl ether and an ethereal solution of hydrochloric acid added until the pH value was 1. The salt was filtered off, dried and washed with 10 ml of diethyl ether. 18 g (yield: 68%) of N-(β-cyanoethyl-α-methyl-β-phenylethylamine hydrochloride were obtained, after recrystallization from absolute ethanol, as a white, microcrystalline, odorless powder having a bitter, acid taste; it was fairly soluble in water, ether and benzene. MP = 146°C on a Kofler block.

References

Merck Index 3922
DOT 9 (6) 213 (1973)
I.N. p. 420
Rohrbach, P. and Blum, J.; US Patent 3,485,924; December 23, 1969; assigned to Manufactures J.R. Bottu (France)

FENSPIRIDE

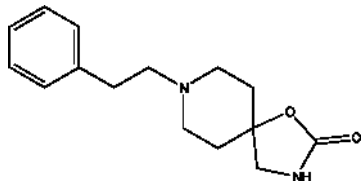
Therapeutic Function: Bronchodilator

Chemical Name: 8-(2-Phenylethyl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one

Common Name: Decaspiride

Chemical Abstracts Registry No.: 5053-06-5; 5053-08-7 (Hydrochloride salt)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Viarespan	Servier	France	1969
Respiride	Schiapparelli	Italy	1979
Abronquil	Soubeiran Chobet	Argentina	-
Decaspir	Pulitzer	Italy	-
Espiran	Fardeco	Italy	-
Fendel	Sidus	Argentina	-
Fluiden	Lafare	Italy	-
Pneumorel	Biopharma	France	-
Teodelin	Cuatrecasas-Darkey	Spain	-

Raw Materials

1-(2-Phenylethyl)-4-piperidone
Potassium cyanide
Lithium aluminum hydride
Diethyl carbonate

Manufacturing Process

A solution of 192 g of 1-phenethyl-4-hydroxy-4-aminomethyl piperidine in 800 cc of diethylcarbonate is heated for 2½ hours to reflux at about 80°C in the presence of sodium methylate (prepared for immediate use from 2 g of sodium). After this time, the ethyl alcohol formed during the reaction is slowly distilled while the maximum temperature is reached. The excess ethyl carbonate is distilled under reduced pressure. A crystallized residue is then obtained, which is stirred with 400 cc of water and 400 cc of ether. The solution is filtered and 125 g (77.6%) of practically pure product melting at 232°C to 233°C, are obtained.

The starting material was prepared in a yield of 58% by reduction of the corresponding cyanohydrin. It in turn was prepared from 1-(2-phenylethyl)-4-piperidone and potassium cyanide to give the cyanohydrin which was reduced by lithium aluminum hydride.

References

Merck Index 3924
Kleeman & Engel p. 397
OCDS Vol. 2 p. 291 (1980)

DOT 5 (4) 130 (1969)
I.N. p. 421
Regnier, G., Canevari, R. and Le Douarec, J.-C.; US Patent 3,399,192; August 27, 1968; assigned to Science Union et Cie, Societe Francaise de Recherche Medicale, France

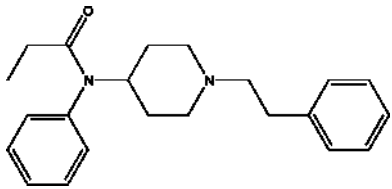
FENTANYL

Therapeutic Function: Narcotic analgesic

Chemical Name: N-Phenyl-N-[1-(2-phenylethyl)-4-piperidinylpropanamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 437-38-7

Trade Name	Manufacturer	Country	Year Introduced
Fentanyl	Janssen	W. Germany	1963
Sublimaze	Janssen	UK	1965
Fentanest	Carlo Erba	Italy	1965
Sublimaze	McNeil	US	1968
Fentanest	Sankyo	Japan	1972
Fentanyl Le Brun	Le Brun	France	1973
Beatryl	Abic	Israel	-
Haldid	Janssen	-	-
Innovar	McNeil	US	-
Leptanal	Leo	Sweden	-
Thalamonal	Janssen	W. Germany	-

Raw Materials

Aniline
1-Benzyl-4-piperidone
Hydrogen
Lithium aluminum hydride
Propionic anhydride
β-Phenylethyl chloride

Manufacturing Process

To the stirred solution of 5 parts of N-(4-piperidyl)propionanilide, 6.85 parts sodium carbonate, 0.05 part potassium iodide in 120 parts hexone is added portionwise a solution of 3.8 parts β-phenylethyl chloride in 24 parts 4-methyl-2-pentanone. The mixture is stirred and refluxed for 27 hours. The reaction mixture is filtered while hot, and the filtrate is evaporated. The oily residue is dissolved in 160 parts diisopropyl ether and the solution is filtered several times until clear, then concentrated to a volume of about 70 parts. The residue is then cooled for about 2 hours at temperatures near 0°C to yield N-[1-(β-phenylethyl)-4-piperidyl]propionanilide, melting at about 83° to 84°C as described in US Patent 3,141,823.

The starting material is prepared by reacting 1-benzyl-4-piperidone with aniline, reducing the condensation product with lithium aluminum hydride, reacting the product thus obtained with propionic anhydride, then hydrogen.

References

Merck Index 3926
Kleeman & Engel p. 397
PDR pp. 954, 957
OCDS Vol. 1 pp. 299, 306, 309 (1977) & 3 p. 116 (1984)
DOT 1 (1) 1 (1965)
I.N. p. 421
REM p.1108
Janssen, P.A.J. and Gardocki, J.F.; US Patent 3,141,823; September 4, 1962; assigned to Research Laboratorium Dr. C. Janssen NV, Belgium
Janssen, P.A.J.; US Patent 3,164,600; January 5, 1965; assigned to Research Laboratorium Dr. C. Janssen, NV, Belgium

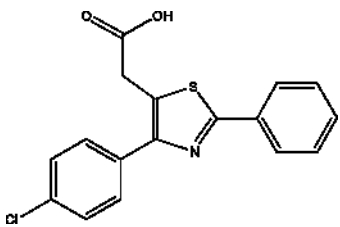
FENTIAZAC

Therapeutic Function: Analgesic, Antipyretic, Antiinflammatory

Chemical Name: 4-(p-Chlorophenyl)-2-phenyl-thiazol-5-yl-acetic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 18046-21-4

Trade Name	Manufacturer	Country	Year Introduced
Norvedan	LPB	Italy	1975
Norvedan	Nippon Chemiphar	Japan	1982
Donorest	Wyeth	Japan	1982
Domureuma	Medici Domus	Italy	-
Flogene	Polifarma	Italy	-

Raw Materials

Benzonitrile
Acetic acid
Potassium thioacetate
Potassium hydroxide
Methyl 3-(p-chlorobenzoyl)-3-bromopropionate

Manufacturing Process

13.6 g methyl 3-(p-chlorobenzoyl)-3-bromopropionate in 30 ml methanol are added to a solution of 5.6 g potassium thioacetate in 30 ml methanol. Immediate precipitation of KBr is observed. The suspension is refluxed for 10 minutes.

It is cooled to ambient temperature, filtered, and the methanol is evaporated to dryness. 13.2 g methyl 3-(p-chlorobenzoyl)-3-thioacetylpropionate in the form of a chromatographically pure orange-colored oil are obtained.

A suspension of 13.2 g methyl 3-(p-chlorobenzoyl)-3-thioacetylpropionate is agitated in 500 ml of a 2 N aqueous solution of KOH for 6 hours at ambient temperature in an atmosphere of nitrogen, followed by extraction with ethyl ether. The aqueous phase, adjusted to a pH equal to 2 with 2N HCl, is extracted with ethyl ether which was washed with water, dried over Na_2SO_4, and finally evaporated to dryness.

9.8 g of crude 3-(p-chlorobenzoyl)-3-mercaptopropionic acid are obtained. By recrystallizing from isopropyl ether there are obtained 8.6 g of pure product, MP 96°C to 97°C (yield: 79%).

1.7 ml benzonitrile and 5.05 ml diethylamine are added to a solution of 4 g 3-(p-chlorobenzoyl)-3-thiol-propionic acid in 50 ml ethanol. The solution is agitated at ambient temperature for 60 minutes in an atmosphere of nitrogen. It is then evaporated to a syrupy consistency and 60 ml 50% aqueous acetic acid are added, whereupon the mixture is refluxed for 60 minutes. It is evaporated to a small volume, adjusted to a pH equal to 8 with a saturated solution of sodium bicarbonate and then extracted with ethyl ether. The aqueous phase is acidified with 2N HCl (Congo red), and then again extracted with ethyl ether. It is dried over Na_2SO_4 and evaporated to dryness. The evaporation residue is recrystallized from benzene and 4 g 4-(p-chlorophenyl)-2-phenyl-thiazol-5-yl-acetic acid are obtained (MP = 152°C to 154°C, yield - 74.3%).

References

Merck Index 3928
DOT 11 (9) 351 (1975) & 15 (7) 325 (1979)
I.N. p. 421
Laboratorio Prodotti Biologici Braglia SpA; British Patent 1,380,507; January 15, 1975
Brown, K.; US Patent 3,476,766; November 4, 1969; assigned to John Wyeth & Brother Ltd.

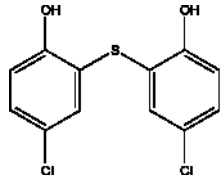
FENTICLOR

Therapeutic Function: Antifungal

Chemical Name: Bis(2-hydroxy-5-chlorophenyl)sulfide

Common Name: Chlorhydrosulfide; Dichlorodihydroxydiphenyl sulfide; Fenticlor; Phentichlorum

Structural Formula:



Chemical Abstracts Registry No.: 97-24-5

Trade Name	Manufacturer	Country	Year Introduced
Fenticlor	Shanghai Lansheng Corporation	-	-
Fenticlor	Isochem	-	-
Fenticlor	Dr. Ehrenstorfer Laboratories	-	-
Ovitrol	Rodleben	-	-

Raw Materials

Sulfuryl chloride
Bis-(2-hydroxy-phenyl)-sulfide
Chlorine

Manufacturing Process

1 mol bis(2-hydroxy-phenyl)-sulfide, prepared from sulfuryl chloride and

phenol, in about 2500 ml glacial acetic acid was dissolved and heated for boiling. 2-3 mol gaseous chlorine was passed through that solution and on cooling bis(2-oxy-5-chlorphenyl)sulfide was fallen. It was recrystallized from acetic acid or light petroleum. MP: 175°C. A residue was dropped from filtrate with water as the white crystals, which melted at the same temperature.

Fenticlor may be also prepared by adding sulfuryl chloride to the solution of bis(2-hydroxy-phenyl)sulfide in dichlorobenzene.

References

Muth F.; DR Patent No. 568,944; Nov. 1, 1931; I.G.Farbenindustrie Akt.-Ges. in Frankfurt a. M.

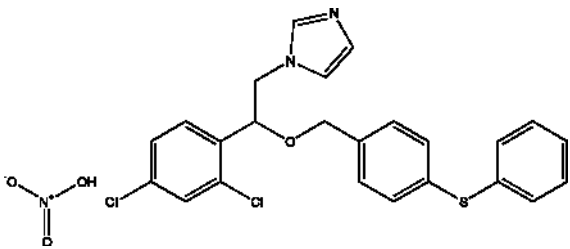
FENTICONAZOLE NITRATE

Therapeutic Function: Antifungal

Chemical Name: 1H-Imidazole, 1-(2-(2,4-dichlorophenyl)-2-((4-(phenylthio) phenyl)methoxy)ethyl)-, mononitrate

Common Name: Fenticonazole nitrate; Terlomexin

Structural Formula:



Chemical Abstracts Registry No.: 72479-26-6 (Base); 73151-29-8

Trade Name	Manufacturer	Country	Year Introduced
Lomexin	Effik	-	-
Falvin	Theramex	-	-
Fenizolan	Organon	-	-
Fentigyn	Effik	-	-
Fentikol	Zorka Pharma	-	-
Gyno-Lomexin	Organon	-	-
Gynoxin	Recordati	-	-
Terlomexin	Effik	-	-

Raw Materials

Imidazole	Sodium borohydride
Sodium	1-(1'-Hydroxy-2'-chloroethyl)-2,4-dichlorobenzene
Sodium hydride	1-Chloromethyl-4-phenylthiobenzene
Nitric acid	Potassium iodide

Manufacturing Process

1-(2',4'-Dichlorophenyl)-2-chloroethanol:

49.5 g of sodium borohydride were added slowly and in small parts to a suspension of 233 g of 1-(1'-hydroxy-2'-chloroethyl)-2,4-dichlorobenzene in 1 liter of methanol stirred at room temperature. The solution thus obtained was stirred at room temperature for a further two hours, and it was then poured into 1 liter of 5 N hydrochloric acid cooled with ice. After extraction with ethyl acetate or chloroform, the extract was washed with water, with 1 N sodium hydroxide, then again with water until neutrality, and finally with a saturated sodium chloride solution. The extract was dried, the solvent evaporated off and 220 g of an oil were obtained. The oil solidified on standing and the solid 1-(2',4'-dichlorophenyl)-2-chloro-ethanol melted at 48-51°C.

1-(2',4'-Dichlorophenyl)-2-(N-imidazolyl)ethanol:

30 g of sodium were added to a solution of 88.5 g of imidazole in 600 ml of methanol; the solvent was then evaporated off. The residue was dissolved in 300 ml of dimethylformamide and heated to 115-120°C. To the solution so obtained was added, dropwise and under stirring, a solution of 225 g of 1-(2',4'-dichlorophenyl)-2-chloroethanol in 400 ml of dimethylformamide. The mixture was heated to 115-120°C and maintained at that temperature for 20 min and, after subsequent cooling to 40°C, 2500 ml of iced water were added under vigorous stirring. The product precipitated under stirring over a period of about two hours, the upper liquid was then decanted off, a further 2500 ml of water were added and, after standing, the whole was filtered. The precipitate thus obtained was dried and crystallized from toluene. 170 g of the 1-(2',4'-dichlorophenyl)-2-(N-imidazolyl)ethanol, melting at 134-135°C, was obtained.

1-[2,4-Dichloro-beta-[[p-(phenylthio)benzyl]oxy]phenethyl]imidazole:

METHOD 1:

A solution of 2.57 g of 1-(2',4'-dichlorophenyl)-2-(N-imidazolyl)ethanol in 10 ml of hexamethylphosphoramide was dropped at 25°C into a suspension of 0.52 g of sodium hydride (50% in oil) in 5 ml of hexamethylphosphoramide. When hydrogen emission was over, the salification was completed by heating for 1 hour at 50°C. After cooling to 25°C, 2.58 g of 1-chloromethyl-4-phenylthiobenzene were added. The temperature was raised to 50°C and maintained at that temperature for 12 hours. At the end of the reaction, the mixture was poured into 200 ml of water, the product was extracted with diethyl ether, the solvent was evaporated off and the residue was purified twice on a silica gel column, using ethyl acetate as eluant and testing the various fractions by TLC. The solvent was evaporated off the middle fractions

to give 2.4 g of the 1-[2,4-dichloro-beta-[[p-(phenylthio)benzyl]oxy] phenethyl]imidazole as a yellowish oil, showing a single spot on TLC.

METHOD 2:

0.66 g of sodium hydride (50% in oil) were added at 20-30°C and under nitrogen atmosphere to 3.86 g of 1-(2',4'-dichlorophenyl)-2-(N-imidazolyl) ethanol in 15 ml of dimethylsulphoxide (dried on calcium hydride). The mixture was heated under stirring at 50-60°C until gas emission was over. After cooling to 20-25°C, 0.5 g of potassium iodide were added and slowly a solution of 3.51 g of 1-chloromethyl-4-phenylthiobenzene in 4 ml of dimethylsulphoxide was dropped in. The mixture was stirred at 20-25°C until addition of the 1-chloromethyl-4-phenylthiobenzene was over. The mixture was then poured into 150 ml of water and extracted with diethyl ether. To the etheric solution, after drying on anhydrous sodium sulphate, was added excess 4 N nitric acid solution in diethyl ether: the desired product precipitated as nitrate, an oil which solidified on standing. After standing for 20 hours, the etheric liquid was decanted off and the residue was crystallized from ethanol. The nitrate thus obtained, not completely pure, was dissolved in water and excess sodium carbonate was added in order to liberate the base which was then extracted with ethyl acetate. The base, obtained by filtration, was purified on a silica gel column using ethyl acetate as eluant. The combined fractions containing the desired product were evaporated to dryness. The residue was dissolved in diethyl ether, again transformed into the nitrate and crystallized from ethanol. Yield: 3.1 g of a white crystalline powder, melting at 136°C; λ_{max} 252 nm (methanol).

References

Nardi D., Massarani E. et al.; US Patent No. 4,221,803; Sept. 9, 1980; Assigned to Recordati, S.A. (Chiasso, CH)

FENTONIUM BROMIDE

Therapeutic Function: Anticholinergic, Spasmolytic

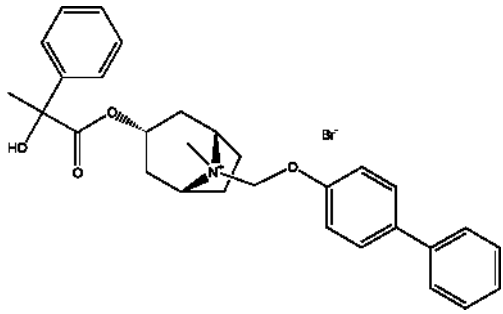
Chemical Name: [3(S)-endo]-8-[2-[1,1'-Biphenyl]-4-yl-2-oxaethyl)-3-(2-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-azoniabicyclo[3.2.1]octane bromide

Common Name: -

Chemical Abstracts Registry No.: 5868-06-4

Trade Name	Manufacturer	Country	Year Introduced
Hoelcesium	Zambon	Italy	1972
Ulcesium	Inpharzam	W. Germany	1978
Dicasten	Fher	Spain	-
Ketoscilium	Zambon	Italy	-

Structural Formula:



Raw Materials

p-Phenylphenacyl bromide
1-Hyoscyamine

Manufacturing Process

5.50g (0.02 mol) of p-phenylphenacyl bromide were dissolved in 56 cc of anhydrous acetone previously heated to about 40°C. This solution was added, with stirring, to a solution of 5.70 g (0.02 mol) of 1-hyoscyamine in 43 cc of anhydrous acetone; the reaction solution was maintained at 45°C and stirred for about six hours.

After standing overnight in the refrigerator, the precipitate was collected by filtration and dried in vacuo at 60°C. Yield: 10.2 g; MP = 193°C to 194°C.

References

Merck Index 3930
Kleeman & Engel p. 398
I.N. p. 422
Teotino, U. and Della Bella, D.; US Patent 3,356,682; December 5, 1967 and US Patent 3,436,458; April 1, 1969; both assigned to Whitefin Holding S.A. (Switz.)

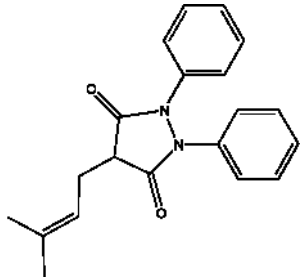
FEPRAZONE

Therapeutic Function: Antiinflammatory

Chemical Name: 1,2-Diphenyl-(3,5-dioxo-4-(3'-methyl-2'-butenyl)-pyrazolidine

Common Name: Phenylprenazone; Prenazone

Structural Formula:



Chemical Abstracts Registry No.: 30748-29-9

Trade Name	Manufacturer	Country	Year Introduced
Zepelin	De Angeli	Italy	1972
Methrazone	W.B. Pharm.	UK	1977
Zepelin	Boehringer Ingelheim	W. Germany	1980
Zontal	Fujisawa	Japan	1983
Analud	Unifa	Argentina	-
Brotazona	Escaned	Spain	-
Danfenona	Larma	Spain	-
Grisona	Cusi	Spain	-
Metrazone	Boehringer Ingelheim	Spain	-
Naloven	De La Cruz	Spain	-
Nazona	Reig Jofre	Spain	-
Nilatin	Llenas	Spain	-
Prenazon	Inexfa	Spain	-
Rangozona	Mazuelos	Spain	-
Represil	Cecef	Spain	-
Tabrien	Callol	Spain	-
Zepelin	Bender	Austria	-
Zoontal	Boehringer Ingelheim	-	-

Raw Materials

Hydrazobenzene
Sodium
Diethyl-3-methyl-2-butenyl malonate
Ethanol

Manufacturing Process

43.8 g (0.237 mol) of hydrazobenzene are added to a solution of sodium ethylate obtained by dissolving 6.55 g (0.285 mol) of sodium in 125 ml of anhydrous ethanol. 59.6 g (0.2612 mol) of diethyl 3-methyl-2-butenyl

malonate are then added, with stirring, at the reflux temperature.

The reaction mixture is refluxed for 1 hour, then the solvent is slowly distilled off, the distillation being completed in vacuo. The solid residue so obtained is dissolved in 400 ml of water and washed with ether. The solution is acidified with 10% HCl and the 1,2-diphenyl-3,5-dioxo-4-(3'-methyl-2'-butenyl)-pyrazolidine which separates is purified by crystallization from ethanol (MP 155°C to 156°C).

References

Merck Index 3934
DOT 8 (10) 330 (1972)
I.N. p. 422
Casadio, S, and Pala, G.; US Patent 3,703,528; November 21, 1972; assigned to Instituto de Angeli S.p.A.

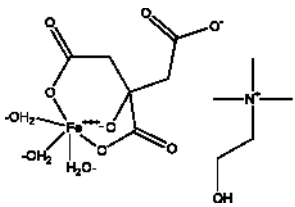
FERROCHOLINATE

Therapeutic Function: Hematinic

Chemical Name: [Hydrogen citrato(3)]triaquoiron, choline salt

Common Name: Iron choline citrate

Structural Formula:



Chemical Abstracts Registry No.: 1336-80-7

Trade Name	Manufacturer	Country	Year Introduced
Ferrolip	Flint	US	1953
Chel-Iron	Kinney	US	1957

Raw Materials

Ferric hydroxide
Tricholine citrate
Choline dihydrogen citrate
Ferric citrate

Manufacturing Process

As described in US Patent 2,575,611, 107 parts of freshly prepared ferric hydroxide are added to 295 parts of choline dihydrogen citrate dissolved in 200 parts of distilled water and heated to approximately 80°C until a homogeneous solution occurs. The resulting reddish brown solution may be used as such or it may be dried by evaporating the water. The dried product is a reddish brown, amorphous solid presenting a glistening surface upon fracture. The dry product is somewhat hygroscopic and is freely soluble in water to give a stable solution. The following paragraph gives an alternative preparation.

One mol of tricholine citrate is dissolved in 6,000 ml of water and two mols of ferric citrate in solid form are added thereto. The reaction mass is then agitated until solution is effected, and until the reaction mass changes from brown to green. Water is removed either under vacuum, or as an azeotrope with benzene or toluene or by heating to a temperature of 110° to 115°C. There is thus obtained a gummy viscous mass which is treated with methanol, about five gallons, whereupon it solidifies, i.e., changes, into a green crystalline compound. Following the treatment with methanol, the mass is filtered and the green compound dried at about 70°C, according to US Patent 2,865,938.

References

Merck Index 3970
I.N. p. 423
Bandelin, F.J.; US Patent 2,575,611; November 20, 1951; assigned to Flint Eaton and Company
Rosenfelder, W.J.; US Patent 2,865,938; December 23, 1958

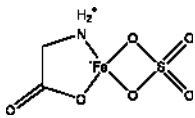
FERROGLYCINE SULFATE

Therapeutic Function: Hematinic

Chemical Name: Ferroglycine sulfate ($(FeSO_4)$ x $(NH_2CH_2COOH)_y$)

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 17169-60-7

Trade Name	Manufacturer	Country	Year Introduced
Ferronord	Cooper	US	1956
Fe-Cap	MCP Pure Drugs	UK	1970
Bonafer	Remeda	Finland	-
Ferrochel	C.F.C.	Australia	-
Ferrocontin	Napp	UK	-
Ferrosanol	Sanol	W. Germany	-
Glycifer	Pharmacia	Sweden	-
Orferon	Pliva	Yugoslavia	-
Plesmet	Napp	UK	-

Raw Materials

Ferric sulfate
Glycine

Manufacturing Process

10.0 g of ferrous sulfate and 2.7 g of glycine are thoroughly mixed and carefully heated under nitrogen to 70°C. Reaction occurs rapidly, and the complex compound is obtained as soon as the color turns uniformly light-brown. After cooling to 20°C, 12.7 g of ferrous sulfate-glycine complex are obtained, which contains 100 mg Fe^{++}-ion sper 0.63 g.

References

Merck Index 3972
I.N. p. 12
Rummel, W.; US Patent 2,877,253; March 10, 1959; assigned to Dr. Schwarz Arzneimittelfabrik GmbH, Germany
Rummel, W.; US Patent 2,957,806; October 25, 1960; assigned to Dr. Schwarz Arzneimittelfabrik GmbH, Germany

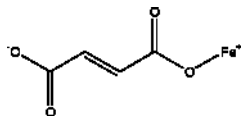
FERROUS FUMARATE

Therapeutic Function: Hematinic

Chemical Name: Ferrous fumarate ($FeC_4H_2O_4$ (exact structure unknown))

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 141-01-5

Trade Name	Manufacturer	Country	Year Introduced
Toleron	Mallinckrodt Inc.	US	1957
Ircon	Key	US	1960
Tolferain	Ascher	US	1961
Feostat	Westerfield	US	1962
Ferlon	Madland	US	1964
Eldec	Parke Davis	US	-
Ercofer	Erco	Denmark	-
Fem-Iron	Williams	US	-
Feosol	Menley and James	US	-
Feostim	Westerfield	US	-
Fero-Folic	Abbott	US	-
Fero-Grad	Abbott	US	-
Feroton	Paul Maney	Canada	-
Ferro-Delalande	Delalande	France	-
Ferrofume	Nordic	Canada	-
Ferrolina	Chemie Linz	Austria	-
Ferronat	Galena	Czechoslovakia	-
Ferrone	Wolfs	Belgium	-
Ferrum Hausmann	Hausmann	Switz.	-
Fersaday	Glaxo	-	-
Fersamal	Glaxo	-	-
Ferumat	Continental Pharma	Belgium	-
Firon	Beard Glynn	US	-
Fumafer	Erco	Denmark	-
Fumafer	Aktiva	Sweden	-
Fumasorb	Marion	US	-
Fumiron	Knoll	W. Germany	-
Hematon	Nova	Canada	-
Heptuna	Roerig	US	-
Iberet	Abbott	US	-
Ircon	Lakeside	US	-
Irospan	Fielding	US	-
Mevanin	Beutlich	US	-
Neo-Fer	Nyegaard	Norway	-
Novofumar	Novopharm	Canada	-
Palafer	Beecham	-	-
Pramet	Ross	US	-
Soparon	Sopar	Belgium	-
Tolifer	Elliott-Marion	Canada	-

Raw Materials

Fumaric acid
Sodium carbonate
Ferric sulfate

Manufacturing Process

Sodium carbonate (53.5 pounds of Na_2CO_3-H_2O) was dissolved in water (40 to 45 gallons) and fumaric acid (50 pounds) was added slowly. During the addition the solution was stirred and heated. The resulting solution of sodium fumarate, having a pH of 6.8, was added slowly with mixing to a solution of ferrous sulfate (118 pounds $FeSO_4$-$7H_2O$ in 33 gallons of water) having a pH of 3.3, both solutions being maintained at or near boiling temperature during the mixing. The resulting slurry of reddish-brown anhydrous ferrous fumarate was filtered and washed in a centrifuge and dried in a tray drier (15 hours at 110°C). Yield: 63 pounds, 86% of theory. Calculated for $FeC_4H_2O_4$: Fe, 32.9%. Found: Fe, 32.6%. Only 0.2% of ferric iron (Fe_{+++}) was found.

References

Merck Index 3981
PDR pp. 524, 673, 876, 993, 1131, 1344, 1526, 1559, 1569
I.N. p. 447
REM p. 840
Bertsch, H.C. and Lemp, J.F.; US Patent 2,848,366; August 19, 1958; assigned to Mallinckrodt Chemical Works

FERUMOXSIL

Therapeutic Function: Diagnostic aid (radiopaque medium)

Chemical Name: See structure

Common Name: -

Structural Formula: Poly[N-(2-aminotethyl)-3-aminopropyl]siloxane-coated non-stoichiometric magnetite

Chemical Abstracts Registry No.: Not applicable to mixtures

Trade Name	Manufacturer	Country	Year Introduced
GastroMARK	Advanced Magnetics, Inc.	USA	-
GastroMARK	Mallinckrodt Inc.	-	-
Lumirem	Guerbet S.A.	France	-

Raw Materials

Ferric chloride
Phosphorous acid
Sodium hydroxide
3-Aminopropyltrimethoxysilane

Manufacturing Process

Preparation of Metal Oxide

A solution of 0.5 M ferrous chloride ($FeCl_2$) and 0.25 M ferric chloride ($FeCl_3$) (200 ml) was mixed with 5 M sodium hydroxide (200 ml) at 60°C by pouring both solutions to 100 ml of distilled water. The mixture was stirred for 2 min during which time a black, magnetic precipitate formed. After settling, the volume of the settled precipitate was approximately 175 ml. The concentration of iron oxide in the precipitate was about 60 mg/ml. The precipitate was then washed with water until a pH of 6-8 was reached.

The following washing technique was employed. The particles were suspended in 1.8 L of water in a beaker and collected by magnetic extraction. The beaker was placed on top of a ring magnet, 1/2 inch high and 6 inches in diameter, which caused the magnetic particles to settle. The water was poured off without the loss of particles by holding the magnet to the bottom of the beaker while decanting. Typically, three washes were sufficient to achieve neutral pH. The magnetic oxide was then washed once with 1.0 liter of 0.02 M sodium chloride.

The water was then replaced with methanol. This was accomplished by aspirating 800 ml of 0.2 M NaCl and bringing the total volume to 1 L with methanol. The material was resuspended, and magnetically extracted; 800 ml of supernatant were removed, and another 800 ml of methanol were added. After three additions of methanol, the oxide was ready for silanization in a solution which was approximately 1% (V/V) water. A portion of the precipitate was dried at 70°C for 24 hours and weighed; 11.2 g of magnetic iron oxide were formed.

Silanization

Superparamagnetic iron oxide with Fe^{2+}/Fe^{3+} ratio of 2 was washed with water. 1 g of particles (about 20 ml of settled particles) was mixed with 2 g of ortophosphorous acid and then with 100 ml of a 10% solution of 3-aminopropyltrimethoxysilane in water. The pH was adjusted to 4.5 with glacial acetic acid. The mixture was mixed for 2 hours at 90-95°C. After cooling, the particles were washed 3 times with water (100 ml), 3 times with methanol (100 ml) and 3 times with water (100 ml). Both the heating and cooling steps were performed under nitrogen with stirring.

Preparation of Carboxylic Acid-Terminated Magnetic Particles

A superparamagnetic iron oxide was silanized with 3-aminopropyltrimethyoxysilane. The amino group of the silane was reacted with glutaric anhydride to convert the amine groups to carboxylic acid groups. The conversion of the termination was accomplished as follows: 5 g of aminopropyl silanized particles in water were washed four times with 1.5 liters of 0.1 M $NaHCO_3$. The volume was adjusted to 100 ml and 2.85 g glutaric anhydride was added. The particles were washed 2 times and the reaction with glutaric anhydride was repeated. The carboxylic acid-terminated magnetic particles were washed 5 times with water to prepare them for reaction with protein.

For binding protein and human serum albumin to carboxylic acid-terminated magnetic particles was used carbodiimide coupling method.

References

Whitehead R.A.; US Patent No. 4,695,392; Sep. 22, 1987; Assigned: Advanced Magnetics Inc. (Cambridge, MA)

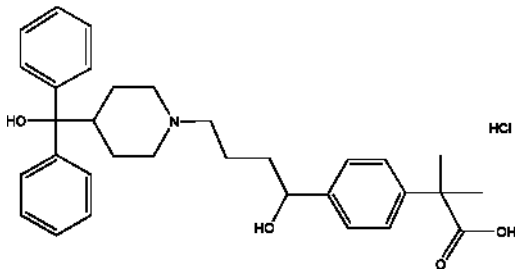
FEXOFENADINE HYDROCHLORIDE

Therapeutic Function: Antihistaminic

Chemical Name: Benzeneacetic acid, 4-(1-hydroxy-4-(4-(hydroxydiphenylmethyl)-1-piperidinyl)butyl)-α,α-dimethyl-, hydrochloride

Common Name: Fexofenadine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 153439-40-8; 83799-24-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Alernex	Dabur Pharmaceuticals Ltd.	India	-
Allegra	Hoechst	Germany	-
Allegra	Aventis Pasteur	India	-
Altiva	Ranbaxy Laboratories Limited	India	-
Fexadin	Ranbaxy	India	-
Fexidine	Ind-Swift Ltd.	India	-
Fexofast	Micro Labs	India	-
Fexona	Lyka Hetro Labs. Ltd.	India	-
Fexotrol	Solares (A division of Sun)	India	-
Telfast	Hoechst	Germany	-
Telfast	Aventis Pharmaceuticals	France	-
Ultigra	Medley Pharmaceuticals Pvt. Ltd.	India	-

Raw Materials

Terfenadine	A. corymbifera LCP 63-1800
Cinchonidine	Aluminum chloride
Sodium hydoxide	4-Chlorobutyryl chloride
Trimethylsilyliodide	4-Piperidinemethanol, α,α-diphenyl-
Sodium borohydride	

Manufacturing Process

Microbiological Preparation of Fexofenadine (Patent U.S. 6,558,931)

Ten 250 ml Erlenmeyer flasks containing 100 ml of medium D are seeded with A. corymbifera LCP 63-1800. 50 mg of Terfenadine in 1 ml of ethanol is added to each Erlenmeyer flask. The content of 10 Erlenmeyer flasks are filtered on gauze (the supernatant has a pH equal to 8.0), and saturation with sodium chloride is carried out for 2 hours (pH = 5-6), followed by extracting 3 times with ethyl acetate and drying over magnesium sulfate. After evaporation under reduced pressure, 409 mg of expected crude product is obtained (yield = 77%, approximately 90% pure product). This product is purified on a column of silica gel (230-400 mesh, 40 g of silica, diameter = 3 cm) eluting with a methylene chloride/methanol/ammonium hydroxide mixture (82.5:15:2.5). 312 mg of pure Fexofenadine is recovered (61.4%).

Synthesis of Fexofenadine (Patent U.S. No. 5,578,610)

Aluminum chloride (44 g; 0.33 mol) was added in portions to a solution of freshly distilled 4-chlorobutyryl chloride (17 mL; 0.15 mol) in 460 mL of carbon disulfide at -10°C under a nitrogen atmosphere. The mixture was stirred for 15 min, then the cooling bath was removed and the mixture was allowed to warm to ambient temperature. The mixture was stirred then for 15 min more, then cooled again to -10°C and a solution of ethyl-α,α-dimethylphenyl acetate (26.6 g; 0.14 mol) in 70 mL of carbon disulfide was added dropwise. The mixture was stirred for 3 hours, then stirred overnight at room temperature. The reaction mixture was partitioned between water and $CHCl_3$. The combined organic portions were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and filtered through a plug of SiO_2, eluting with 10% EtOAc in hexane. Yield of ethyl 3- and 4-(4-chloro-1-oxobutyl)-α,α-dimethylphenylacetate 39.4 g (as a mixture of aromatic regioisomers).

To a solution of 39.4 g of ethyl 3- and 4-(4-chloro-1-oxobutyl)-α,α-dimethylphenylacetate dissolved in 800 mL of methanol and 200 mL of water was added 40 g of NaOH. The mixture was refluxed for one hour. The cooled mixture was then concentrated in vacuo. The concentrate was diluted with water and washed with 2 portions of EtOAc. The aqueous layer was acidified with concentrated HCl and extracted with 2 portions of EtOAc. The extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 30.3 g of crude product. The crude product was dissolved in 600 mL of EtOAc, 38 g of cinchonidine was added, and the mixture was stirred overnight. The resulting solids were filtered and washed with EtOAc and sucked dry under a rubber dam to afford 25 g of a solid 4-(cyclopropyl-oxo-methyl)-α,α-dimethylphenylacetic acid.

A solution of 10.5 g of 4-(cyclopropyl-oxo-methyl)-α,α-dimethylphenylacetic acid in 250 mL of CH_2Cl_2 was cooled in an ice-MeOH bath and 25 g of trimethylsilyliodide was then added via pipette. The mixture was stirred in the ice bath for one hour, warmed to ambient temperature, and stirred for one hour. A solution of aqueous sodium bisulfite was then added and the mixture was stirred well. The phases were partitioned and the aqueous layer was extracted with CH_2Cl_2. The combined organics were washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 12.6 g (77%) of 4-(4-iodo-1-oxobutyl)-α,α-dimethylphenylacetic acid.

To a solution of 12.6 g of 4-(4-iodo-1-oxobutyl)-α,α-dimethylphenylacetic acid in 100 mL of ether cooled in an ice bath, was added 40 mL of ethereal CH_2N_2. The mixture was stirred at 0°C for few minutes, then let stand for 2 hours. A few drops of AcOH were added to decompose excess CH_2N_2, then the mixture was filtered and stripped to afford 12.6 g (96%) of methyl 4-(4-iodo-1-oxobutyl)-α,α-dimethylphenylacetate.

A solution of 12.6 g of methyl 4-(4-iodo-1-oxobutyl)-α,α-dimethylphenylacetate in 500 mL of toluene in a one liter three neck flask was added 8.8 g of 4-(α,α-diphenyl)piperidinemethanol and 23 g of K_2CO_3 and the mixture was refluxed for 7 hours. The cooled reaction mixture was then filtered and concentrated in vacuo. The residue was dissolved in ether and treated with excess ethereal HCl. The mixture was then concentrated to a solid. The solid was treated with EtOAc and collected by filtration. The product was then partitioned between EtOAc and 2 N Na_2CO_3. The organics were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 13.5 g (79%) of methyl 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]-α,α-dimethylphenylacetate.

A solution of 13.5 g of methyl 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]-α,α-dimethylphenylacetate in 250 mL of methanol was cooled in an ice-methanol bath and 1.8 g of $NaBH_4$ was added in portions. After 1 hour, the mixture was concentrated to a solid. The residue was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The aqueous portion was extracted with EtOAc. The combined organics were washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 9.5 g (70%) of methyl 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]-α,α-dimethylphenylacetate as a foam.

To a solution of 9.5 g of methyl-4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]-α,α-dimethylphenylacetate in 300 mL of methanol and 150 mL of water was added 10 g of NaOH. The mixture was refluxed for 1 hour, then cooled. The methanol was removed in vacuo. The concentrate was diluted with water and $CHCl_3$ and the pH adjusted to approximately 5.5 to 6.0. The phases were separated and the aqueous phase was extracted with $CHCl_3$. The combined organics were dried over $MgSO_4$, filtered, and stripped to afford 9.0 g of crude product. The crude product was dissolved in CH_2Cl_2 and chromatographed on Davisil Grade 633 SiO_2 eluting with a gradient of $CHCl_3$, to 10% of methanol in $CHCl_3$, to 25% of methanol in $CHCl_3$. The product was concentrated to afford 5.2 g of white crystals of 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]-α,α-

dimethylphenylacetic acid (Fexofenadine).

In practice it is usually used as hydrochloride salt.

References

Azerad R. et al.; US Patent No. 6,558,931; May 6, 2003; Assignee to Aventis Pharma S.A. (FR)
D'Ambra T.E.; US Patent No. 5,578,610; Nov. 26, 1996; Assigned to Albany Molecular Research, Inc. (Albany, NY)

FIBRINOLYSIN

Therapeutic Function: Thrombolytic

Chemical Name: Complex protein, molecular weight about 75,000

Common Name: -

Structural Formula: -

Chemical Abstracts Registry No.: 9001-90-5

Trade Name	Manufacturer	Country	Year Introduced
Actase	Ortho	US	1959
Thrombolysin	MSD	US	1960
Elase	Parke Davis	US	1960
Lyovac	MSD	US	-
Thromboclase	Choay	France	-

Raw Materials

Human blood plasma
Oxalic acid
Calcium chloride
Ammonium sulfate

Manufacturing Process

A 5 gallon drum of frozen plasma oxalated with a known anticoagulant quantity and proportion of oxalic acid and sodium oxalate as described in US Patent 2,394,566 is permitted to stand at room temperature (24° to 26°C) for 24 hours after which the remaining unmelted portion is broken up with an ice pick and a stainless steel warming coil containing running warm water at about 40°C is inserted into the mixture and the mixture stirred. The remaining frozen material is rapidly melted. The warming is then continued with vigorous agitation.

When the temperature of the plasma reaches about 5° to 8°C, the calculated quantity of calcium chloride solution is added in amount which is from 0.2 to 0.3% in excess of that needed to react with and precipitate the anticoagulant. The temperature of the plasma is allowed to rise to about 24°C. At 18° to 24°C strands of fibrin begin to appear and the vigor of stirring is increased to prevent a gel of fibrin from forming. Stirring is continued or 30 minutes after the fibrin is whipped out to allow for complete conversion of all prothrombin to thrombin and for the antithrombin to completely destroy all thrombin. At the end of this time the stirring is stopped, the fibrin allowed to rise to the surface and the clear serum siphoned off.

If, through failure to stir with enough vigor, a gel forms instead of strands of fibrin, when the temperature reaches about 18°C, the serum can also be obtained from the fibrin by working and kneading the gel in a cheesecloth bag while draining off the clear serum. However, this method is time-consuming and it is preferred to prevent gel formation by very vigorous stirring of the mixture.

The clear serum of this example is an amber liquid free from prothrombin, thrombin, fibrinogen and fibrin. It contains profibrinolysin and is excellently suited to further purification by salt precipitation fractionation, as given below.

The special serum is brought to a temperature of about 4° to 6°C (preferably 5°C) and saturated ammonium sulfate solution added drop by drop with constant stirring to about 24 to 26% of saturation (preferably 25%). The precipitated protein impurities are then centrifuged off and the supernatant brought to about -1° to +1°C (preferably 0°C). The degree of its saturation is then brought to about 28 to 31% of saturation (preferably 29%) by further addition of ammonium sulfate solution with stirring. This further degree of saturation precipitates the profibrinolysin which is collected by centrifugation and separated from soluble impurities. By washing the profibrinolysin several times with ammonium sulfate solution of a strength which is 29% of saturation a practically white solid is obtained which can be freeze-dried (frozen and dried under reduced pressure) to give a dry, white, product containing purified profibrinolysin free from thromboplastin, prothrombin, thrombin, fibrinogen and fibrin, (from US Patent 2,624,691), which is then activated to fibrinolysin.

References

Merck Index 4001
Kleeman & Engel p. 400
PDR p.1343
I.N. p. 424
REM p. 1038
Loomis, E.C.; US Patent 2,624,691 ; January 6, 1953; assigned to Parke, Davis and Co.
Singher, H.O.; US Patent 3,136,703; June 9, 1964; assigned to Ortho Pharmaceutical Corp.
Hink, J.H. Jr. and McDonald, J.K.; US Patent 3,234,106; February 8, 1966; assigned to Cutter Laboratories, Inc.

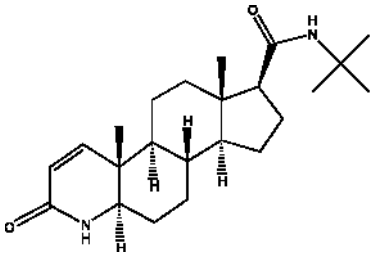
FINASTERIDE

Therapeutic Function: Antineoplastic

Chemical Name: 4-Azaandrost-1-ene-17-carboxamide, N-(1,1-dimethylethyl)-3-oxo-, (5α,17β)-

Common Name: Finasteride

Structural Formula:



Chemical Abstracts Registry No.: 98319-26-7

Trade Name	Manufacturer	Country	Year Introduced
Fincar	Cipla Limited	India	-
Finast	Dr. Reddy's Laboratories Ltd.	India	-
Finpecia	Cipla Limited	India	-
Fintride	Kopran Limited	India	-
Fistide	Samarth Pharma Pvt. Ltd.	India	-
Propecia	Merck Sharp and Dohme Idea Inc.	Switz.	-
Proscar	Merck Sharp and Dohme Idea Inc.	Switz.	-
Prosteride	Gedeon Richter	Hungary	-

Raw Materials

t-Butylamine
Acetic acid
17β-Carboxylate 17β-carbomethoxy ester of 4-aza-5α-androst-1-en-3-one
Ethyl magnesium bromide
Ammonium chloride

Manufacturing Process

In a flask equipped with an overhead stirrer, a nitrogen inlet, and reflux condenser was placed 840 ml of dry THF and 20.0 g of 17β-carboxylate 17β-carbomethoxy ester of 4-aza-5α-androst-1-en-3-one (synthesized according to

Patent US 4,377,584, issued Mar. 22,1883, and J. Med. Chem., 29, 2298 (1986)). The resulting slurry was cooled to -5-10°C, and 27.6 mL of t-butylamine was added. A solution of ethylmagnesium bromide in THF (122 mL, 2 M) was added maintaining the temperature of the reaction mixture below 10°C. The reaction mixture was heated at reflux for 12 hours and was added to a cold (10°C) solution of 25% ammonium chloride in water. The mixture was warmed to 25°C and allowed to settle. The THF solution was separated and concentrated by atmospheric distillation to 200 mL and the product was crystallized by adding approximately 600 mL of dilute aqueous HCl. The resulting white solid was isolated by filtration and was dried at 70°C under vacuum to give 21.7 g (97% yield) 2-butyl-1-(4-carboxybenzyl)-4-chloroimidazole-5-acetic acid of finasteride. The finasteride can be purified by conventional procedures, e.g. recrystallization from methylene chloride/ethyl acetate or acetic acid/water, melting point 261°C.

References

McCauley J.A., Varsolona R.J.; US Patent No. 5,652,365; 07.29.1997; Assigned to Merck and Co., Inc.
Davis R., Millar A.; US Patent No. 5,670,643; 09.3.1997; Assigned to Glaxo Wellcome Inc.
Rasmusson G.H., Reynolds G.F.; US Patent No. 4,760,071; 07.26.1988; Assigned to Merck and Co., Inc.

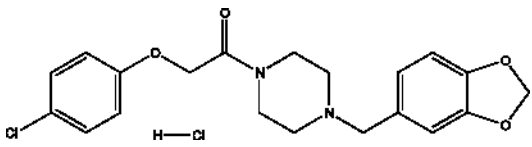
FIPEXIDE HYDROCHLORIDE

Therapeutic Function: Antidepressant, Psychostimulant

Chemical Name: 1-((p-Chlorophenoxy)acetyl)-4-piperonylpiperazine monohydrochloride

Common Name: Fipexide hydrochloride; Vigalor

Structural Formula:



Chemical Abstracts Registry No.: 34161-24-5 (Base); 34161-23-4

Trade Name	Manufacturer	Country	Year Introduced
Attentil	Ravizza	-	-
Vigilor	Bouchard	-	-
Vigilor	Bristol-Myers Squibb	-	-

Trade Name	Manufacturer	Country	Year Introduced
Fipexide hydrochloride	Shanghai Lansheng Corporation	-	-

Raw Materials

Piperazine
Piperonyl chloride
Sodium bicarbonate
Cetyltrimethylammonium bromide
Chloride of p-chlorophenoxyacetic acid
Hydrochloric acid

Manufacturing Process

25.8 g (0.3 moles) of anhydrous piperazine and 32.5 ml (1.8 moles) of distilled water (or simply 58.3 g (0.3 moles) of piperazine hexahydrate) are loaded into a 250 ml flask provided with an agitator, a thermometer and a reflux condenser, together with 51.2 g (0.3 moles) of piperonyl chloride, whereupon 2 g of cetyltrimethylammonium bromide are added to the mixture with vigorous agitation, and the flask is cooled with water so that the temperature of the reaction mass under agitation does not rise above 110°C. Once the exothermic stage is exhausted, the temperature is maintained at 130°C by an external oil bath, for 90 min under agitation.

After cooling, a solid mass is obtained which is taken up with 400 ml of an aqueous solution containing 10% by weight of caustic soda to dissolve the product from the mass. The alkaline solution thus obtained is extracted twice with 500 ml of chloroform. The extract is washed with water and then evaporated to dryness. The residue is crystallised from 96% ethanol.

50.5 g (theoretical value 53.18 g) of 1,4-bispiperonylpiperazine as a pale-yellowish white crystals are obtained with a melting point of 155-156°C; the hydrochloride melts with decomposition above 260°C.

Preparation of fipexidum hydrochloride:

106.3 g (0.3 moles) of 1,4-bispiperonylpiperazine are dissolved in 750 ml of hot benzene in a 2,000 ml flask provided with a stirrer and a reflux condenser and 38 g (0.45 moles) of dry, powdered sodium bicarbonate are added. After cooling to ambient temperature, 92.3 g (0.45 moles, corresponding to 63 ml) of the chloride of p-chlorophenoxyacetic acid are added slowly, with agitation, and the mixture is heated under reflux for 7 hours. The benzene is then almost totally recovered by distillation at atmospheric pressure and the residue is evaporated to dryness under vacuum. The solid residue thus obtained is taken up with 400 ml of aqueous solution at 10% sodium hydroxide (1 mole) and the alkaline liquid phase is extracted twice with 600 ml of chloroform. The chloroform extracts are joined together and washed with a little water and then agitated vigorously with a solution of 200 ml of concentrated hydrochloric acid in 300 ml of water. An abundant white precipitate is obtained. After filtration under vacuum, the precipitate is treated with boiling ethanol; the 1-((p-chlorophenoxy)acetyl)-4-piperonylpiperazine hydrochloride (fipexide hydrochloride) passes into solution while the dihydrochloride of hydrochloric acid remains undissolved and is separated by filtration while hot. The alcoholic filtrate is cooled, with consequent slow crystallization of the fipexide hydrochloride. 70.2 g of the product are obtained

with a yield of 55%; melting point is (in Kofler) 228-230°C.

References

Merck Index, Monograph number: 4126, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Gardini; Gian P. et al.; US Patent No. 4,225,714; September 30, 1980; Assigned: Farmaceutici Geymonat Sud S.p.A. (Anagni, IT)
Buzas A., Pierre R.; Patent FR-M 7,524; Dec. 12, 1968; Assigned to Laboratoires F. Bouchard, France

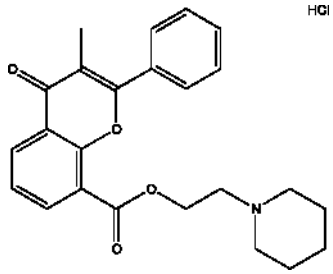
FLAVOXATE HYDROCHLORIDE

Therapeutic Function: Spasmolytic

Chemical Name: 3-Methyl-4-oxo-2-phenyl-4H-1-benzopyran-8-carboxylic acid 2-piperidinoethyl ester hydrochloride

Common Name: 2-Piperidinoethyl 3-methylflavone-8-carboxylate

Structural Formula:



Chemical Abstracts Registry No.: 3717-88-2; 15301-69-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Urispas	SKF	US	1971
Urispas	Syntex	UK	1971
Genurin	Recordati	Italy	1973
Spasuret	Ascher	W. Germany	1978
Bladderon	Nippon Shinyaku	Japan	1979
Urispas	Negma	France	1981
Spasmal	Ikapharm	Israel	-
Urispadol	Pharmacia	Sweden	-
Urispan	Byk Gulden	-	-
Urispas	Protea	Australia	-

Raw Materials

Salicylic acid	Propionyl chloride
Aluminum chloride	Benzoic anhydride
Thionyl chloride	Piperidinoethanol

Manufacturing Process

A mixture of 13.3 grams of anhydrous aluminum chloride and 100 ml of carbon disulfide is added to 19.4 grams of 2-propionyloxybenzoic acid (prepared from the reaction of propionyl chloride and 2-hydroxybenzoic acid). After an initial evolution of hydrogen chloride, the solvent is removed by distillation and the mixture is heated at 150° to 160°C for 4 hours. The cooled reaction mixture is treated with ice and hydrochloric acid and the product, 2-hydroxy-3-carboxypropiophenone, is obtained from the oily residue by distillation in vacuo.

A mixture of 1.9 grams of 2-hydroxy-3-carboxypropiophenone, 5.0 grams of sodium benzoate and 20.0 grams of benzoic anhydride is heated at 180° to 190°C for 6 hours. A solution of 15.0 grams of potassium hydroxide in 50 ml of ethanol and 20 ml of water is added and refluxed for 1 hour. The mixture is evaporated and the residue after addition of water yields 3-methylflavone-8-carboxylic acid.

To a suspension of 12.0 grams of 3-methylflavone-8-carboxylic acid in 200 ml of anhydrous benzene is added 10.0 grams of thionyl chloride. The mixture is refluxed for 2 hours during which the suspended solid goes into solution. The solvent is completely removed by distillation, the residue extracted with benzene and the extract evaporated to dryness. The product, 3-methylflavone-8-carboxylic acid chloride, is recrystallized from ligroin to give crystals melting at 155° to 156°C.

To 11.0 grams of 3-methylflavone-8-carboxylic acid chloride dissolved in 150 ml of anhydrous benzene is added at room temperature 4.8 grams of piperidinoethanol and the mixture refluxed for 2 to 3 hours. The separated solid is filtered, washed with benzene and dried. The product, piperidinoethyl 3-methylflavone-8-carboxylate hydrochloride is obtained as a colorless crystalline solid, MP 232° to 234°C, (from US Patent 2,921,070).

References

Merck Index 4018
Kleeman & Engel p. 400
PDR p. 1731
OCDS Vol. 2 p. 392 (1980)
DOT 7 (5) 171 (1971)
I.N. p. 426
REM p. 920
Da Re, P.; US Patent 2,921,070; January 12, 1960; assigned to Recordati-Laboratorio Farmacologico SPA, Italy
Da Re, P.; US Patent 3,350.41 1; October 31, 1967; assigned to Societe d'Exploitation Chimiques et Pharmaceutiques Seceph SA, Switzerland

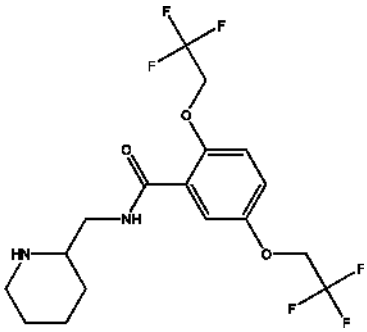
FLECAINIDE

Therapeutic Function: Antiarrhythmic

Chemical Name: N-(2-Piperidylmethyl)-2,5-bis(2,2,2-trifluoroethoxy) benzamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 54143-55-4

Trade Name	Manufacturer	Country	Year Introduced
Tambocor	Kettelhack Riker	W. Germany	1982
Tambocor	Riker	UK	1983

Raw Materials

2-Aminomethylpiperidine
2,2,2-Trifluoroethyl-2,5-bis(2,2,2-trifluoroethoxy)benzoate
Hydrogen chloride

Manufacturing Process

Under a nitrogen atmosphere 2-aminomethylpiperidine (0.249 mol, 28.4 g) is treated dropwise over 25 minutes with 2,2,2-trifluoroethyl 2,5-bis(2,2,2-trifluoroethoxy)benzoate (0.0249 mol, 10.0 g). After 3 hours 50 ml of benzene is added to the thick mixture and stirred for about 40 hours at 45°C. The mixture is then concentrated under vacuum with heating to remove the volatile components. The residue solidifies after cooling, is steam distilled for further purification and is separated by filtration and extracted into dichloromethane. The dichloromethane solution is washed with saturated sodium chloride solution, and the organic layer is dried over anhydrous magnesium sulfate. The magnesium sulfate is removed by filtration and 4 ml of 8.4 N hydrogen chloride in isopropanol is added to the dichloromethane solution with stirring.

After 2 hours the mixture is cooled to about 0°C and the crude product is collected by filtration, washed with diethyl ether and dried in a vacuum oven. After treatment with decolorizing charcoal and recrystallization from an equivolume mixture of isopropanol and methanol, the product, 2,5-bis(2,2,2-trifluoroethoxy)-N-(2-piperidylmethyl)benzamide hydrochloride has a MP of 228°C to 229°C.

References

Merck Index 4019
DFU 2 (9) 586 (1977)
OCDS Vol. 3 p. 59 (1984)
DOT 18 (10) 549 (1974), 19 (2) 112 & (5) 252 (1983)
I.N. p. 426
Banitt, E.H. and Brown, W.R.; US Patent 3,900,481; August 19, 1975; assigned to Riker Laboratories, Inc.

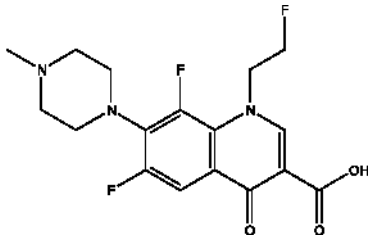
FLEROXACIN

Therapeutic Function: Antibacterial

Chemical Name: 3-Quinolinecarboxylic acid, 1,4-dihydro-6,8-difluoro-1-(2-fluoroethyl)-7-(4-methyl-1-piperazinyl)-4-oxo-

Common Name: Fleroxacin; Megalosin

Structural Formula:



Chemical Abstracts Registry No.: 79660-72-3

Trade Name	Manufacturer	Country	Year Introduced
Megalocin	Tianjin Pacific Pharmaceutical Co., Ltd	-	-
Quinodis	Roche	-	-

Raw Materials

1-Methylpiperazine

6,7,8-Trifluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid
Hydrochloric acid

Manufacturing Process

6,8-Difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid hydrochloride:

A mixed solution of 1-methylpiperazine (0.34 g) and pyridine (3 ml) was added to 6,7,8-trifluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (0.12 g) and heated to reflux for 6 hours. After the solvent evaporated and cooled, the residue was adjusted to pH 1 with aqueous hydrochloric acid. The cooled mixture was filtered off and the solid recrystallized from water to give 6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid hydrochloride (0.08 g), melting point 269-271°C (decomp.).

References

Irikura T., Koga H., Murayama S.; US Patent No. 4,398,029; August 9, 1983; Assigned to Kyorin Seiyaku Kabushiki Kaisha (Tokyo, JP)

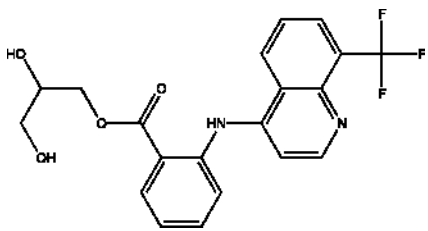
FLOCTAFENINE

Therapeutic Function: Analgesic

Chemical Name: 2-[[8-(Trifluoromethyl)-4-quinolinyl]amino]benzoic acid 2,3-dihydroxypropyl ester

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 23779-99-9

Trade Name	Manufacturer	Country	Year Introduced
Idarac	Diamant	France	1976
Idarac	Roussel Maestretti	Italy	1977

Trade Name	Manufacturer	Country	Year Introduced
Idarac	Albert Roussel	W. Germany	1978
Floktin	Yurtoglu	Turkey	-
Idalon	Roussel	-	-

Raw Materials

Sodium hydride
Methyl anthranilate
Hydrogen chloride
2,2-Dimethyl-4-hydroxymethyl-1,3-dioxolane
o-Trifluoromethylaniline
Ethoxymethylene ethyl malonate
Phosphorus oxychloride

Manufacturing Process

Step A: Ortho-Trifluoromethylanilinomethylene Ethyl Malonate - A mixture of 54.8 grams of ortho-trifluoromethylaniline and 73.5 grams of ethoxymethylene ethyl malonate was heated to 120°C under an inert atmosphere and maintained for 1 hour at this temperature while distilling off the ethanol formed. The mixture was cooled and the elimination of ethanol was completed by distillation under reduced pressure. The mixture was cooled to obtain 115 grams of ortho-trifluoromethylanilinomethylene ethyl malonate which was used as is for the following stage. A sample of the product was crystallized from petroleum ether (BP = 65° to 75°C) to obtain a melting point of 94°C.

Step B: 3-Carbethoxy-4-Hydroxy-8-Trifluoromethylquinoline - A mixture of 113 grams of crude ortho-trifluoromethylanilinomethylene ethyl malonate from Step A, and 115 cc of phenyl oxide was heated rapidly under an inert atmosphere. At about 195°C, the ethanol formed began to distill off. At the end of about 30 minutes, the interior temperature reached 250°C and the reaction mixture was heated to reflux. Reflux was maintained for 1 hour and the mixture was then cooled, 25 cc of acetone were added and the mixture was allowed to crystallize. The mixture was filtered and the crystals thus formed were washed and dried to obtain 71.5 grams of 3-carbethoxy-4-hydroxy-8-trifluoromethylquinoline with a melting point of 210° to 214°C, which was used as is for the following stage. A sample of this product was crystallized from ethanol to show a melting point of 216°C.

Step C: 3-Carboxy-4-Hydroxy-8-Trifluoromethylquinoline - 70 grams of crude 3-carbethoxy-4-hydroxy-8-trifluoromethylquinoline, obtained in Step B, were introduced under an inert atmosphere into a mixture of 300 cc of water and 100 cc of aqueous 10 N solution of sodium hydroxide. The reaction mixture was heated to reflux and maintained there for 2 hours and forty-five minutes. The solution obtained was poured over a mixture of water, ice and 100 cc of aqueous 11.8 N solution of hydrochloric acid. The precipitate thus formed was isolated by filtration, washed with water and introduced into a solution of 20 grams of sodium bicarbonate in 2 liters of water.

The mixture was heated to 90°C and filtered to remove slight persisting insolubles. The filtrate was acidified with acetic acid to bring the pH to about 5.5 and the precipitate formed was isolated by filtration, washed and dried to obtain 58 grams of 3-carboxy-4-hydroxy-8-trifluoromethylquinoline having a

melting point of 290° to 292°C, which was used as is for the following stage. A sample of the product was crystallized from hot and cold acetone, treated with charcoal to obtain pure 3-carboxy-4-hydroxy-8-trifluoromethylquinoline having a melting point of 292°C.

Step D: 4-Hydroxy-8-Trifluoromethylquinoline - Under an inert atmosphere, 56.5 grams of crude 3-carboxy-4-hydroxy-8-trifluoromethylquinoline, obtained in Step C were introduced into 110 cc of phenyl oxide. The reaction mixture was rapidly heated to reflux and maintained at reflux for an hour and fifteen minutes. The reaction mixture was cooled to about 50°C and 20 cc of isopropyl ether were added thereto. The mixture was cooled to 20°C and allowed to crystallize. The precipitate formed was isolated by filtration, washed and dried to obtain 45.8 grams of 4-hydroxy-8-trifluoromethylquinoline having a melting point of 180°C. A sample of this product was crystallized from acetone, treated with charcoal to obtain pure 4-hydroxy-8-trifluoromethylquinoline having a melting point of 180°C.

Step E: 4-Chloro-8-Trifluoromethylquinoline - 44.3 grams of crude 4-hydroxy-8-trifluoromethylquinoline obtained in Step D were introduced in small amounts into 130 cc of phosphorus oxychloride and then the reaction mixture was held for 15 minutes at ambient temperature and heated to reflux and maintained at reflux for 1hour. The mixture was cooled and excess phosphorus oxychloride was removed by distillation under reduced pressure. Water, ice, and then 80 cc of aqueous solution of ammonia at 22°Be were added to the residue and the mixture was stirred and the aqueous phase was extracted with ether. The ethereal extracts were washed with a dilute aqueous solution of ammonia, then with water, dried, treated with charcoal and concentrated to dryness to obtain 45.4 grams of 4-chloro-8-trifluoromethylquinoline having a melting point of 78°C, which was used as is for the preparation of 4-(ortho-methoxycarbonylphenylamino)-8-trifluoromethylquinoline. A sample of crude 4-chloro-8-trifluoromethylquinoline was crystallized from petroleum ether (BP = 65° to 75°C) to get a product with a melting point of 78°C.

Step F: 4-(Ortho-Methoxycarbonyl)-Phenylamino-8-Trifluoromethylquinoline - Into 100 cc of aqueous 2 N solution of hydrochloric acid, 23.15 grams of crude 4-chloro-8-trifluoromethylquinoline, obtained in Step E, then 15.85 grams of methyl anthranilate were introduced. The reaction mixture was heated to reflux and maintained there for 50 minutes. The mixture was cooled and the crystallation developed. The precipitate formed was recovered by filtration and introduced into 300 cc of a saturated aqueous solution of sodium bicarbonate. The mixture was agitated, methylene chloride was added and the mixture agitated and filtered to remove persisting insolubles. The organic phase was separated by decantation, washed with water and concentrated to dryness. The residue was crystallized from methanol to obtain 21.3 grams of 4-(ortho-methoxy-carbonylphenylamino)-8-trifluoromethylquinoline with a melting point of 176°C.

Step G: 4-[Ortho-(2',3'-Dihydroxypropyloxycarbonyl)-Phenyl]-Amino-8-Trifluoromethylquinoline Acetonide - 100 cc of toluene were added to 80 cc of 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane and the toluene was distilled off under reduced pressure to eliminate the water present. To the anhydrous 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane thus obtained, 0.25 gram of an oily 50% suspension of sodium hydride and then 21.3 grams of 4-(ortho-

methoxycarbonylphenylamino)-8-trifluoromethylquinolinewere added under inert atmosphere. The mixture was agitated for 5 hours at 85°C under a vacuum of 50 to 100 mm of mercury. After cooling, an aqueous solution of sodium chloride was added to the reaction mixture and it was stirred. The aqueous phase was extracted with methylene chloride and the methylene chloride extracts were washed with water, dried and concentrated to dryness by distillation under reduced pressure.

The residue was washed with petroleum ether (BP 65° to 75°C), dried and crystallized from isopropyl ether to obtain 23.8 grams of 4-[ortho-(2',3'-dihydroxypropyloxycarbonyl)phenyl] -amino-8-trifluoromethylquinoline acetonide having a melting point of 108°C.

Step H: Preparation of 4-[Ortho-(2',3'-Dihydroxypropyloxycarbonyl)-Phenyl]-Arnino-8-Trifluoromethylquinoline - Into a mixture of 60 cc of water and 12 cc of aqueous solution of 22°Be hydrochloric acid there was introduced 19.8 grams of 4-[ortho-(2',3'-dihydroxypropyloxycarbonyl)-phenyl]-amino-8-trifluoromethylquinoline acetonide (obtained in Step G) and the temperature of the reaction mixture was raised to 95°C and maintained at this temperature for 15 minutes. The mixture was cooled to 0°C and crystallization was allowed. The crude hydrochloride was recovered by filtration, washed and introduced into a mixture of 60 cc of dimethylformamide, 40 cc of water and 10 cc of triethylamine.

Dissolution and the crystallization occurred and the precipitate was recovered by filtration and was washed and dried to obtain 16 grams of crude base having a melting point of 179° to 180°C. The crude base was crystallized from methanol with treatment with charcoal to obtain 11.95 grams of 4-[ortho-(2',3'-dihydroxypropyloxycarbonyl)-phenyl]-amino-8-trifluoromethylquinoline with a melting point of 179° to 180°C. The product is soluble in ether, chloroform and methylene chloride and insoluble in water.

References

Merck Index 4021
DFU 1 (2) 59 (1976)
Kleeman & Engel p. 401
OCDS Vol. 3 p. 184 (1984)
DOT 13 (4) 143 (1977)
I.N. p. 427
Allais, A. and Meier, J.; US Patent 3,644,368; February 22, 1972; assigned to Roussel-UCLAF, France

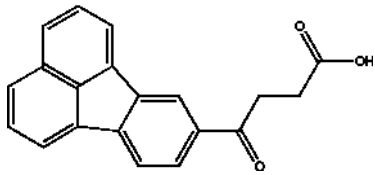
FLORANTYRONE

Therapeutic Function: Hydrocholeretic

Chemical Name: γ-Oxo-8-fluoranthenebutanoic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 519-95-9

Trade Name	Manufacturer	Country	Year Introduced
Zanchol	Searle	US	1957
Bilyn	Janus	Italy	-
Cistoplex	Borromeo	Italy	-
Idroepar	Beolet	Italy	-
Zanchol	Dainippon	Japan	-

Raw Materials

Fluoranthene
Succinic anhydride

Manufacturing Process

50 g of fluoranthene and 26 g of succinic anhydride in 500 cc of nitrobenzene were treated at 0°C to 5°C with 75 g of anhydrous aluminum chloride. The temperature was held at 0°C for 4 hours and then allowed gradually to come to room temperature. The reaction mixture was allowed to stand for 16 hours. The reaction mixture was then worked up. In so doing, the reaction mixture was decomposed with dilute HCl, the nitrobenzene was removed by steam distillation and the residue after filtration was dissolved in hot sodium carbonate solution and filtered free of a small amount of nonacidic material. Precipitation from solution with HCl gave a light yellow product which crystallized from a 50-50 mixture of dioxane alcohol as fine platelets which melted at 192°C to 194°C and showed a neutral equivalent of 308 which corresponds closely to the theoretical value of 302 for β-fluoranthoylpropionic acid.

25 g of the crude acid was dissolved in 100 cc of water containing 13 g of sodium carbonate. On cooling a thick syrup was obtained. On dilution to 1 liter precipitation started and after standing 16 hours, the solid which separated was filtered (filtrate treated as below), suspended in water, acidified with HCl and filtered. Crystallization from alcohol gave a light yellow material melting at 199°C to 200°C and having a neutral equivalent of 303.

The filtrate mentioned above, upon acidification thereof with HCl gave a darker acid which melted over a wide range, but had a neutral equivalent which also corresponds to that of β-fluoranthoylpropionic acid.

References

Merck Index 4023
Kleeman & Engel p. 403
I.N. p. 427
Fancher, O.E.; US Patent 2,560,425; July 10, 1951; assigned to Miles Laboratories, Inc.

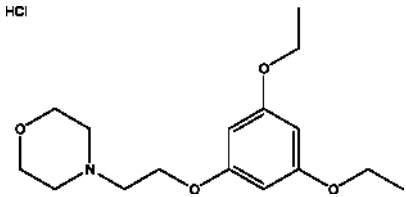
FLOREDIL HYDROCHLORIDE

Therapeutic Function: Coronary stabilizer

Chemical Name: 1-(3',5'-Diethoxyphenoxy)-2-morpholinoethane hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 53731-36-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Carfonal	Lafon	France	1973

Raw Materials

Sodium
Ethanol
3,5-Diethoxyphenol
1-Chloro-2-morpholinoethane hydrochloride

Manufacturing Process

Starting from 2.3 g (0.1 g atom) of sodium in 60 cc ethanol, 9.1 g (0.05 mol) of 3,5-diethoxyphenol in 25 cc of ethanol, and 9.3 g (0.05 mol) of 1-chloro-2-morpholinoethane hydrochloride in 15 cc of ethanol, 12 g (yield 72.4%) of white crystals melting at 183°C to 184°C were obtained after recrystallization from 50 cc of boiling isopropanol, which were soluble in water, slightly soluble

in ethanol, and insoluble in hydrocarbons.

References

Merck Index 4024
Kleeman & Engel p. 403
DOT 9 (7) 285 (1973)
I.N. p. 428
Lafon, L.; British Patent 1,262,785; February 9, 1972; assigned to Orsymonde

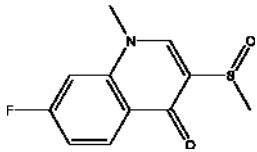
FLOSEQUINAN

Therapeutic Function: Antihypertensive, Vasodilator

Chemical Name: 4(1H)-Quinolinone, 7-fluoro-1-methyl-3-(methylsulfinyl)-

Common Name: Flosequinan

Structural Formula:



Chemical Abstracts Registry No.: 76568-02-0

Trade Name	Manufacturer	Country	Year Introduced
Flosequinan	ZYF Pharm Chemical	-	-
Manoplax	Boots Pharmaceuticals	-	-

Raw Materials

Dimethyl sulfate	Potassium carbonate
Phosgene	2-Amino-4-fluorobenzoic acid
Piperidine	Sodium hydride
Acetic acid	Triethyl orthoformate

Manufacturing Process

7-Fluoro-3-methylsulphinyl-4-quinolone (5.0 g) was dissolved in hot butanone (250 ml) containing anhydrous potassium carbonate (3.06 g). The resulting suspension was stirred and treated dropwise with dimethyl sulphate (2.09 ml). The mixture was stirred and boiled under reflux for 1 hour and filtered while hot. The filtrate was allowed to cool, giving a crystalline product. The product was collected and dried to give 7-fluoro-1-methyl-3-methylsulphinyl-4-

quinolone, melting point 226-228°C.

The intermediate 7-fluoro-3-methylsulphinyl-4-quinolone, was prepared in the following way:

A solution of 2-amino-4-fluorobenzoic acid (62 g) in aqueous sodium carbonate (44 g sodium carbonate in 1.6 liters water) was stirred and treated dropwise with a solution of phosgene (120 g) in toluene (500 ml) during 1.5 hours. The resulting suspension was stirred at room temperature for 24 hours. The solid product was collected by filtration, washed with water and dried to give 7-fluoro-1,2-dihydro-3,1(4H)-benzoxazine-2,4-dione; melting point 217-219°C.

A mixture of dimethyl sulphoxide (230 ml), toluene (300 ml) and 50% w/w dispersion of sodium hydride in mineral oil (20.7 g) was heated under nitrogen at 65-70°C for 1 hour, then cooled to room temperature to form dimethylsulphoxide anion, sodium salt. The resulting suspension was stirred under nitrogen and the above benzoxazine-2,4-dione (27.5 g) was added portionwise. The resulting solution was stirred at room temperature for 15 minutes and then poured into ether (3 liters). The resulting solid was collected by filtration and dissolved in water (300 ml) and the solution acidified with glacial acetic acid to a final pH of 6.0. The solution was saturated with solid potassium carbonate. The resulting precipitate was collected, dried and recrystallised from ethanol/diethyl ether to give the novel compound 2'-amino-4'-fluoro-(2-methylsulphinyl)acetophenone, melting point 115-117°C.

This compound (14 g) was dissolved in triethyl orthoformate (160 ml) at 100°C under nitrogen. The resulting solution was treated dripwise with piperidine (7 ml). The mixture was heated with stirring at 120°C under nitrogen for 30 min allowing ethanol produced to distil off, then cooled to room temperature. The solid product was collected, dried and crystalized from ethanol using charcoal to give the 7-fluoro-3-methylsulphinyl-4-quinolone; melting point 265°C.

References

Davies R.V., Fraser J., Nichol K.J., Parkinson R., Sim M.F., Yates D.B.; US Patent No. 4,302,460; Nov. 24, 1981; Assigned to The Boots Company Limited (Nottingham, GB2)

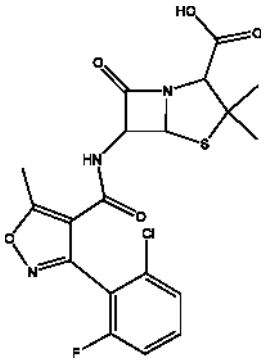
FLOXACILLIN

Therapeutic Function: Antibacterial

Chemical Name: 6-[3-(2-Chloro-6-fluorophenyl)-5-methyl-4-isoxazolecarboxamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylic acid

Common Name: Flucloxacillin; 3-(2-Chloro-6-fluorophenyl)-5-methyl-4-isoxazolylpenicillin

Structural Formula:



Chemical Abstracts Registry No.: 5250-39-5

Trade Name	Manufacturer	Country	Year Introduced
Floxapen	Beecham	UK	1970
Clupen	Fujisawa	Japan	1970
Staphylex	Beecham	W. Germany	1972
Flupen	Alfa	Italy	1974
Flupen	C.S.L.	Australia	-
Fluclox	Ayerst	-	-
Heracillin	Astra	-	-
Penplus	Farma Labor	Italy	-

Raw Materials

Chlorine
Thionyl chloride
Sodium hydroxide
6-Aminopenicillanic acid
2-Chloro-6-fluorobenzaldoxime
Methyl acetoacetate
Sodium methoxide

Manufacturing Process

3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carboxylicacid, MP 206° to 207°C, was obtained by chlorinating 2-chloro-6-fluorobenzaldoxime, then condensing the resulting hydroxamoyl chloride with methyl acetoacetate in methanolic sodium methoxide and hydrolyzing the resulting ester with hot alkali. The acid chloride resulted from treatment of the acid with thionyl chloride.

A suspension of 6-aminopenicillanic acid (36.4 grams) in water was adjusted to pH 7.2 by the addition of N aqueous sodium hydroxide and the resulting solution was treated with a solution of 3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carbonyl chloride (46.1 grams) in isobutyl methyl ketone. The mixture was stirred vigorously for 1½ hours and then filtered through

Dicalite. The layers were separated and the isobutyl methyl ketone layer was shaken with saturated brine. Then, precipitation of the sodium salt only took place after dilution of the mixture with ether. In this way there was obtained 60.7 grams of the penicillin sodium salt having a purity of 88% as determined by alkalimetric assay.

References

Merck Index 4025
Kleeman & Engel p. 405
OCDS Vol. 1 p. 413 (1977)
DOT 7 (1) 18 (1971)
I.N. p. 429
REM p. 1201
Nayler, J.H.C.; US Patent 3,239,507; March 8, 1966; assigned to Beecham Group Limited, England

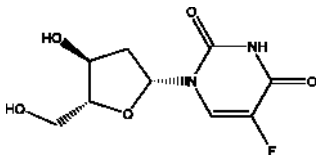
FLOXURIDINE

Therapeutic Function: Antiviral, Cancer chemotherapy

Chemical Name: 2'-Deoxy-5-fluorouridine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 50-91-9

Trade Name	Manufacturer	Country	Year Introduced
FUDR	Roche	US	1971

Raw Materials

5-Fluorouracil	Bacterium *Streptococcus fecalis*
Thymidine	Nutrient medium

Manufacturing Process

Cells of Streptococcus fecalis (ATCC-8043) were grown in the AOAC folic acid assay medium [Lepper, Official and Tentative Methods of the Association of

Official Agricultural Chemists, Washington, D.C., 7th edition, 784 (1950)], supplemented with 2 mg per liter of thymine; following the teachings of Prusoff, Proc. Soc. Exp. Biol. & Med. 85, 564 (1954). After 20 hours of incubation at 37°C, the cells were harvested by centrifugation. The collected cells were washed three times with four volumes of potassium phosphate buffer solution (M/15 aqueous KH_2PO_4 solution, adjusted to pH 8.0 by addition of 2 N aqueous KOH) and the wet cells were weighed. The cells were finally suspended in the above potassium phosphate buffer solution and ground in a glass tissue homogenizer.

An amount of enzyme preparation equivalent to 900 mg of wet cells was made up to 25 ml with the above potassium phosphate buffer solution. 150 mg (1.15 mmol) of 5-fluorouracil and 1.0 gram of thymidine (4.12 mmol) were dissolved in 15 ml of the above potassium phosphate buffer solution. The mixture was incubated at 37°C for 18 hours. After this time, enzyme action was stopped by the addition of four volumes of acetone and one volume of peroxide-free diethyl ether. The precipitated solids were removed by filtration, and the filtrate was evaporated under nitrogen at reduced pressure until substantially all volatile organic solvent had been removed. About 20 ml of aqueous solution, essentially free of organic solvent, remained. This solution was diluted to 100 ml with distilled water.

Ten microliters of this solution were submitted to descending chromatography on a paper buffered with 0.2 N KH_2PO_4 (pH 7.8), using a solvent mixture of tertiary amyl alcohol:water:n-butyl ether (80:13:7 by volume). A spot visible under ultraviolet light and having R_f = 0.55 was leached with 0.1 N HCl and assayed for deoxyribose by the method of Stumpf, J. Biol. Chem. 169, 367 (1947). This analysis indicated the presence of a minimum of 85.5 mg (0.35 mmol) of 2'-deoxy-5-fluorouridine in the protein-free reaction mixture according to US Patent 2,885,396. An alternate route from 5-fluorouracil via the mercury derivative, through toluoyl deoxyuridines and then toluoyl removal to give floxuridine is described in US Patent 3,041,335.

References

Merck Index 4026
PDR p. 1485
DOT 8 (2) 63 (1972)
I.N. p. 428
REM p. 1155
Heidelberg, C. and Duschinsky, R.; US Patent 2,885,396; May 5, 1959
Hoffer, M.; US Patent 2,949,451; August 16, 1960; assigned to Hoffmann-La Roche Inc.
Duschinsky, R., Farkas, W.G. and Heidelberger, C.; US Patent 2,970,139; January 31, 1961
Hoffer, M.; US Patent 3,041,335; June 26, 1962; assigned to Hoffmann-La Roche Inc.

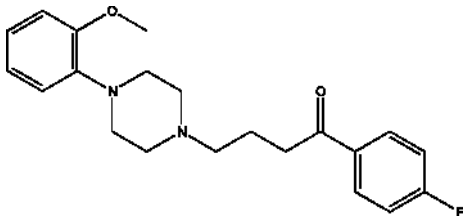
FLUANISONE

Therapeutic Function: Neuroleptic

Chemical Name: 1-Butanone, 1-(4-fluorophenyl)-4-(4-(2-methoxyphenyl)-1-piperazinyl)-

Common Name: Fluanisone; Haloanisone

Structural Formula:



Chemical Abstracts Registry No.: 1480-19-9

Trade Name	Manufacturer	Country	Year Introduced
Sedalande	J and J	-	-
Sedalande	Synthelabo	-	-
Sedalande	Delalande	-	-

Raw Materials

Aluminum chloride
Fluorobenzene
γ-Chlorobutyryl chloride
1-(o-Anisyl)piperazine

Manufacturing Process

To a suspension of 341 parts of aluminum chloride in 1740 parts of carbon disulfide are added 96 parts of fluorobenzene with stirring and cooling. While the temperature is maintained at about 10°C, 141 parts of γ-chlorobutyryl chloride are added. After the addition is completed, the cooling bath is removed and the stirring is continued for 2 hours. The reaction mixture is poured into ice water. The organic layer is separated, washed with water, dried over anhydrous sodium sulfate, and filtered. The filtrate is concentrated under reduced pressure, and the residue is distilled to yield γ-chloro-p-fluoro-butyrophenone boiling at about 136°-142°C/6 mm.

A mixture of 6.6 parts of γ-chloro-p-fluoro-butyrophenone and 12.5 parts of 1-(o-anisyl)piperazine is heated for 10 hours at a temperature of 110°C. The reaction mixture is treated with 800 parts of ether and filtered. The ether layer is washed with water, dried over anhydrous potassium carbonate and filtered, whereupon hydrogen chloride gas is introduced into the solution. The precipitate is collected on a filter and dissolved in a mixture of 240 parts of 2-propanol and 80 parts of acetone to yield 1-[γ-(p-fluorobenzoyl)propyl]-4-(o-

anisyl)piperazine hydrochloride. This monohydrochloride is collected on a filter and dissolved in 240 parts of 2-propanol. Anhydrous, gaseous hydrogen chloride is passed through the solution. On cooling, the 1-[γ-(p-fluorobenzoyl) propyl]-4-(o-anisyl)piperazine dihydrochloride precipitates.

A second crop of product is obtained by passing hydrogen chloride gas through the solution of mother liquors. The pale-brown, amorphous powder is collected on a filter and found to melt at about 205°-205.5°C.

This salt is dissolved in water and treated with sodium hydroxide. The precipitated base is recovered by filtration and recrystallized from diisopropyl ether. The white crystals melt at about 67.5°-68.5°C.

References

Janssen P.A.; US Patent No. 2,997,472; Aug. 22, 1961

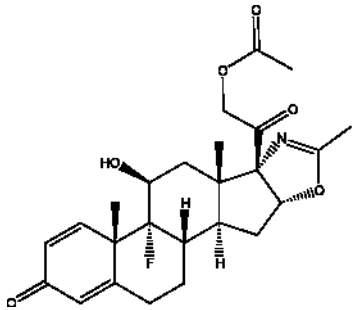
FLUAZACORT

Therapeutic Function: Antiinflammatory

Chemical Name: 21-(Acetyloxy)-9-fluoro-11-hydroxy-2'-methyl-5'H-pregna-1,4-dieno[17,16-d]oxazole-3,20-dione

Common Name: Fluazacortenol acetate

Structural Formula:



Chemical Abstracts Registry No.: 19888-56-3

Trade Name	Manufacturer	Country	Year Introduced
Azacortid	Richter	Italy	1975
Azacortid	Lepetit	France	1981

Raw Materials

Pregna-1,4,9(11)-triene-21-ol-3,20-dione-[17α,16α-d]-2'-methyloxazoline-21-acetate
N-Bromoacetamide
Sodium hydroxide
Hydrogen fluoride

Manufacturing Process

To a solution of 2.4 g of pregna-1,4,9(11)-triene-21-ol-3,20-dione-[17α,16α-d]-2'-methyloxazoline 21-acetate in 24 ml of tetrahydrofuran, 12.8 ml of 0.46 N perchloric acid are added at 15°C under stirring. N-bromoacetamide (1.1 g) is then added to the mixture which is kept far from light, and stirred for 4 hours at room temperature. After lowering the temperature to 10°C, a saturated solution of sodium bisulfite is added in order to decolorize the mixture, which is then poured into 120 ml of ice water. A product separates, which is collected by filtration, washed with water and then dried, thus obtaining 2.81 g of crude 9α-bromo-pregna-1,4-diene-11β,21-diol-3,20-dione-[17α,16α-d]-2'-methyloxazoline-21-acetate (yield 93%), MP 175°C to 176°C. An amount of 2.75 g of 9α-brorno-pregna-1,4-diene-11β,21-diol-3,20-dione-[17α,16α-d]-2'-methyloxazoline-21-acetate is dissolved under nitrogen in 137 ml of a mixture methanol:chloroform (3:2). The solution is put in ice bath and 5.5 ml of 1 N NaOH are then added within 10 minutes followed by 5.5 ml within the next 40 minutes. A strong stirring is provided for 2 hours and the temperature is kept between 0°C and 5°C, then the pH is adjusted to 7 to 8 with glacial acetic acid. The solvent is evaporated in vacuo to 20 ml of volume of solution, that is poured into ice water (130 ml). The product is collected by filtration, washed with water and dried. Yield: 1.6 g (80%), MP 221°C to 222°C. It is pregna-1,4-diene-9β,11β-epoxy-21-ol-3,20-dione-[17α,16α-d]-2'-methyloxazoline.

An amount of 1 g of the above product is dissolved in 9.4 ml of a mixture obtained by mixing 4.67 ml of hydrofluoric acid with 8.5 ml of tetrahydrofuran at the temperature of 0°C. This solution is stirred for 20 hours at the same temperature, then under strong stirring and cooling 20 ml of tetrahydrofuran are added. The solution is subsequently neutralized by the addition of 24 g of sodium bicarbonate followed by 1 g of sodium sulfate. The inorganic substance is collected and washed with ethyl acetate. The filtrate is evaporated to dryness and the product is crystallized from acetone: 0.65 g (yield 61%) of pregna-1,4-dien-9α-fluoro-11β,21-diol-3,20-dione-[17α,16α-d]-2'-methyloxazoline are obtained, MP 241°C to 244°C $[\alpha]_D$ = +83.5 (c. 0.5, $CHCl_3$).The 21-acetate has MP 252°C to 255°C $[\alpha]_D$ = +54.8 (c. 0.5, $CHCl_3$).

References

Merck Index 4028
Kleeman & Engel p. 404
DOT 12 (10) 396 (1976)
I.N.p.428
Nathansohn, G., Winters, G. and Testa, E.; US Patent 3,461,119; August 12, 1969; assigned to Lepetit S.p.A. (Italy)

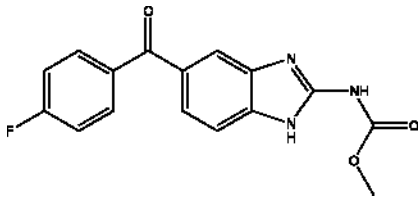
FLUBENDAZOLE

Therapeutic Function: Anthelmintic

Chemical Name: Methyl-N-[5(6)-p-fluorobenzoyl-2-benzimidazolyl]carbamate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 31430-15-6

Trade Name	Manufacturer	Country	Year Introduced
Fluvermal	Janssen-Le Brun	France	1980
Flubenol	Janssen	W. Germany	1982
Flumoxane	Le Brun	France	-

Raw Materials

Fluorobenzene
Ammonia
Hydrogen
S-Methylthiourea sulfate
Aluminum chloride
4-Chloro-3-nitrobenzoyl chloride
Methyl chloroformate

Manufacturing Process

To a stirred and cooled (ice bath) suspension of 25 parts of aluminum chloride in 52 parts of fluorobenzene is added dropwise a solution of 27.5 parts of 4-chloro-3-nitrobenzoyl chloride in 52 parts of fluorobenzene. Upon completion, stirring is continued overnight at room temperature. The reaction mixture is poured onto water and the product is extracted with methylene chloride. The extract is washed successively with sodium hydrogen carbonate solution and water, dried, filtered and evaporated in vacuo. The solid residue is crystallized from 2-propanol, yielding 4-chloro-4'-fluoro-3-nitrobenzophenone; MP 97.9°C.

A mixture of 24.5 parts of 4-chloro-4'-fluoro-3-nitrobenzophenone, 72 parts of methanol, 13 parts of sulfolane and 3.12 parts of ammonia is heated in a sealed tube for 20 hours at 120°C. To the reaction mixture is added successively 50 parts of water and 25 parts of a diluted hydrochloric acid solution and the whole is stirred and refluxed for 5 minutes. The reaction mixture is cooled and the precipitated product is filtered off. It is washed with

2-propanol and recrystallized from 640 parts of toluene, yielding 4-amino-4'-fluoro-3-nitrobenzophenone; MP 199°C.

A mixture of 14.5 parts of 4-amino-4'-fluoro-3-nitrobenzophenone, 160 parts of methanol, 6 parts of concentrated hydrochloric acid solution and 0.5 part of platinum oxide is hydrogenated at normal pressure and at room temperature. After the calculated amount of hydrogen is taken up, hydrogenation is stopped. The catalyst is filtered off and the filtrate is evaporated. The residue is washed with 2-propanol and dried, yielding 3,4-diamino-4'-fluorobenzophenone hydrochloride; MP 226°C to 230.5°C.

A mixture of 89 parts of S-methylisothiourea sulfate, 6.05 parts of methyl chloroformate in 7 parts of water is cooled, and at a temperature of 5°C to 10°C, sodium hydroxide solution 25% is added until pH equals 8. Then there are added successively 6.4 parts of acetic acid, 2.6 parts of sodium acetate and 8.9 parts of 3,4-diamino-4'-fluorobenzophenone hydrochloride and the whole is stirred while heating at 85°C for 45 minutes (during this reaction time, water and 2-propanol is added). The precipitated product is filtered off, washed with methanol and recrystallized from a mixture of 200 parts of acetic acid and 80 parts of methanol, yielding methyl N-[5(6)-p-fluorobenzoyl-2-benzimidazolyl] carbamate; MP > 260°C.

References

Merck Index 4030
DFU 3 (10) 739 (1978)
Kleeman & Engel p. 404
OCDS Vol. 2 p. 354 (1980)
DOT 16 (9) 307 (1980) & 17 (6) 259 (1981)
I.N. p. 428
Van Gelder, J.L.H., Roevens, L.F.C. and Raeymaekers, A.H.M.; US Patent 3,657,267; April 18, 1972; assigned to Janssen Pharmaceutica NV

FLUCLORONIDE

Therapeutic Function: Glucocorticoid

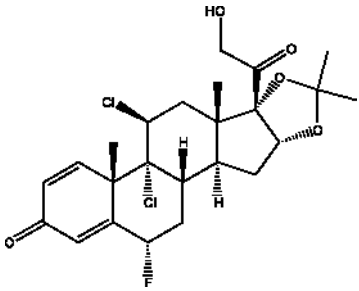
Chemical Name: 9,11β-Dichloro-6α-fluoro-21-hydroxy-16α,17-[(1-methylethylidene)bis(oxy)]-pregna-1,4-diene-3,20-dione

Common Name: Fluclorolone acetonide

Chemical Abstracts Registry No.: 3693-39-8

Trade Name	Manufacturer	Country	Year Introduced
Topilar	Syntex	UK	1971
Topilar	Syntex Daltan	France	1979
Gutanit	I.F.L.	Spain	-
Synemol	Syntex	-	-

Structural Formula:



Raw Materials

Acetic anhydride
Chlorine
Acetone
Methanesulfonyl chloride
Selenium dioxide
Potassium hydroxide
6α-Fluoro-16α-hydroxycortisone-21-acetate

Manufacturing Process

To 6α-fluoro-16α-hydroxy-hydrocortisone 21-acetate, described by Mills et al, J. Am. Chem. Soc., volume 81, pages 1264 to 1265, March 5, 1959, there was added acetic anhydride in dry pyridine. The reaction mixture was left at room temperature overnight and was then poured with stirring into ice water. The resulting precipitate was filtered, washed with water and crystallized from acetone-hexane to give 6α-fluoro-16α-hydroxy-hydrocortisone-16α,21-diacetate. This was reacted with methane-sulfonyl chloride in dimethyl formamide in the presence of pyridine at 80°C for 1 hour. The mixture was cooled, diluted with water and extracted with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate and the ethyl acetate was evaporated. By recrystallization of the residue from acetone-hexane there was obtained 6α-fluoro-$\Delta^{4,9(11)}$-pregnadiene-16α,17α,21-triol-3,20-dione-16α,21-diacetate.

This was reacted with chlorine to give the dichloropregnene compound, then with selenium dioxide to give the dichloropregnadiene compound. By hydrolysis with methanolic potassium hydroxide there was obtained the free 6α-fluoro-9α,11β-dichloro-$\Delta^{1,4}$-pregnadiene-16α,17α,21-triol-3,20-dione. By treatment with acetone in the presence of perchloric acid, the 16,17-acetonide of 6α-fluoro-9α,11β-dichloro-$\Delta^{1,4}$-pregnadiene-16α,17α,21-triol-3,20-dione was formed.

References

Merck Index 4033
Kleeman & Engel p. 405
OCDS Vol. 2 p. 198 (1980)
DOT 7 (4) 130 (1971)
I.N. p. 429
Bowers, A.: US Patent 3,201,391; August 17, 1965; assigned to Syntex Corporation, Panama

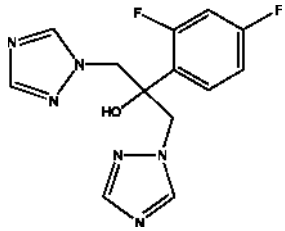
FLUCONAZOLE

Therapeutic Function: Antifungal

Chemical Name: 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)-

Common Name: Fluconazole

Structural Formula:



Chemical Abstracts Registry No.: 86386-73-4

Trade Name	Manufacturer	Country	Year Introduced
Diflucan	Pfizer	France	-
Forcan	Cipla Limited	India	-
Flucomycid Sedico	Sedico	Egypt	-
Fluconazole	Vorin Laboratories Limited	India	-
Fluconazole	Chemo Iberica	Spain	-
Flucoral	Bilim Ilac Sanayi Ve Tic. AS	Turkey	-
Flusenil	Anfarm-Hellas	Greece	-
Medoflucon	Medochemie Ltd.	Cyprus	-
Mycoflucan	Dr. Reddy's Laboratories Ltd.	India	-
Mycosyst	Gedeon Richter	Hungary	-
Zoltec	Pfizer	-	-

Raw Materials

Aluminum trichloride
Chloroacetyl chloride
Trimethyl sulfoxonium iodide
1,3-Difluorobenzene
Potassium hydroxide

Manufacturing Process

141.1 g of aluminum trichloride was first added to 86 ml of DFB and 77 ml of

chloroacetyl chloride was then added to the mixture, which was allowed to react at 60°C for 3 hours. After the reaction mixture had cooled down, 500 g of cold water was added. The mixture was stirred for about 20 min and then filtered to afford about 158.5 g of 2-chloro-2',4'-difluoroacetophenone in solid form (91% yield).

A solution of 158.5 g of 2-chloro-2',4'-difluoroacetophenone and 88.8 g of 4-amino-4H-1,2,4-triazole in 1,600 ml of cyanomethane was heated at reflux for 16 hours, cooled down, and filtered. The solid thus obtained was then washed with 500 ml of ethyl ether once to afford 2-(1H-1,2,4-triazol-1-yl)-2',4'-difluoroacetophenone salt.

The crude product obtained was dissolved in 1,320 ml of 1.5 N hydrochloric acid. To the solution thus obtained, an aqueous solution (330 ml) of sodium nitrite (58.2 g) was dropwise added and the mixture was allowed to react for 30 min. Aqueous ammonium was then used to adjust the reaction mixture to a neutral pH. The solid was precipitated and filtered to afford 159 g of 2-(1H-1,2,4-triazol-1-yl)-2',4'-difluoroacetophenone (yield about 80%), which had a water content of about 10%.

4 g of 4-amino-4H-1,2,4-triazole, 57.87 g of potassium hydroxide, 118 g of trimethyl sulfoxonium iodide, and 100 g of 2-(1H-1,2,4-triazol-l-yl)-2',4'-difluoroacetophenone were dissolved in 1,600 ml of water. The solution was heated at 70°C to react for 16 hours. Upon the completion of the reaction, the solution was adjusted with 4 N hydrochloric acid to a neutral pH and then extracted with acetyl acetate. The organic layer was collected, dried with 30 g of anhydrous calcium dichloride, decolorized with 15 g of active charcoal, and finally filtered off solid residues. The filtrate was concentrated to afford 99.3 g of the crude product (yield 72%). The crude product was further recrystallized from 500 ml of a solvent mixture of acetyl acetate and n-hexane (2:1) to afford 66.3 g of the Fluconazole in the form of white solid (yield 48%).

References

Shih K.-Sh.; US Patent No. 5,710,280; Jan. 20, 1998; Assigned to Development Center for Biotechnology (TW)

FLUCYTOSINE

Therapeutic Function: Antifungal

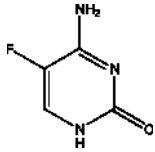
Chemical Name: 5-Fluorocytosine

Common Name: -

Raw Materials

5-Fluorouracil	Phosphorus oxychloride
Ammonia	Hydrogen chloride

Structural Formula:



Chemical Abstracts Registry No.: 2022-85-7

Trade Name	Manufacturer	Country	Year Introduced
Ancobon	Roche	US	1972
Ancotil	Roche	France	1974
Alcobon	Roche	UK	1974
Ancotil	Roche	W. Germany	1975
Ancotil	Roche	Japan	1979
Ancotil	Roche	Italy	1982

Manufacturing Process

The preparation of 5-fluorouracil is given under "Fluorouracil." As described in US Patent 3,040,026, 5-fluorouracil is then subjected to the following steps to give flucytosine.

Step 1: 2,4-Dichloro-5-Fluoropyrimidine - A mixture of 104 grams (0.8 mol) of 5-fluorouracil, 1,472 grams (9.6 mols) of phosphorus oxychloride and 166 grams (1.37 mols) of dimethylaniline was stirred under reflux for 2 hours. After cooling to room temperature, phosphorus oxychloride was removed by distillation at 18 to 22 mm and 22° to 37°C. The residue was then poured into a vigorously stirred mixture of 500 ml of ether and 500 gram of ice. After separating the ether layer, the aqueous layer was extracted with 500 ml, then 200 ml of ether. The combined ether fractions were dried over sodium sulfate, filtered, and the ether removed by vacuum distillation at 10° to 22°C. The residue, a yellow solid melting at 37° to 38°C, weighed 120 grams corresponding to a 90% yield. Vacuum distillation of 115 grams of this material at 74° to 80°C (16 mm) gave 108 grams of white solid melting at 38° to 39°C corresponding to an 84.5% yield.

Step 2: 2-Chloro-4-Amino-5-Fluoropyrimidine - To a solution of 10.0 grams (0.06 mol) of 2,4-dichloro-5-fluoropyrimidine in 100 ml of ethanol, 25 ml of concentrated aqueous ammonia were slowly added. A slightly opalescent solution resulted. The temperature gradually rose to 35°C. The solution was then cooled in ice to 18°C and thereafter remained below 30°C. After three hours, a Volhard titration showed that 0.0545 mol of chlorine was present in ionic form. Storage in a refrigerator overnight resulted in some crystallization of ammonium chloride. A white sludge, resulting from the evaporation of the reaction mixture at 40°C, was slurried with 75 ml of water, filtered and washed free of chloride. After drying in vacuo, the product melted at 196.5° to 197.5°C, yield 6.44 grams. Evaporation of the mother liquors yielded a second crop of 0.38 gram, raising the total yield to 6.82 grams (79.3%).

Step 3: 5-Fluorocytosine - A slurry of 34.0 grams (0.231 mol) of 2-chloro-4-amino-5-fluoropyrimidine in 231 ml of concentrated hydrochloric acid was heated in a water bath at 93° to 95°C for 125 minutes. The reaction was followed by means of ultraviolet spectrophotometry using the absorption at 245, 285, and 300 mμ as a guide. The absorption at 300 mμ rose to a maximum after 120 minutes and then dropped slightly. The clear solution was cooled to 25°C in an ice bath, then evaporated to dryness under vacuum at 40°C. After slurrying with water three times and reevaporating, the residue was dissolved in 100 milliliters of water. To this solution, cooled in ice, 29 ml of concentrated ammonia were added dropwise. The resulting precipitate was filtered, washed free of chloride with water, then with alcohol and ether. After drying in vacuo at 65°C, the product weighed 22.3 grams. An additional 6.35 grams was obtained by evaporation of the mother liquor, thus yielding a total of 28.65 grams (96.0%).

References

Merck Index 4035
Kleeman & Engel p. 406
PDR p. 1472
DOT 8 (11) 418 (1972)
I.N. p. 429
REM p. 1227
Heidelberger, C. and Duschinsky, R.; US Patent 2,802,005; August 6, 1957
Duschinsky, R. and Heidelberger, C.; US Patent 2,945,038; July 12, 1960; assigned to Hoffmann-La Roche Inc.
Duschinsky, R.; US Patent 3,040,026; June 19, 1962; assigned to Hoffmann-La Roche Inc.
Berger, J. and Duschinsky, R.; US Patent 3,368,938; February 13, 1968; assigned to Hoffmann-La Roche Inc.

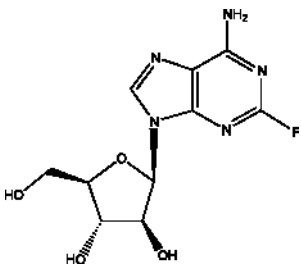
FLUDARABINE

Therapeutic Function: Antineoplastic

Chemical Name: Adenine, 9β-D-arabinofuranosyl-2-fluoro-

Common Name: Fludarabine; Fluorovidarabine

Structural Formula:



Chemical Abstracts Registry No.: 21679-14-1

Trade Name	Manufacturer	Country	Year Introduced
Fludarabine	Union Pharmaceutical Chemical Ltd.	-	-
Fludarabine	Shanghai Lancheng Corporation	-	-

Raw Materials

Guanosine
Acetic anhydride
Phosphorous oxychloride
Aniline, N,N-dimethyl-
Potassium fluoride
Ammonia

Manufacturing Process

Guanosine (87 g, 0.31 mL, predried for two days under vacuum at 100°C over P2O5) was combined with acetic anhydride (180 mL, 1.9 mol), pyridine (90 mL, 1.11 mol) and DMF (245 mL) and heated in oil bath at 75°C. The reaction was monitored by TLC on silica gel plates eluted with mixture of ethyl acetate:DMF:1-butanol (6:3:1). After 2 hours, the guanosine was consumed and the 2',3',5'-tri-O-acetylguanosine was observed to be the major product. The mixture was concentrated under vacuum. The residue was suspended in ethyl ether:2-propanol (1:1) and the solid collected by filtration was recrystallized from absolute ethanol. The product was dried at 80°C under vacuum to obtain 106.9 g (84%) of 2',3',5'-tri-O-acetylguanosine as a fluffy white solid; M.P. 229-233°C.

Distilled phosphorous oxychloride (47.7 mL, 510 mmol) was added to a solution of dried 2',3',5'-tri-O-acetylguanosine (36.1 g, 88 mmol), benzyltriethylammonium chloride (40.2 g, 176 mmol), and N,N-dimethylaniline (11.2 mL, 88 mmol, distilled from CaH_2 in anhydrous acetonitrile (200 mL, distilled from P_2O_5). The flask was fitted with a reflux condenser and placed in an oil bath preheated at 100°C. The mixture was heated to reflux, and heating was continued for 10 min. The mixture was concentrated under vacuum, and the residue was dissolved in dichloromethane (800 mL). The solution was stirred with ice for 15 min before the layers were separated. The aqueous layer was then washed with several portions of dichloromethane. The combined organic extracts were washed with water and then with portions of saturated sodium bicarbonate until neutral. Finally, it was dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was recrystallized twice from 300 mL of 2-propanol to obtain the purified 2',3',5'-tri-O-acetyl-6-chloroguanosine; 32.2 g (85%); M.P. 146-148°C.

A round bottom flask fitted with a mechanical stirrer and cold finger condenser was charged with potassium fluoride (140 g, 2.4 mole), 2',3',5'-tri-O-acetyl-6-chloroguanosine (70 g, 0. 16 mol) and anhydrous DMF (1.5 L). About 5-7 mL of trimethylamine was condensed into the flask. The suspension

was stirred at ambient temperature for 24 hours and then the mixture was concentrated under vacuum. The residue was suspended in chloroform and filtered and the insoluble material was washed thoroughly with chloroform (1.5 L total). The filtrate was concentrated under vacuum and the residue was recrystallized from 2-propanol to obtain 61.7 g (92%) of the 6-fluoro-2',3',5'-tri-O-acetylguanosine, M.P. 143-144°C.

The protecting groups in 6-fluoro-2',3',5'-tri-O-acetylguanosine was then deleted (alcaline saponification by action lithium hydroxide or NH_3) and the product was transformed into 9-beta-D-arabinofuranosyl-2-fluoro-adenine.

References

Merck Index, Monograph number: 4162, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Bauman J. G., Wirsching R. C.; US Patent No. 5,602,246; Feb. 11, 1997; Assigned to Schering Aktiengesellschaft (Berlin, DE)
Robins et al.; Can. J. Chem.; 1981, 59, 2601-2607

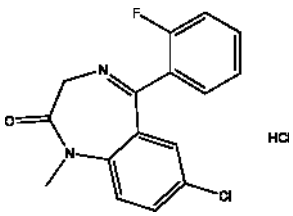
FLUDIAZEPAM HYDROCHLORIDE

Therapeutic Function: Anxiolytic

Chemical Name: 1-Methyl-7-chloro-5-(o-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepine-2-one hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 3900-31-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Erispan	Sumitomo	Japan	1981

Raw Materials

2-Aminomethyl-1-methyl-5-chloro-3-(o-fluorophenyl)indole HCl
Chromic anhydride

Ammonia
Hydrogen chloride

Manufacturing Process

A solution of 60 g of chromic anhydride in 40ml of water was added dropwise to a suspension of 60 g of 2-aminomethyl-1-methyl-5-chloro-3-(o-fluorophenyl)-indole hydrochloride in 600 ml of acetic acid. The mixture was stirred at room temperature overnight. To the reaction mixture was added 1.1 liters of ether and 1 liter of water and then 800 ml of 28% ammonium hydroxide, in small portions. The ethereal layer separated, washed with water, dried, and concentrated under reduced pressure. The residue (51.8 g) was dissolved in 100 ml of ethanol, and 100 ml of 20% ethanolic hydrogen chloride was added to the solution and the mixture was cooled. The precipitate was collected by filtration to yield 46.5 g of 1-methyl-7-chloro-5-(o-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepine-2-one hydrochloride, melting point 218°C (decomposed). Recrystallization from ethanol raised the melting point to 218.5°C to 219°C (decomposed).

References

Merck Index 4036
DFU 6 (12) 774 (1981)
DOT 18 (2) 68 (1982)
I.N.p.430
Yamamato, H., Inaba, S., Okamoto, T., Hirohashi, T., Ishizumi, K., Yamamoto, M., Maruyama, I., Mori, K. and Kobayashi, T.; US Patents 3,723,461; March 27, 1973; 3,828,027; August 6, 1974 and 3,925,364; December 9, 1975; all assigned to Sumitomo Chemical C

FLUDROCORTISONE ACETATE

Therapeutic Function: Antiinflammatory

Chemical Name: 9-Fluoro-11β,17,21-trihydroxy-pregn-4-ene-3,20-dione acetate

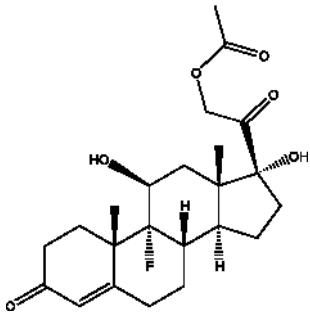
Common Name: -

Chemical Abstracts Registry No.: 514-36-3; 127-31-1 (Base)

Raw Materials

Hydrocortisone acetate
Phosphorus oxychloride
Hypobromous acid
Hydrogen fluoride

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Alflorone Acetate	MSD	US	1954
Florinef Acetate	Squibb	US	1955
F-Cortef Acetate	Upjohn	US	1955
Alfa-Fluorone	Ausonia	Italy	-
Alfanonidrone	Difer	Italy	-
Astonin	Merck	W. Germany	-
Blephaseptyl	Chauvin-Blache		-
Cortineff	Polfa	Poland	-
Florotic	Squibb	US	-
Fludrocortone	MSD	-	-
Myconef	Squibb	US	-
Panotile	Inpharzam	W. Germany	-
Panotile	Arsac	France	-
Schlerofluron	Schering	W. Germany	-

Manufacturing Process

Hydrocortisone acetate is first reacted with phosphorus oxychloride in pyridine to give the corresponding olefin. Then a sequence consisting of hypobromous acid addition, ring closure to the epoxide and ring opening with hydrogen fluoride gives fludrocortisone acetate. Preparation of a crystalline product is described then in US Patent 2,957,013.

References

Merck Index 4037
Kleeman & Engel p. 407
OCDS Vol. 1 p. 192 (1977)
DOT 7 (6) 203 (1971)
I.N. p. 430
REM p. 965
Graber, R.P. and Snoddy, C.S. Jr.; US Patent 2,957,013; October 18, 1960; assigned to Merck & Co., Inc.

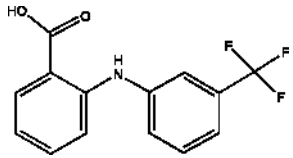
FLUFENAMIC ACID

Therapeutic Function: Antiinflammatory, Antirheumatic

Chemical Name: Anthranilic acid, N-(α,α,α-trifluoro-m-tolyl)-

Common Name: Acide flufenamique; Acidum flufenamicum; Flufenamic acid; Sputal

Structural Formula:



Chemical Abstracts Registry No.: 530-78-9

Trade Name	Manufacturer	Country	Year Introduced
Flufenamic acid	AroKor Holdings Inc.	-	-
Achless	Tatsumi	-	-
Ansatin	Ono	-	-
Arlef	Parke, Davis	-	-
Arlef	Sankyo	-	-
Dignodolin	Sankyo Pharma GMBH	-	-
Felunamin	Hokuriko	-	-
Flufacid	Wakamoto	-	-
Fullsafe	Ohta	-	-
Meralen	HMR	-	-
Meralen	Merrell	-	-
Paraflu	Dainippon	-	-
Pinox Cap	Alexandria Co.	-	-
Parlef	Parke, Davis	-	-
Ristogen	Kowa Yakuhin	-	-
Sastridex	Lindopharm	-	-
Surika	Thiemann	-	-
Romazal	Tobishi	-	-
Romafen	Biofarma	-	-
Tecramine	Teisan	-	-

Raw Materials

o-Chlorobenzoic acid
Trifluoromethyl-m-aminobenzene
Copper
Potassium carbonate

Manufacturing Process

A mixture 31.3 g of o-chlorobenzoic acid, 32.2 g of trifluoromethyl-m-aminobenzene, 3 g of copper powder, 13.8 g of waterless potassium carbonate and 100 ml amyl alcohol was refluxed for 4 hours. To the cooled mixture was added 25 ml of 10 N solution NaOH and the mixture was concentrated and filtrated. Addition to the filtrate hydrochloric acid and water give a sediment of 2-((3-trifluromethyl)phenyl)aminobenzoic acid. After recrystallization from hexane 2-((3-trifluromethyl)phenyl)aminobenzoic acid have melting point 134-136°C.

References

Merck Index, Monograph number: 4167, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
JACS 1960, 82, 1605
Fr. Patent M-1,341; Aug. 11, 1961; Assigned to Parke, Davis and Company

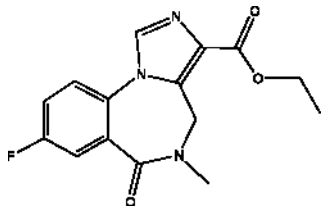
FLUMAZENIL

Therapeutic Function: Benzodiazepine receptor antagonist, Anticonvulsant

Chemical Name: 4H-Imidazo[1,5-a][1,4]benzodiazepine-3-carboxylic acid, 8-fluoro-5,6-dihydro-5-methyl-6-oxo-, ethyl ester

Common Name: Flumazenil; Flumazepil

Structural Formula:



Chemical Abstracts Registry No.: 78755-81-4

Trade Name	Manufacturer	Country	Year Introduced
Anexate	Roche Co.	-	-
Flumazenil	American Pharmaceutical Partners, Inc.	-	-
Romazicon	Roche Co.	-	-

Raw Materials

Sarcosine	5-Fluoroisatoic acid anhydride
Acetic acid	Potassium t-butylate
Diethylchlorophosphate	Ethyl isocyanoacetate

Manufacturing Process

24 g (132.5 mmol) of 5-fluoroisatoic acid anhydride are dissolved in 140 ml of dimethyl sulphoxide and treated with 11.8 g (132.5 mmol) of sarcosine. The solution is stirred at 100°C until the gas evolution ceases (duration: ca 1.5 h) and subsequently poured into ca 1.2 L of water. After stirring for 10 min, a solid crystallizes out. The crystals are filtered off under suction, washed with 1 L of water and dried. There is obtained 7-fluoro-3,4-dihydro-4-methyl-2H-1,4-benzodiazepine-2,5(1H)-dione of melting point 262°-263°C.

A solution of 6.5 g (32 mmol) of 7-fluoro-3,4-dihydro-4-methyl-2H-1,4-benzodiazepine-2,5(1H)-dione in 30 ml of dry dimethylformamide is treated with 4.3 g (38 mmol) of potassium t-butylate under an argon atmosphere. The temperature thereby rises to 35°C. After 10 min, the mixture is cooled to -30°C and 5.8 g (34 mmol) of diethylchlorophosphate are added dropwise thereto at -30°C to -20°C. The solution is subsequently stirred at -200°C for 10 min.

Separately, 4 g (35 mmol) of potassium tert-butylate are dissolved in 10 ml of dimethylformamide and treated at ca. -40°C with 4 g (35 mmol) of ethyl isocyanoacetate. This solution is added dropwise at -10°C to -20°C to the mixture obtained according to the preceding paragraph. The resulting mixture is then stirred without cooling for 1 h, 3.2 ml of glacial acetic acid are added thereto, the mixture is poured into ca. 400 ml of water and extracted three times with 150 ml of ethyl acetate each time. The combined organic extracts are washed five times with 200 ml of water each time, dried over magnesium sulfate and evaporated. From the oily residue there is obtained, by column chromatography on silica gel and subsequent recrystallisation from ethyl acetate and ether, ethyl 8-fluoro-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate of melting point 199°-200°C.

References

Gerecke M. et al.; US Patent No. 4,346,031; August 24, 1982; Assigned: Hoffmann-La Roche Inc., Nutley, N.J.

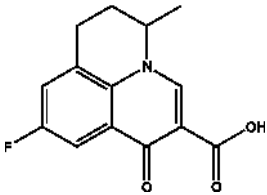
FLUMEQUINE

Therapeutic Function: Antibacterial

Chemical Name: 9-Fluoro-6,7-dihydro-5-methyl-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 42385-25-6

Trade Name	Manufacturer	Country	Year Introduced
Apurone	Riker	France	1977
Uribact	Diethelm	Switz.	1983
Flumural	SPA	Italy	-

Raw Materials

6-Fluoro-2-methyltetrahydroquinoline
Diethyl ethoxymethylenemalonate
Polyphosphoric acid
Sodium hydroxide

Manufacturing Process

6-Fluoro-2-methyltetrahydroquinoline (32.2 g, 0.2 mol) is mixed with diethyl ethoxymethylenemalonate, and the mixture is heated at 125°C to 130°C for 3 hours. Polyphosphoric acid (200 g) is added, and the solution is gradually heated to 115°C to 120°C in an oil bath with occasional stirring. The temperature is maintained for 1 hour, then the mixture is poured into 600 ml of water and neutralized with 40% sodium hydroxide solution. The product ester which precipitates is separated by filtration, washed with water and suspended in 2 liters of 10% sodium hydroxide solution. The mixture is heated on the steam bath for 1 hour, treated with decolorizing charcoal, filtered, then neutralized with concentrated hydrochloric acid. The solid product is isolated by filtration of the hot solution, washed with water and recrystallized from dimethylformamide.

References

Merck Index 4041
Kleeman & Engel p. 411
OCDS Vol. 3 p. 186 (1984)
DOT 11 (10) 410 & 14 (8) 365 (1978)
I.N. p. 431
Gerster, J.F.; US Patent 3,896,131; July 22, 1975; assigned to Riker Laboratories, Inc.

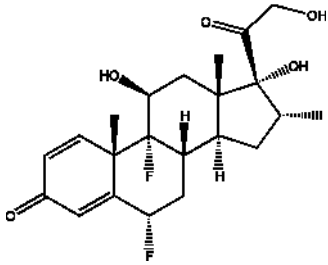
FLUMETHASONE

Therapeutic Function: Glucocorticoid, Antiinflammatory

Chemical Name: 6,9-Difluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione

Common Name: 6α-Fluorodexamethasone

Structural Formula:



Chemical Abstracts Registry No.: 2135-17-3

Trade Name	Manufacturer	Country	Year Introduced
Locacorten	Ciba	W. Germany	1964
Locorten	Ciba	Italy	1965
Locorten	Ciba	UK	1965
Locorten	Ciba Geigy	Japan	1970
Locorten	Ciba Geigy	US	1970
Cerson	VEB Leipziger Arz.	E. Germany	-
Loriden	Polfa	Poland	-
Topicorten	Trima	Israel	-

Raw Materials

6α-Fluoro-9β,11β-epoxy-16α-methyl-17α,21-dihydroxy-1,4-pregnadiene-3,20-dione-21-acetate
Hydrogen fluoride

Manufacturing Process

To approximately 1.3 g of hydrogen fluoride contained in a polyethylene bottle and maintained at -60°C was added 2.3 ml of tetrahydrofuran and then a solution of 500 mg (0.0012 mol) of 6α-fluoro-9β,11β-epoxy-16α-methyl-17α,21-dihydroxy-1,4-pregnadiene-3,20-dione-21-acetate in 2 ml of methylenechloride. The steroid solution was rinsed in with an additional 1 ml of methylene chloride. The light red colored solution was then kept at approximately -30°C for 1 hour and at -10°C for 2 hours. At the end of this

period it was mixed cautiously with an excess of cold sodium bicarbonate solution and the organic material extracted with the aid of additional methylene chloride. The combined extracts were washed with water, dried over anhydrous sodium sulfate and concentrated to approximately 35 ml. The solution was chromatographed over 130 g of Florisil anhydrous magnesium silicate. The column was developed with 260 ml portions of hexanes (Skellysolve B) containing increasing proportions of acetone. There was thus eluted 6α,9α-difluoro-11β,17α,21-trihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 21-acetate which was freed of solvent by evaporation of the eluate fractions.

References

Merck Index 4042
Kleeman & Engel p. 411
OCDS Vol. 1 p. 200 (1977)
I.N. p. 431
REM p. 965
Lincoln, F.H., Schneider, W.P. and Spero, G.B.; US Patent 3,557,158; January 19, 1971; assigned to The Upjohn Co.

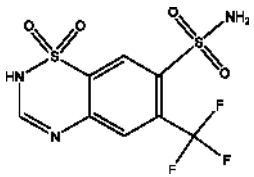
FLUMETHIAZIDE

Therapeutic Function: Carbonic anhydrase inhibitor

Chemical Name: 6-(Trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide

Common Name: Trifluoromethylthiazide

Structural Formula:



Chemical Abstracts Registry No.: 148-56-1

Trade Name	Manufacturer	Country	Year Introduced
Ademol	Squibb	US	1959

Raw Materials

Chlorosulfonic acid
Ammonia
3-Trifluoromethylaniline
Formic acid

Manufacturing Process

Chilled 3-trifluoromethylaniline (32.2 g) is added dropwise over a 45-minute period to 150 ml of chlorosulfonic acid with stirring and cooling. The ice bath is removed and 140 g of sodium chloride is added over 3 hours. The mixture is heated on a water bath for 30 minutes, then gradually up to 160°C over 6 hours. The cooled reaction mixture is diluted with 500 ml of an ice water slurry and taken into ether. The ether is dried and evaporated to leave 5-trifluoromethylamine-2,4-disulfonyl chloride.

The crude residue is heated on the steam bath for 1 hour with 75 ml of concentrated ammonium hydroxide. Cooling and filtration gives 2,4-disulfamyl-5-trifluoromethylaniline, MP 241°C to 243°C.

This intermediate is treated with an excess of 98% formic acid at steam bath temperature for 3 hours. Evaporation and dilution with water gives 7-sulfamyl-6-trifluoromethyl-1,2,4-benzothiadiazine-1,1-dioxide, MP 304°C to 308°C.

References

Merck Index 4043
OCDS Vol. 1 p. 355 (1977) & 2 p. 355 (1980)
I.N. p.431
Smith Kline & French Laboratories; British Patent 861,809; March 1, 1961

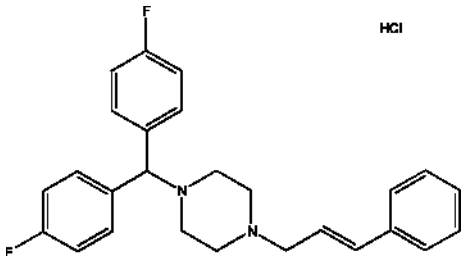
FLUNARIZINE HYDROCHLORIDE

Therapeutic Function: Vasodilator

Chemical Name: 1-[Bis(4-fluorophenyl)methyl]-4(3-phenyl-2-propenyl) piperazine hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 30484-77-6; 52468-60-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Sibelium	Janssen	W. Germany	1977
Sibelium	Janssen	Switz.	1980
Issium	Farmochimica	Italy	1981
Fluxarten	Zambeletti	Italy	1981
Dinaplex	Sidus	Argentina	-
Flugeral	Italfarmaco	Italy	-
Flunagen	Gentili	Italy	-
Gradient Polifarma	Polifarma	Italy	-
Mondus	Labinca	Argentina	-

Raw Materials

Sodium carbonate
Di-(p-Fluorophenyl)chloromethane
1-Cinnamylpiperazine

Manufacturing Process

A mixture of 14.3 parts of di-(p-fluorophenyl)-chloromethane, 10.1 parts of 1-cinnamylpiperazine, 12.7 parts of sodium carbonate, a few crystals of potassium iodide in 200 parts of 4-methyl-2-pentanone is stirred and refluxed for 21 hours. The reaction mixture is cooled and 50 parts of water are added. The organic layer is separated, dried, filtered and evaporated.

The oily residue is dissolved in 480 parts of anhydrous diisopropyl ether. This solution is boiled with activated charcoal, filtered and to the clear filtrate is added an excess of 2-propanol, previously saturated with gaseous hydrogen chloride. The precipitated salt is filtered off and recrystallized from a mixture of 2-propanol and ethanol, yielding 1-cinnamyl-4-(di-p-fluorobenzhydryl) piperazine dihydrochloride, MP 251.5°C.

References

Merck Index 4045
Kleeman & Engel p. 412
OCDS Vol. 2 p. 31 (1980)
DOT 14 (3) 109 (1978)
I.N. p. 432
Janssen, P.A.J.; US Patent 3,773,939; November 20, 1973; assigned to Janssen Pharmaceutica N.V.

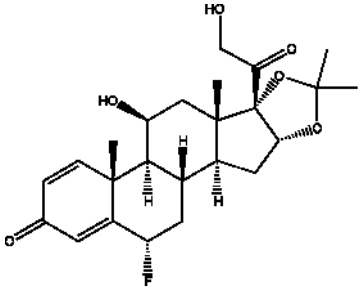
FLUNISOLIDE

Therapeutic Function: Antiinflammatory

Chemical Name: 16α,17α-Isopropylidenedioxy-6α-fluoro-1,4-pregnadiene-11β,21-diol-3,20-dione

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 3385-03-3

Trade Name	Manufacturer	Country	Year Introduced
Syntaris	Syntex	UK	1978
Syntaris	Syntex	W. Germany	1979
Syntaris	Syntex	Switz.	1980
Nasalide	Syntex	US	1981
Syntaris	Recordati	Italy	1982
Lunis	Valeas	Italy	1983
Aero Bid	Key	US	-
Bronalide	Krewel	W. Germany	-
Lobilan Nasal	Astra	-	-
Lokilan Nasal	Syntex	-	-
Rhinalar	Syntex	-	-

Raw Materials

6α-Fluoroprednisolone
Bacterium *Streptomyces roseochromogenus*
Acetone
Perchloric acid

Manufacturing Process

(a) Preparation of 6α-fluoro-16α-hydroxyprednisolone: 1.9 liters of whole mash containing 400 mg of 6α-fluoroprednisolone (6α-fluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione) acted upon by Streptomyces roseochromogenus AE-751 (or Waksman No. 3689) is filtered and the filtrate extracted three times with 2 liter portions of ethyl acetate. The mycelium is extracted with 500 ml of ethyl acetate and the mixture filtered. The combined ethyl acetate extracts are washed with 200 ml of water and concentrated to a residue. The residue is subjected to partition chromatograph using a 200 g column of diatomaceous earth moistened with the lower phase of an equilibrated solvent system composed of 1 volume of water, 5 volumes of dioxane, and 3 volumes of cyclohexane. The upper phase is used to develop

the column and the activity of the eluent is followed by measuring the ultraviolet absorbance at 240 mμ. The cuts containing most of the activity are concentrated to a syrupy residue and triturated with acetone. Crystals (25 mg) form and recrystallization gives a product with a MP of 226°C to 230°C.

(b) Preparation of 16α,17α-isopropylidenedioxy-6α-fluoro-1,4-pregnadiene-11β,21-diol-3,20-dione: 15 mg of crystalline 6α-fluoro-11β,16α,17α,21-tetrahydroxy-1,4-pregnadiene-3,20-dione [6α-fluoro-16α-hydroxyprednisolone described in US Patent 2,838,546 and prepared as described in (a) above] is dissolved in 2 ml of acetone and 0.02 ml of 70% perchloric acid is added. The solution is allowed to stand 1 hour. Then 0.5 ml of saturated sodium bicarbonate solution is added and the solution concentrated under reduced pressure to about 1 ml. The solution is allowed to stand overnight and the crystals which form are filtered, washed with ether and recrystallized from acetone-hexane. The crystals are the 16α,17α-isopropylidene derivative of 6α-fluoro-16α-hydroxyprednisolone.

References

Merck Index 4046
DFU 3 (2) 81 (1979)
Kleeman & Engel p. 413
PDR pp. 966,1803
OCDS Vol. 2 p. 181 (1980)
DOT 16 (8) 252 (1980)
I.N. p. 432
REM p. 972
American Cyanamid Co.; British Patent 933,867; August 14, 1963

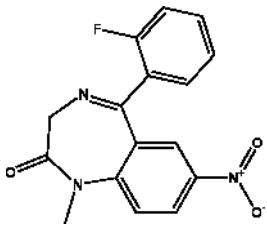
FLUNITRAZEPAM

Therapeutic Function: Hypnotic

Chemical Name: 5-(2-Fluorophenyl)-1,3-dihydro-1-methyl-7-nitro-2H-1,4-benzodiazepin-2-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 1622-62-4

Trade Name	Manufacturer	Country	Year Introduced
Roipnol	Roche	Italy	1976
Rohypnol	Roche	France	1978
Rohypnol	Roche	W. Germany	1979
Rohypnol	Sauter	UK	1982
Hypnodorm	Teva	Israel	-
Hipnosedon	Roche	-	-
Narcozep	Roche	France	-

Raw Materials

Hydrogen
Ammonia
Sulfuric acid
Methyl iodide
Sodium hydride
p-Chloroaniline
o-Fluorobenzoyl chloride
Bromoacetyl bromide
Potassium nitrate

Manufacturing Process

A mixture of 176 grams of orthofluorobenzoyl chloride and 64 grams of para-chloroaniline was stirred and heated to 180°C, at which temperature 87 grams of zinc chloride was introduced, the temperature raised to 200° to 205°C and maintained there for 40 minutes. The golden colored melt was quenched by the careful addition of 500 ml of 3 N hydrochloric acid and the resulting mixture refluxed for 5 minutes. The acid solution was decanted and the process repeated three times to remove all orthofluorobenzoic acid. The grey granular residue was dissolved in 300 ml of 75% (v/v) sulfuric acid and refluxed for 40 minutes to complete hydrolysis. The hot solution was poured over 1 kg of ice and diluted to 2 liters with water. The organic material was extracted with four 300 ml portions of methylene chloride, and the combined extracts subsequently washed with two 500 ml portions of 3 N hydrochloric acid to remove traces of para-chloroaniline, three 500 ml portions of 5 N sodium hydroxide solution to remove orthofluorobenzoic acid, and finally two 200 ml portions of saturated brine solution.

The combined methylene chloride extracts were dried over anhydrous sodium sulfate and the solvent removed to give the crude 2-amino-5-chloro-2'-fluorobenzophenone which upon recrystallization from methanol formed yellow needles melting at 94° to 95°C.

50.0 grams of 2-amino-5-chloro-2'-fluorobenzophenone in 300 cc of tetrahydrofuran was hydrogenated at atmospheric pressure in the presence of 10 grams of charcoal (Norite), 30.0 grams of potassium acetate and 2.5 cc of a 20% palladous chloride solution (20% by weight of palladium). After an initiation period varying from 10 minutes to an hour, hydrogen uptake was rapid and stopped completely after the absorption of the theoretical amount.

Filtration of the catalyst over a Hyflo pad and removal of the solvent left a yellow crystal line residue. The crude mixture of ketone and potassium acetate was partitioned between methylene chloride (300 cc) and water (1 liter). The layers were separated and the water layer washed with methylene chloride (3 x 50 cc). The organic layers were combined, washed with 3 N

sodium hydroxide solution (2 x 50 cc), water (3 x 100 cc), dried over anhydrous sodium sulfate and filtered. The solvent was removed and the product recrystallized from ethanol to give 2-amino-2'-fluorobenzophenone as yellow prisms melting at 126° to 128°C.

A solution of 21.5 grams of 2-amino-2'-fluorobenzophenone in 500 cc of ether was treated with 20 cc of a 20% (v/v) solution of bromoacetyl bromide in ether. The mixture was shaken and allowed to stand for 5 minutes and then washed with water (20 cc). The process was repeated five times. The final solution was washed thoroughly with water (5 x 500 cc) and concentrated to 100 cc. The crystals were filtered and recrystallized from methanol to give 2-bromacetamido-2'-fluorobenzophenone as white needles melting at 117° to 118.5°C.

A solution of 23.7 grams of 2-bromoacetamido-2'-fluorobenzophenone in tetrahydrofuran (100 cc) was added to liquid ammonia (approximately 500 cc) and allowed to evaporate overnight. The residue was treated with water (1 liter) and the crystals filtered off and refluxed in toluene (100 cc) for 30 minutes. The mixture was treated with decolorizing carbon (Norite) and filtered over Hyflo. The solution was concentrated to a small volume (25 cc) cooled, diluted with 20 cc of ether and allowed to stand. The product was recrystallized from acetone/hexane to give 5-(2-fluorophenyl)-3H-1,4-benzodiazepin-2(1H)-one as white needles melting at 180° to 181°C.

23.8 grams of 5-(2-fluorophenyl)-3H-1,4-benzodiazepin-2(1H)-one was dissolved in 50 cc of concentrated sulfuric acid at 0°C. To the resulting mixture there was then added dropwise with stirring a solution of 7.1 grams of potassium nitrate in 20 cc of concentrated sulfuric acid. The mixture was stirred for 2½ hours at 0°C and then diluted with 300 grams of ice. The resulting solution was made alkaline with concentrated ammonium hydroxide solution, keeping the temperature at 0°C. The formed suspension was extracted thoroughly with methylene chloride (6 x 100 cc). The organic layers were combined, washed with saturated brine solution, dried over anhydrous sodium sulfate and filtered. Removal of the solvent yielded a brown gum which was taken up in a small amount of methylene chloride and filtered through a pad of grade I alumina. The alumina was eluted with methylene chloride, the solvent removed, and the residue crystallized from acetone/hexane to yield 7-nitro-5-(2-fluorophenyl)-3H-1,4-benzodiazepin-2(1H)-oneas white needles melting at 210° to 211°C.

20.2 grams of the abovementioned 7-nitro-5-(2-fluorophenyl)-3H-1,4-benzodiazepin-2(1H)-one was dissolved in 60 cc of N,N-dimethyl formamide to which was then added 3.49 grams of a 50% suspension of sodium hydride in heavy mineral oil. The mixture was allowed to stir for 15 minutes in the cold, 11.2 grams of methyl iodide was added and the solution was stirred for a further 20 minutes. Solvent was removed under reduced pressure to give an oil which was partitioned between water and methylene chloride (1 liter/300 cc), the water layer was extracted with methylene chloride (5 x 200 cc), the organic layers combined and washed with water (2 x 100 cc), 3N hydrochloric acid (1 x 50 cc), water (3 x 100 cc), dried over anhydrous sodium sulfate and filtered.

Removal of the solvent gave an oil which was taken up in ether and filtered through a pad of Woelm grade I alumina. The eluent was concentrated and

the residue was crystallized from methylene chloride/hexane yielding 1-methyl-7-nitro-5-(2-ftuorophenyl)-3H-1,4-benzodiazepin-2(1H)-one as pale yellow needles melting at 166° to 167°C.

References

Merck Index 4047
Kleeman & Engel p. 413
OCDS Vol. 2 p. 406 (1980)
DOT 11 (5) pp. 177, 211 (1975) & 19 (3) p. 163 (1983)
I.N. p. 432
REM p. 1064
Kariss, J. and Newmark, H.L.; US Patent 3,116,203; December 31, 1963; assigned to Hoffmann-La Roche Inc.
Kariss, J. and Newmark, H.L.; US Patent 3,123,529; March 3, 1964; assigned to Hoffmann - La Roche Inc.
Keiler, O., Steiger, N. and Sternbach, L.H.; US Patent 3,203,990; August 31, 1965; assigned to Hoffmann-La Roche Inc.

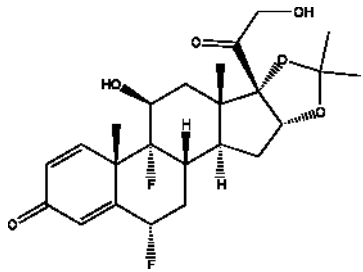
FLUOCINOLONE ACETONIDE

Therapeutic Function: Glucocorticoid, Antiinflammatory

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

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 67-73-2

Trade Name	Manufacturer	Country	Year Introduced
Synalar	Syntex	US	1961
Synalar	Cassenne	France	1961
Synalar	I.C.I.	UK	1961
Localyn	Recordati	Italy	1963

Trade Name	Manufacturer	Country	Year Introduced
Fellin	Gruenenthal	W. Germany	1964
Synemol	Syntex	US	1975
Fluonid	Herbert	US	1983
Fluotrex	Savage	US	1983
Alfabios	Iton	Italy	-
Alvadermo	Alvarez-Gomez	Spain	-
Benamizol	Mohan Yakuhin	Japan	-
Biscosal	Onta Seiyaku	Japan	-
Boniderma	Boniscontro	Italy	-
Coderma	Biotrading	Italy	-
Co-FIuosin	Sanchez-Covisa	Spain	-
Cordes F	Ichthyol	W. Germany	-
Cortalar	Bergamon	Italy	-
Cortiderma	Gazzini	Italy	-
Cortiphate	Tokyo Tanabe	Japan	-
Cortiespec	Centrum	Spain	-
Cortoderm	Lennon	S. Africa	-
Dermacort	P.S.N.	Italy	-
Dermaisom	Isom	Italy	-
Dermalar	Teva	Israel	-
Dermaplus	Ripari-Gero	Italy	-
Dermil	Cifa	Italy	-
Dermobeta	Amelix	Italy	-
Dermobiomar	Dermologia Marina	Spain	-
Dermofil	N.C.S.N.	Italy	-
Dermo Framan	Oftalmiso	Spain	-
Dermolin	Lafare	Italy	-
Dermomagis	Magis	Italy	-
Dermophyl	Rougier	Canada	-
Dermotergol	Wolner	Spain	-
Doricum	Farmila	Italy	-
Ekaton	Pharma Farm. Spec.	Italy	-
Esacinone	Lisapharma	Italy	-
Esilon	S.I.T.	Italy	-
Flucinar	Polfa	Poland	-
Flucort	Syntex-Tanabe	Japan	-
Fluocinil	Coli	Italy	-
Fluocinone	Panther-Osfa	Italy	-
Fluocit	C.T.	Italy	-
Fluoderm	Unipharm	Israel	-
Fluodermol	Medosan	Italy	-
Fluogisol	Washington	Italy	-
Fluolar	Riva	Canada	-
Fluomix	Savoma	Italy	-
Fluonide Dermica	Janus	Italy	-

Trade Name	Manufacturer	Country	Year Introduced
Fluordima	Intersint	Italy	-
Fluoskin	Dessy	Italy	-
Fluovitef	Italfarmaco	Italy	-
Flupollon	Kaigai	Japan	-
Flupollon	Ohta	Japan	-
Fluvean	Kowa	Japan	-
Fluzon	Taisho	Japan	-
Gelargin	Leciva	Czechoslovakia	-
Gelidina	I.F.L.	Spain	-
Intradermo	Pental	Spain	-
Isnaderm	Isnardi	Italy	-
Isoderma	Isola-Ibi	Italy	-
Jellin	Gruenenthal	-	-
Mecloderm	I.C.I.	Italy	-
Monoderm	Pharbil	Netherlands	-
Omniderm	Face	Italy	-
Oxidermiol Fuerte	Mazuelos	Spain	-
Percutina	Mitim	Italy	-
Prodermin	Eufarma	Italy	-
Radiocin	Radiopharma	Italy	-
Roliderm	Neopharmed	Italy	-
Sterolone	Francia	Italy	-
Straderm	I.T.A.	Italy	-
Synandone	I.C.I.	UK	-
Tefunote	Taiyo	Japan	-
Topifluor	Tiber	Italy	-
Ultraderm	Ecobi	Italy	-
Ungovac	I.C.N.	-	-

Raw Materials

6α-Fluoro-16α-hydroxy-hydrocortisone
Acetic anhydride
Methanesulfonyl chloride
N-Bromoacetamide
Hydrogen fluoride
Selenium dioxide
Potassium hydroxide

Manufacturing Process

A mixture of 1.2 grams of 6α-fluoro-16α-hydroxy-hydrocortisone, 4 cc of acetic anhydride and 8 cc of pyridine was heated at 60°C for 2 hours and then kept at room temperature for 2 hours. Ice and water were added and the solid was collected, washed with water, dried and recrystallized from methylene chloride-methanol, thus giving 1.05 grams of the 16,21-diacetate of 6α-fluoro-16α-hydroxy-hydrocortisone (solvated) of MP 182° to 187°C;

concentration of the mother liquors afforded an additional 130 mg of the same compound, MP 184° to 187°C. By recrystallization from the same solvents there was obtained the compound with a lower constant melting point of 175° to 177°C.

2.94 grams of the 16,21-diacetate of 6α-fluoro-16α-hydroxy-hydrocortisone was mixed with 60 cc of dimethylformamide, 3.6 cc of pyridine and 2.4 cc of methane-sulfonyl chloride was heated on the steam bath for 2 hours. The diacetate of 6α-fluoro-16α-hydroxy-hydrocortisone had been prepared as set forth above, and further dried by azeotropic distillation with benzene; the dimethylformamide had been previously distilled. After the 2 hours on the steam bath the mixture was cooled and poured into saturated aqueous sodium bicarbonate solution; the product was extracted with methylene chloride, the extract was washed with water, dried over anhydrous sodium sulfate and the solvent was evaporated.

The residue was chromatographed on 90 grams of silica gel eluting the product with methylene chloride-acetone (9:1) and then recrystallizing from methylene chloride-methanol. There was thus obtained 1.6 grams of the 16,21-diacetate of 6α-fluoro-$\delta^{4,9(11)}$-pregnadiene-16α,-17α,21-triol-3,20-dione with MP 110° to 114°C; the analytical sample melted at 115° to 117°C, $[\alpha]_D$+23.5° (chloroform), λ max. 234 to 236 nm, log ε 4.18.

A mixture of 1.38 grams of the above compound and 15 cc of dioxane was treated with 1.9 cc of a 0.5 N aqueous solution of perchloric acid and 600 mg of N-bromoacetamide, adding the latter in the dark, in three portions, in the course of half an hour and under continuous stirring, It was then stirred for a further 1% hours in the dark, then the excess of reagent was decomposed by the addition of aqueous sodium bisulfite solution and ice water was added; the product was extracted with methylene chloride, washed with water, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure, thus giving a yellow oil consisting of the 16,21-diacetate of 6α-fluoro-9α-bromo-16α-hydroxy-hydrocortisone which was used for the next step without further purification.

The above crude bromohydrin was mixed with 2.5 grams of potassium acetate and 60 cc of acetone and refluxed for 6 hours, at the end of which the acetone was distilled, water was added to the residue and the product was extracted with methylene chloride. The extract was washed with water, dried over anhydrous sodium sulfate and the solvent was evaporated. Recrystallization of the residue from methanol furnished 800 mg of the 16,21-diacetate of 6α-fluoro-9β,11β-oxido-δ^4-pregnene-16α,17α,21-triol-3,20-dione with MP 120° to 124°C; by chromatography of the mother liquors on silica gel there was obtained 180 milligrams more of the same compound with MP 117° to 119°C. The analytical sample was obtained by recrystallization from methanol; it showed MP 125° to 127°C.

To a solution of 1.6 grams of anhydrous hydrogen fluoride in 2.85 grams of tetrahydrofurane and 10 cc of methylene chloride cooled to -60°C was added a solution of 650 mg of the 16,21-diacetate of 6α-fluoro-9β,11β-oxido-δ^4-pregnene-16α,17α,21-triol-3,20-dione in 20 cc of methylene chloride and the mixture was kept at -10°C for 72 hours. It was then poured into saturated aqueous sodium bicarbonate solution and the organic layer was separated, washed with water, dried over anhydrous sodium sulfate and evaporated. The

residue was reacetylated by heating with 3 cc of acetic anhydride and 6 cc of pyridine for 1 hour on the steam bath. The reagents were evaporated under reduced pressure and the residue was chromatographed on 30 grams of silica gel. Upon elution with methylene chloride-acetone (9:1) and recrystallization of the residue from methylene chloride-methanol there was obtained 290 mg of the 16,21-diacetate of 6α,9α-difluoro-16α-hydroxy-hydrocortisone which melted with loss of solvent at 140° to 150°C. Recrystallization from acetone-hexane afforded the analytical sample which was dried at 130°C; it then showed a MP of 182° to 185°C.

A mixture of 290 mg of the 16,21-diacetate of 6α,9α-difluoro-16α-hydroxy-hydrocortisone, 30 cc of t-butanol, 0.5 cc of pyridine and 150 mg of selenium dioxide was refluxed for 53 hours under an atmosphere of nitrogen and cooled; ethyl acetate was added and filtered through celite; the solvent was evaporated to dryness under reduced pressure, the residue was triturated with water, the solid was collected by filtration, washed with water and dried. The product was then chromatographed on 10 grams of silica gel. The solid fractions eluted with acetone-methylene chloride (1:19) were recrystallized from methylene chloride, thus affording 68 mg of the 16,21-diacetate of 6α,9α-difluoro-16α-hydroxy-prednisolone; MP 212° to 215°C.

A mixture of 430 mg of the 16,21-diacetate of 6α,9α-difluoro-16α-hydroxy-prednisolone, 15 cc of methanol and 2.2 cc of a 4% aqueous solution of potassium hydroxide was stirred at 0°C in an atmosphere of nitrogen; the material entered rapidly in solution and reprecipitated after 30 minutes. The mixture was then stirred for 1 hour more at 0°C and under an atmosphere of nitrogen, then neutralized with acetic acid and the methanol was distilled under reduced pressure. The residue was triturated with water, the solid was collected, washed with water, dried and recrystallized from ethyl acetate-methanol, thus giving 285 milligrams of the free 6α,9α-difluoro-16α-hydroxy-prednisolone, MP 258° to 260°C; the analytical sample showed MP 266° to 268°C.

References

Merck Index 4050
Kleeman & Engel p. 414
PDR pp. 888, 930, 1429, 1606, 1800
I.N. p. 433
REM p. 966
Mills, J.S. and Bowers, A.; US Patent 3,014,938; December 26, 1961; assigned to Syntex SA, Mexico

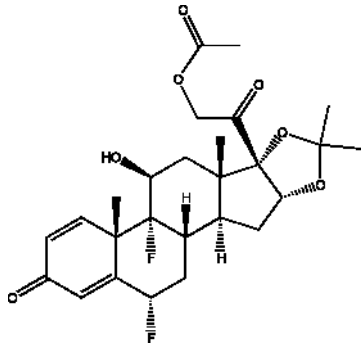
FLUOCINONIDE

Therapeutic Function: Antiinflammatory, Glucocorticoid

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

Common Name: Fluocinolone acetonide acetate

Structural Formula:



Chemical Abstracts Registry No.: 356-12-7

Trade Name	Manufacturer	Country	Year Introduced
Topsyn	Recordati	Italy	1970
Lidex	Syntex	US	1971
Metosyn	I.C.I.	UK	1971
Topsym	Gruenenthal	W. Germany	1971
Topsyne	Cassenne	France	1971
Topsyn	Tanabe	Japan	1975
Bestasone	Kodama	Japan	-
Cusigel	Cusi	Spain	-
Flu 21	Lanat	Italy	-
Fludex	San Carlo	Italy	-
Fluzon	Taisho	Japan	-
Novoter	Cusi	Spain	-
Supracort	Teva	Israel	-

Raw Materials

6α-Fluoro-triamcinolone
Perchloric acid
Acetone
Acetic anhydride

Manufacturing Process

To a suspension of 500 mg of 6α-fluoro-triamcinolone in 75 ml of acetone is added 0.05 milliliters of 72% perchloric acid and the mixture agitated-at room temperature for 3 hours. During this period the crystals gradually dissolve and the clear solution is neutralized with dilute bicarbonate and the acetone removed in vacuo. The resulting crystalline suspension is filtered and the

crystals washed with water. The dried material is recrystallized from 95% alcohol to give the pure acetonide.

A solution of 50 mg of 6α-fluoro-triamcinolone acetonide in 1 ml of pyridine and 1 ml of acetic anhydride is allowed to stand at room temperature for 18 hours. Removal of the reagents in vacuo gives a crystalline residue which after crystallization from acetone-hexane gives the pure 16α,17α-isopropylidene 6α-fluoro-triamcinolone 21 acetate (fluocinonide), as described in US Patent 3,197,469.

References

Merck Index 4051
Kleeman and Engel p. 415
PDR p. 1800
DOT 7 (6) 207 (1971)
I.N. p. 433
REM p.966
Ringold, H.J. and Rosenkranz, G.; US Patent 3,124,571; March 10,1964; assigned to Syntex Corporation, Panama
Ringold, H.J., Zderic, J.A., Djerassi, C. and Bowers, A.; US Patent 3,126,375; March 24, 1964; assigned to Syntex Corporation, Panama
Fried, J.; US Patent 3,197,469; July 27, 1965; assigned to Pharmaceutical Research Products, Inc.

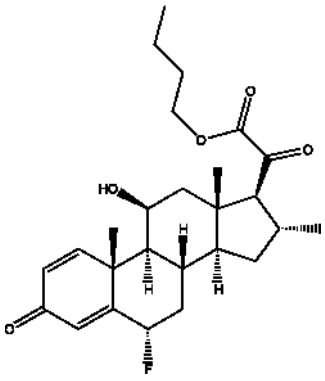
FLUOCORTIN BUTYL

Therapeutic Function: Antiinflammatory

Chemical Name: 6-Fluoro-11-hydroxy-16-methyl-3,20-dioxopregna-1,4-dien-21-oic acid butyl ester

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 41767-29-7; 33124-50-40 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Vaspit	Schering	W. Germany	1977
Vaspit	Schering	Switz.	1978
Vaspit	Schering	Italy	1981
Vaspit	Schering	Australia	-

Raw Materials

Copper acetate
Manganese dioxide
6α-Fluoro-11β,21-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione
Methanol
Butanol

Manufacturing Process

(a) A solution of 11.3 g of 6α-fluoro-11β,21-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione in 500 ml of absolute methanol is mixed with 3.0 g of copper(II) acetate in 500 ml of absolute methanol. The solution is agitated at room temperature for 170 hours, then clarified by filtration, and concentrated under vacuum. The residue is mixed with 10% ammonium hydroxide solution and extracted with methylene chloride. The organic phase is washed several times with water, dried over sodium sulfate, and concentrated under vacuum. The residue is chromatographed on 1.3 kg of silicagel. After recrystallization from acetone-hexane, with 6-7% acetone-methylene chloride, 1.40 g of the methyl ester of 6α-fluoro-11β,20α_F-di-hydroxy-3-oxo-16α-methyl-1,4-pregnadiene-21-oic acid is obtained, MP 191°C to 192°C.

(b) 2.1 g of a mixture of the methyl ester of 6α-fluoro-11β,20α_F-dihydroxy-3-oxo-16α-methyl-1,4-pregnadiene-21-oic acid and the methyl ester of 6α-fluoro-11β,20β_F-dihydroxy-oxo-16α-methyl-1,4-pregnadiene-21-oic acid is dissolved in 20 ml of methylene chloride. The solution is mixed with 20 g of active manganese(IV) oxide ("precipitation active for synthesis purposes" by Merck, A.G.) and refluxed for 6 hours. Then, the reaction mixture is filtered off from the manganese(IV) oxide. The filtrate is evaporated and the residue is recrystallized from acetone-hexane, thus obtaining 450 mg of the methyl ester of 6α-fluoro-11β-hydroxy-3,20-dioxo-16α-methyl-1,4-pregnadiene-21-oic acid, MP 182°C to 184°C.

(c) A solution of 250 mg of the methyl ester of 6α-fluoro-11β,20α_F-dihydroxy-3-oxo-16α-methyl-1,4-pregnadiene-21-oic acid in 3 ml of methylene chloride is mixed with 2.5g of active manganese(IV) oxide and stirred for 45 minutes at room temperature. The manganese(IV) oxide is removed by filtration, the filtrate is evaporated to dryness, and the residue is recrystallized from acetone hexane, thus producing 145 mg of the methyl ester of 6α-fluoro-11β-hydroxy-3,20-dioxo-16α-methyl-1,4-pregnadiene-21-oic acid, MP 188°C.

(d) 4.3 g of the methyl ester of 6α-fluoro-11β,20β_F-dihydroxy-3-oxo-16α-methyl-1,4-pregnadiene-21-oic acid is dissolved, with the addition of 50 g of active manganese(IV) oxide, in 50 ml of isopropanol. The reaction mixture is agitated at room temperature for 25 hour sand filtered off from the

manganese(IV) oxide. After evaporation of the solvent, the residue is recrystallized twice from hexane-acetone. Yield: 1.3 g of the methyl ester of 6α-fluoro-11β-hydroxy-3,20-dioxo-16α-methyl-1,4-pregnadiene-21-oic acid, MP 189°C to 191°C.

(e) 500 mg of 6α-fluoro-11β-hydroxy-3,20-dioxo-16α-methyl-1,4-pregnadiene-21-oic acid is dissolved in 100 ml of absolute ether, and mixed with 7 ml of butanol and 1.5 ml of dicyclohexyl carbodiimide. After 18 hours of agitation at room temperature, the reaction mixture is vacuum-filtered from the thus-precipitated dicyclohexyl urea. The filtrate is concentrated, and the crude product is chromatographed on silica gel. With 9-11% acetone-hexane, after recrystallization from acetone-hexane, 256 mg of the butyl ester of 6α-fluoro-11β-hydroxy-3,20-dioxo-16α-methyl-1,4-pregnadiene-21-oic acid is obtained, MP 185°C to 187°C.

References

Merck Index 4052
DFU 2 (10) 669 (1977)
Kleeman & Engel p. 416
DOT 13 (12) 528 (1977) & 17 (9) 388 (1981)
I.N. p. 434
Laurent, H., Wiechert, R., Prezewowsky, K., Hofmeister, H., Gerhards, E., Kolb, K.H. and Mengel, K.; US Patent 3,824,260; July 16, 1974; assigned to Schering A.G. (West Germany)

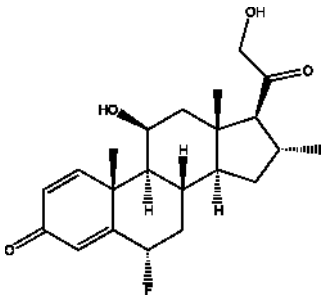
FLUOCORTOLONE

Therapeutic Function: Glucocorticoid

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

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 152-97-6

Trade Name	Manufacturer	Country	Year Introduced
Ultralan	Schering	W. Germany	1965
Ultralan	Schering	Italy	1974
Ficoid	Fisons	UK	-
Myco-Ultralan	S.E.P.P.S.	France	-
Syracort	Beiersdorf	W. Germany	-
Ultrasalon	Schering	W. Germany	-

Raw Materials

Chromic acid
Hydrogen fluoride
Acetic anhydride
16α-Methyl-δ(5)-pregnene-3β,21-diol-20-one-21-acetate
N-Bromoacetamide
Bacterium *Curvularia lunata*
Bacterium *Corynebacterium simplex*

Manufacturing Process

(a) 16α-Methyl-6α-Fluoro-δ4-11β,21-Diol-3,20-Dione:16α-methyl-6α-fluoro-δ4-pregnene-21-ol-3,20-dione-21-acetate (MP 132°/134° to 138°C, UVε_{238}= 15,000) is hydroxylated with *Curvularia lunata* in 11β-position using the fermentation method whereby the 21-acetate group is simultaneously saponified. The hitherto unknown starting material 16α-methyl-6α-fluoro-δ4-pregnene-21-ol-3,20-dione-21-acetate is obtained from 16α-methyl-δ5-pregnene-3β,21-diol-20-one-21-acetate, MP 152° to 154°C, by the addition of bromofluorine (from N-bromoacetamide and hydrogen fluoride) onto the 5-6 double bond, oxidation of the 3β-hydroxyl group with chromic acid, introduction of the δ4-double bond by splitting of the hydrogen bromide and acid isomerization of the 6β-fluoro substituent to the 16α-methyl-6α-fluoro-δ4-pregnene-21-ol-3,20-dione-21-acetate. By chromatographic purification on silica gel the 16α-methyl-6α-fluoro-δ4-pregnene-11β,21-diol-3,20-dione is: MP 166°/167° to 171°C.

(b) 16α-Methyl-6α-Fluoro-δ4-Pregnene-11β,21-Diol-3,20-Dione-21-Acetate:By reaction of the compound of (a) with acetic anhydride in pyridine at room temperature, the acetate is obtained and recrystallized from ethyl acetate, MP 248°/249° to 251°C.

(c) 16α-Methyl-6α-Fluoro-δ1,4-Pregnadiene-11β,21-Diol-3,20-Dione:16α-methyl-6α-fluoro-δ4-pregnene-11β,21-diol-3,20-dione is dehydrogenated with *Corynebacterium simplex*. The extraction residue is subjected to chromatography on silica gel and after recrystallization there is obtained from methylene chloride-isopropyl ether 16α-methyl-6α-fluoro-δ1,4-pregnadiene-11β,21-diol-3,20-dione, MP 180°/181° to 182°C.

References

Merck Index 4053
Kleeman and Engel p. 417
OCDS Vol. 1 p. 204 (1977)

I.N. p. 434
Kieslich, K., Kerb, U. and Raspe, G.; US Patent 3,426,128; February 4,1969; assigned to Schering AG, Germany

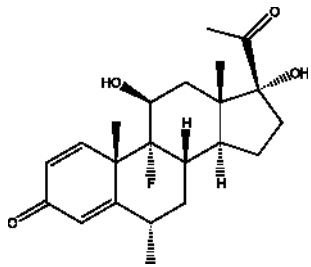
FLUOROMETHOLONE

Therapeutic Function: Glucocorticoid, Antiinflammatory

Chemical Name: 9-Fluoro-11β,17-dihydroxy-6α-methylpregna-1,4-diene-3,20-dione

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 426-13-1

Trade Name	Manufacturer	Country	Year Introduced
Oxylone	Upjohn	US	1959
Efflumidex	Pharm-Allergan	W. Germany	1975
FML Liquifilm	Allergan	UK	1977
Fluaton	Tubi Lux	Italy	1977
Flumerol	Sumitomo	Japan	1971
Flucon	Alcon	France	1983
Cortilet	Hoechst	-	-
Cortisdin	Isdin	Spain	-
Delmeson	Hoechst	W. Germany	-
Ehrtolan	Albert Roussel	W. Germany	-
Flu-Base	Kowa	Japan	-
Flumetholon	Santen	Japan	-
Flumetol	Farmila	Italy	-
Fluoderm	B.D.H.	UK	-
Fluolon	Lundbeck	-	-
Loticort	Hoechst	Italy	-
Okilon	Sumitomo	Japan	-
Regresin	Hoechst	-	-
Trilcin	B.D.H.	UK	-
Ursnon	Nippon Chemiphar	Japan	-

Raw Materials

1-Dehydro-6α-methyl-9α-fluorohydrocortisone
Methanesulfonyl chloride
Sodium iodide
Sodium thiosulfate

Manufacturing Process

The following description is taken from US Patent 2,867,637.

(a) Preparation of 6α-Methyl-9α-Fluoro-11β,17α,21-Trihydroxy-1,4-Pregnadiene-3,20-Dione 21-Methanesulfonate: A solution was prepared containing 250 mg of 1-dehydro-6α-methyl-9α-fluorohydrocortisone [G.B. Spero et al, J. Am. Chem. Soc.79, 1515 (1957)] in 6 ml of pyridine. This solution was cooled to 0°C and treated with 0.25 ml of methanesulfonyl chloride. Thereafter the solution was allowed to stir at a temperature between 0° and 5°C for a period of 18 hours. Thereafter ice and 2 ml of water were added, followed by 30 ml of sufficient dilute (5%) hydrochloric acid to neutralize the pyridine. The mixture was then filtered, the precipitate washed with water and dried to give 197 mg of crude 6α-methyl-9α-fluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-methanesulfonate of MP 165° to 185°C.

(b) Preparation of 6α-Methyl-9α-Fluoro-11β,17α-Dihydroxy-21-Iodo-1,4-Pregnadiene-3,20-Dione: The crude 197 mg of methanesulfonate of 6α-methyl-9α-fluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione was dissolved in 5 ml of acetone and treated with a solution of 197 mg of sodium iodide in 5 ml of acetone. The mixture was heated under reflux with stirring for a period of 15 minutes. The heating was then discontinued and the mixture concentrated to dryness at reduced pressure to give 6α-methyl-9α-fluoro-11β,17α-dihydroxy-21-iodo-1,4-pregnadiene-3,20-dione.

(c) Preparation of 6α-Methyl-9α-Fluoro-11β,17α-Dihydroxy-1,4-Pregnadiene-3,20-Dione: The crude 6α-methyl-9α-fluoro-11β,17α-dihydroxy-21-iodo-1,4-pregnadiene-3,20-dione was slurried with 5 ml of acetic acid and stirred for a period of 45 minutes. Thereafter was added a solution of 250 mg of sodium thiosulfate pentahydrate in 5 ml of water causing the iodine color to disappear. Additional water was added (30 ml) and the reaction mixture was filtered. The resulting solid precipitate was washed with water and dried to give 146 mg of crude 6α-methyl-9α-fluoro-11β,17α-dihydroxy-1,4-pregnadiene-3,20-dione.

The crude material was then chromatographed by dissolving 120 mg of 6α-methyl-9α-fluoro-11β,17α-dihydroxy-1,4-pregnadiene-3,20-dione in 300 ml of methylene chloride and allowing the thus obtained solution to be absorbed by a chromatographic column containing 10 grams of Florisil anhydrous magnesium silicate. The column was developed taking fractions of 20 ml each as follows:

Fraction	Solvent
1-5	Skellysolve B-hexane-5%acetone

6-10	Skellysolve B-hexane-10%acetone
11-15	Skellysolve B-hexane-15%acetone
16-20	Skellysolve B-hexane-20%acetone
21-25	Skellysolve B-hexane-30%acetone
26-28	Acetone

Fractions 11 through 24 inclusive were combined, evaporated and twice recrystallized from acetone to give pure 6α-methyl-9α-fluoro-11β,17α-dihydroxy-1,4-pregnadiene-3,20-dione of melting point 292° to 303°C.

References

Merck Index 4081
Kleeman and Engel p. 418
OCDS Vol. 1 p. 203 (1977)
I.N. p. 435
REM p. 966
Fried, J.; US Patent 2,852,51 September 16,1958; assigned to Olin Mathieson Chemical Corporation
Lincoln, F.H. Jr., Schneider, W.P. and Spero, G.B.; US Patent 2,867,637; January 6, 1959; assigned to The Upjohn Company
Lincoln,F.H. Jr., Schneider, W.P. and Spero, G.B.; US Patent 2,867,638; January 6, 1959; assigned to The Upjohn Company
Magerlein, B.J., Kagan, F. and Schlagel, C.A.; US Patent 3,038,914; June 12, 1962; assigned to The Upjohn Company

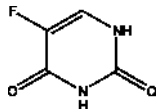
FLUOROURACIL

Therapeutic Function: Cancer chemotherapy

Chemical Name: 5-Fluoro-2,4(1H,3H)-pyrimidinedione

Common Name: 5-Fluorouracil

Structural Formula:



Chemical Abstracts Registry No.: 51-21-8

Trade Name	Manufacturer	Country	Year Introduced
Efudex	Roche	US	1962
Efudix	Roche	France	1963
Efudix	Roche	W. Germany	1966

Trade Name	Manufacturer	Country	Year Introduced
Fluoroplex	Herbert	US	1970
Efudix	Roche	UK	1972
Adrucil	Adria	US	1977
Arumel	SS Pharmaceutical	Japan	-
Benton	Toyo Jozo	Japan	-
Carzonal	Tobishi	Japan	-
Cinco-Fu	Montedison	W. Germany	-
Flacule	Nippon Kayaku, Co.	Japan	-
Fluoroblastin	Erba	Italy	-
Fluorotop	Abic	Israel	-
Fluorouracil	Roche	US	-
Kecimeton	Tatsumi	Japan	-
Lifril	Kissei Pharmaceutical Co., Ltd.	Japan	-
Timadin	Torii	Japan	-
Ulosagen	Kyowa Yakunin Osaka	Japan	-
Ulup	Maruko	Japan	-
Verrumal	Hermal	W. Germany	-

Raw Materials

Sodium fluoroacetate
Hydrogen chloride
Diethyl sulfate
Sodium methoxide
Potassium ethylate
S-Methylisothiouronium sulfate
Ethyl formate

Manufacturing Process

A mixture of 200 grams (2 mols) of dry sodium fluoroacetate and 442 grams (2.86 mols) of diethyl sulfate was refluxed for 31½ hours in an oil bath. The reaction mixture was then distilled through a fractionating column, yielding 177.3 grams of crude ethyl fluoroacetate, having a boiling range of 116° to 120°C. The material was redistilled through a fractionating column, yielding purified ethyl fluoroacetate boiling at 114° to 118°C.

In a 2-liter, 3-neck, round bottom flask, provided with stirrer, dropping funnel and reflux condenser, was placed 880 ml of absolute diethyl ether, and 47.6 grams (1.22 mols) of potassium, cut into 5 mm pieces, was suspended therein. 220 ml of absolute ethanol was added dropwise, while stirring, whereby the heat of reaction produced refluxing. In order to obtain complete dissolution of the potassium, the mixture was finally refluxed on a steam bath. The reaction mixture was then cooled in an ice bath, and a mixture of 135 grams (1.22 mols) of ethyl fluoroacetate and 96.4 grams (1.3 mols) of freshly distilled ethyl formate was added dropwise, while stirring and cooling, over a period of 2½ hours. Upon completion of the addition of the ethyl formate, the reaction mixture was stirred for an additional hour while cooling, and then was allowed to stand overnight at room temperature.

At the end of this time the crystalline precipitate which had formed was

filtered off with suction, washed with diethyl ether, and dried in a vacuum desiccator. The product comprised essentially the potassium enolate of ethyl fluoromalonaldehydate (alternative nomenclature, the potassium salt of fluoromalonaldehydic acid ethyl ester).

A mixture of 103.6 grams (0.6 mol) of the freshly prepared potassium enolate of ethyl fluoromalonaldehydate, 83.4 grams (0.3 mol) of S-methylisothiouronium sulfate and 32.5 grams (0.6 mol) of sodium methoxide was refluxed with stirring in 1,500 ml of absolute methanol. At first the reactants dissolved to a great extent, but very shortly thereafter precipitation occurred. The reaction mixture was refluxed for 2 hours and at the end of this time was evaporated to dryness in vacuo. The residue was treated with 280 ml of water; incomplete dissolution was observed.

The mixture obtained was clarified by filtering it through charcoal. The filtrate was acidified (to a slight Congo red acid reaction) by adding concentrated aqueous hydrochloric acid, containing 37% by weight HCl (48 ml required). The material which crystallized from the acidified solution was filtered off, washed free of sulfates with water and dried at 100°C, yielding crude S-methyl ether of 2-thio-5-fluorouracil, having a melting range from 202° to 221°C. The latter material was recrystallized by dissolving it in 2,035 ml of boiling ethylacetate and cooling to -20°C, yielding S-methyl ether of 2-thio-5-fluorouracil, MP 230° to 237°C, in a sufficient state of purity that it could be used directly for the next step. A sample of the material was recrystallized from water (alternatively, from ethyl acetate) thereby raising the melting point to 241° to 243°C. For analysis the material was further purified by subliming it in vacuo at 140° to 150°/0.1 mm

A solution of 10.0 grams of purified S-methyl ether of 2-thio-5-fluorouracil, MP 230° to 237°C, in 150 ml of concentrated aqueous hydrochloric acid (containing approximately 37% by weight HCl) was refluxed under nitrogen for 4 hours. The reaction mixture was then evaporated in vacuo. The crystalline brownish residue was recrystallized from water. The resulting recrystallized product was further purified by sublimation in vacuo at 190° to 200°C (bath temperature)/0.1 mm pressure. There was obtained 5-fluorouracil, in the form of colorless or pinkish-tan crystals, MP 282° to 283°C (with decomposition).

References

Merck Index 4088
Kleeman & Engel p. 419
PDR pp. 559, 931,1483
OCDS Vol. 3 p. 155 (1984)
DOT 9 (12) 495 (1973) and 16 (5) 174 (1980)
I.N. p. 436
REM p. 1149
Heidelberger, C. and Duschinsky, R.; US Patent 2,802,005; August 6, 1957
Heidelberger, C. and Duschinsky, R.; US Patent 2,885,396; May 5, 1959

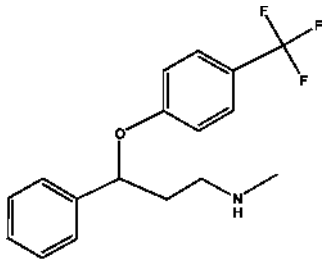
FLUOXETINE

Therapeutic Function: Antidepressant, Anorexic

Chemical Name: Benzenepropanamine, N-methyl-gamma-(4-(trifluoromethyl)phenoxy)-, (+-)-

Common Name: Fluoxetine

Structural Formula:



Chemical Abstracts Registry No.: 54910-89-3

Trade Name	Manufacturer	Country	Year Introduced
Actan	Eurolab	-	-
Deprax	Ache	-	-
Fluxin	Polfa	-	-
Fluxil	Aegis	-	-
Pragmaten	Novamed	-	-
Pragmaten	Sanofi Synthelabo S.A.	-	-
Fondozal	Orifarm	-	-
Alental	Soubeiran Chobet	-	-
Fluoxetina Fabra	Fabra	-	-
Animex-on	Micro-Bernabo	-	-
Eburnate	Vannier	-	-
Equilibrane	T.Lostalo	-	-
Fluopiram	Ariston	-	-
Fluozac	Klonal	-	-
Foxetin	Gador	-	-
Mitilase	Andromaco	-	-
Nervosal	Neuropharma	-	-
Neupax	Bago	-	-
Saurat	Armstrong	-	-

Raw Materials

Diborane
Hydrochloric acid
Sulfuric acid
Cyanogen bromide
Ethylene glycol
β-Dimethylaminopropiophenone hydrochloride
Sodium hydroxide
Thionyl chloride
p-Trifluoromethylphenol
Potassium hydroxide
Hydrogen chloride

Manufacturing Process

About 600 g of β-dimethylaminopropiophenone hydrochloride were converted to the corresponding free base by the action of 1.5 N aqueous sodium hydroxide. The liberated free base was taken up in ether, the ether layer separated and dried, and the ether removed therefrom in vacuo. The residual oil comprising β-dimethylaminopropiophenone was dissolved in 2 L of tetrahydrofuran, and the resulting solution added in dropwise fashion with stirring to a solution of four moles of diborane in 4 L of tetrahydrofuran. The reaction mixture was stirred overnight at room temperature. An additional mole of diborane in 1 L of tetrahydrofuran was added, and the reaction mixture stirred again overnight at room temperature. Next, 2 L of aqueous hydrochloric acid were added to decompose any excess diborane present. The tetrahydrofuran was removed by evaporation. The acidic solution was extracted twice with 1 L portions of benzene, and the benzene extracts were discarded. The acidic solution was then made basic with an excess of 5 N aqueous sodium hydroxide. The basic solution was extracted three times with 2 L portions of benzene. The benzene extracts were separated and combined, and the combined extracts washed with a saturated aqueous sodium chloride and then dried. Evaporation of the solvent in vacuo yields 442 g of N,N-dimethyl-3-phenyl-3-hydroxypropylamine.

A solution containing 442 g of N,N-dimethyl-3-phenyl-3-hydroxypropylamine in 5 L of chloroform was saturated with dry gaseous hydrogen chloride. 400 ml of thionyl chloride were then added to the chloroform solution at a rate sufficient to maintain reflux. The solution was refluxed an additional 5 h. Evaporation of the chloroform and other volatile constituents in vacuo yielded N,N-dimethyl-3-phenyl-3-chloropropylamine hydrochloride which was collected by filtration, and the filter cake washed twice with 1500 ml portions of acetone. The washed crystals weighed about 500 g and melted at 181°-183°C with decomposition. An additional 30 g of compound were obtained from the acetone wash by standard crystallization procedures. The structure of the above compound was verified by NMR and titration.

A solution of 50 g p-trifluoromethylphenol, 12 g of solid sodium hydroxide and 400 ml of methanol was placed in a 1 L round-bottom flask equipped with magnetic stirrer, condenser and drying tube. The reaction mixture was stirred until the sodium hydroxide had dissolved. Next, 29.8 g of N,N-dimethyl-3-phenyl-3-chloropropylamine hydrochloride were added. The resulting reaction mixture was refluxed for about 5 days and then cooled. The methanol was then removed by evaporation, and the resulting residue taken up in a mixture of ether and 5 N aqueous sodium hydroxide. The ether layer was separated and washed twice with 5 N aqueous sodium hydroxide and three times with water. The ether layer was dried, and the ether removed by evaporation in

vacuo to yield as a residue N,N-dimethyl-3-(p-trifluoromethylphenoxy)-3-phenylpropylamine.

A solution containing 8.1 g of cyanogen bromide in 500 ml benzene and 50 ml of toluene was placed in a 1 L three-neck round-bottom flask equipped with thermometer, addition funnel, drying tube and inlet tube for nitrogen. The solution was cooled to about 5°C with stirring, and nitrogen gas was bubbled thru the solution. Next, a solution of 12.146 g of N,N-dimethyl-3-(p-trifluoromethylphenoxy)-3-phenylpropylamine dissolved in 40 ml of benzene was added in dropwise fashion. The temperature of the reaction mixture was allowed to rise slowly to room temperature, at which temperature stirring was continued overnight while still maintaining a nitrogen atmosphere 100 ml of benzene were added. The reaction mixture was washed twice with water, once with 2 N aqueous sulfuric acid and then with water until neutral. The organic layer was dried, and the solvents removed therefrom by evaporation in vacuo to yield about 9.5 g of an oil comprising N-methyl-N-cyano-3-(p-trifluoromethylphenoxy)-3-phenylpropylamine.

A solution of 100 g potassium hydroxide, 85 ml water, 400 ml ethylene glycol and 9.50 g of N-methyl-N-cyano-3-(p-trifluoromethylphenoxy)-3-phenylpropylamine was prepared in a 1 L three-neck, round-bottom flask equipped with magnetic stirrer and condenser. The reaction mixture was heated to refluxing temperature (130°C) for 20 h, and was then cooled. 500 ml of water were added. The reaction mixture was extracted with three 500 ml portions of ether. The ether extracts were combined, and the combined extracts washed with water. The water wash was discarded. The ether solution was next contacted with 2 N aqueous hydrochloric acid. The acidic aqueous layer was separated. A second aqueous acidic extract with 2 N hydrochloric acid was made followed by three aqueous extracts and an extract with saturated aqueous sodium chloride. The aqueous layers were all combined and made basic with 5 N aqueous sodium hydroxide. N-Methyl-3-(p-trifluoromethylphenoxy)-3-phenylpropylamine, formed in the above reaction, was insoluble in the basic solution and separated. The amine was extracted into ether. Two further ether extractions were carried out. The ether extracts were combined, and the combined extracts washed with saturated aqueous sodium chloride and then dried. Evaporation of the ether in vacuo yielded about 6.3 g of N-methyl-3-(p-trifluoromethylphenoxy)-3-phenylpropylamine.

References

Molloy B.B., Schmiiegel K.K.; US Patent No. 4,314,081; February 2, 1982; Assigned: Eli Lilly and Company, Indianapolis, Ind.

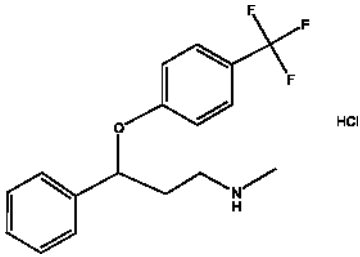
FLUOXETINE HYDROCHLORIDE

Therapeutic Function: Antidepressant

Chemical Name: Benzenepropanamine, N-methyl-γ-(4-(trifluoromethyl) phenoxy)-, hydrochloride

Common Name: Fluoxetine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 56296-78-7

Trade Name	Manufacturer	Country	Year Introduced
Fluoxetine hydrochloride	Quimica Sintetica	Spain	-
Fluoxetine hydrochloride	Industriale Chimica S.R.L.	Italy	-
Fluoxetine hydrochloride	Eli Lilly and Company	USA	-
Prozac	Eli Lilly and Company	USA	-
Prozac	Dista	-	-

Raw Materials

Diborane	β-Dimethylaminopropiophenone hydrochloride
Thionyl chloride	Hydrogen chloride
Ethylene glycol	4-Trifluoromethylphenol
Sodium hydroxide	Cyanogen bromide

Manufacturing Process

About 600 g of β-dimethylaminopropiophenone hydrochloride were converted to the corresponding free base by the action of 1.5 N aqueous sodium hydroxide. Free base was dissolved in 2 L of THF, and the resulting solution added in dropwise fashion to a solution of 4 moles of diborane in 4 L of THF. The reaction mixture was stirred overnight. An additional mole of diborane in 1 L of THF was added, and the reaction mixture stirred again overnight. Next, 2 L of aqueous hydrochloric acid were added to decompose any excess diborane present. The tetrahydrofuran was removed by evaporation. The acidic solution was extracted twice with 1 L portions of benzene, and the benzene extracts were discarded. The acidic solution was then made basic with an excess of 5 N aqueous sodium hydroxide. The basic solution was extracted three times with 2 L portions of benzene. The combined extracts washed with a saturated aqueous sodium chloride and then dried. Evaporation of the solvent in vacuo yields 442 g of N,N-dimethyl-3-phenyl-3-hydroxypropylamine.

A solution containing 442 g of N,N-dimethyl-3-phenyl-3-hydroxypropylamine in 5 L of chloroform was saturated with dry gaseous hydrogen chloride. 400 mL of thionyl chloride were then added to the solution at a rate sufficient to maintain reflux. The solution was refluxed an additional 5 hours. Evaporation of the chloroform and other volatile constituents in vacuo yielded N,N-dimethyl-3-phenyl-3-chloropropylamine hydrochloride which was collected by filtration, and the filter cake washed twice with 1.5 L portions of acetone. The washed crystals weighed about 500 g and melted at 181-183°C with decomposition. An additional 30 g of compound were obtained from the acetone wash by standard crystallization procedures. The structure of the above compound was verified by NMR and titration.

A solution of 50 g p-trifluoromethylphenol, 12 g of solid sodium hydroxide and 400 mL of methanol were added 29.8 g of N,N-dimethyl 3-phenyl-3-chloropropylamine hydrochloride. The resulting reaction mixture was refluxed for about 5 days and then cooled. The methanol was removed by evaporation, and the resulting residue taken up in a mixture of ether and 5 N aqueous sodium hydroxide. The ether layer was separated and washed twice with 5 N aqueous sodium hydroxide and three times with water. The ether layer was dried, and the ether removed by evaporation in vacuo to yield as a residue N,N-dimethyl-3-(p-trifluoromethylphenoxy)-3-phenylpropylamine.

To a solution 8.1 g of cyanogen bromide in 500 mL benzene and 50 mL of toluene at 5°C in nitrogen was added dropwise a solution of 12.146 g of N,N-dimethyl-3-(p-trifluoromethylphenoxy)-3-phenylpropylamine in 40 mL of benzene. The temperature of the reaction mixture was allowed to rise slowly to room temperature, at which temperature stirring was continued overnight while still maintaining a nitrogen atmosphere. 100 mL of benzene were added. The reaction mixture was washed twice with water, once with 2 N aqueous sulfuric acid and then with water until neutral. The organic layer was dried, and the solvents removed therefrom by evaporation in vacuo to yield about 9.5 g of an oil comprising N-methyl-N-cyano-3-(p-trifluoromethylphenoxy)-3-phenylpropylamine.

The reaction mixture containing 100 g potassium hydroxide, 85 mL water, 400 mL ethylene glycol and 9.50 g of N-methyl-N-cyano-3-(p-trifluoromethylphenoxy)-3-phenylpropylamine was heated to refluxing temperature for 20 hours, and was then cooled. 500 mL of water were added. The reaction mixture was extracted with three 500 mL portions of ether. The combined extracts washed with water. The water wash was discarded. The ether solution was next contacted with 2 N aqueous hydrochloric acid. The acidic aqueous layer was separated. A second aqueous acidic extract with 2 N hydrochloric acid was made followed by three aqueous extracts and an extract with saturated aqueous sodium chloride. The aqueous layers were all combined and made basic with 5 N aqueous sodium hydroxide. N-methyl 3-(p-trifluoromethylphenoxy)-3-phenylpropylamine, formed in the above reaction, was insoluble in the basic solution and separated. The amine was extracted into ether. Two further ether extractions were carried out. The ether extracts were combined, and the combined extracts washed with saturated aqueous sodium chloride and then dried. Evaporation of the ether in vacuo yielded about 6.3 g of N-methyl-3-(p-trifluoromethylphenoxy)-3-phenylpropylamine. The amine free base was converted to the corresponding hydrochloride salt.

References

Kairisalo P.J. et al.; US Patent No. 5,166,437; Nov. 24, 1992; Assigned: Orion-Yhtyma Oy (Espoo, FI)
Molloy B.B. et al.; US Patent No. 4,314,081; Feb. 2, 1982; Assigned: Eli Lilly and Company (Indianapolis, IN)
GB Patent Application No. 2,060,618
Nedelec L. et al.; US Patent No. 4,296,126; Oct. 20, 1981; Assigned: Roussel Uclaf (Paris, FR)

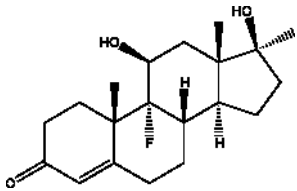
FLUOXYMESTERONE

Therapeutic Function: Androgen

Chemical Name: 9-Fluoro-11β,17β-dihydroxy-17-methylandrost-4-en-3-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 76-43-7

Trade Name	Manufacturer	Country	Year Introduced
Halotestin	Upjohn	US	1957
Ora-Testryl	Squibb	US	1958
Ultandren	Ciba	US	1958
Halotestin	Upjohn	France	1961
Android-F	Brown	US	1981
Afluteston	Arcana	Austria	-
Androsterolo	Pierrel	Italy	-
Oralsterone	Bouty	Italy	-
Testoral	Midy	Italy	-
U-Gono	Upjohn	-	-

Raw Materials

Sodium hydroxide
N-Bromoacetamide
p-Toluenesulfonyl chloride
11α-Hydroxy-17-methyltestosterone
Hydrogen fluoride

Manufacturing Process

The following description is taken from US Patent 2,793,218.

(a) Preparation of 9/(11)-Dehydro-17-Methyltestosterone: A warm solution of 1 gram of 11α-hydroxy-17-methyltestosterone (US Patent 2,660,586) in 2 ml of dry pyridine was mixed with 1 gram of para-toluenesulfonyl chloride. The mixture was maintained at room temperature for 18 hours and then poured into 25 ml of water. The mixture was stirred until the precipitated oil solidified. The solid was filtered, washed with water and dried to give 1.41 grams of 11α-(p-toluenesulfonyloxy)-17α-methyl-17β-hydroxy-4-androsten-3-one which melted at 144° to 148°C with decomposition and, after crystallization from a mixture of methylene chloride and hexane hydrocarbons, melted at 141° to 144°C with decomposition.

A mixture of 1 gram of the thus-produced 11α-(p-toluenesulfonyloxy)-17α-methyl-17β-hydroxy-4-androsten-3-one, 0.2 gram of sodium formate, 0.57 ml of water and 14 ml of absolute ethanol was heated at its refluxing temperature for 19 hours. The solution was cooled and then poured onto 50 grams of a mixture of ice and water with stirring. The resulting precipitate was filtered and dried to give 0.59 gram of 9(11)-dehydro-17-methyltestosterone which melted at 156° to 160°C and, after crystallization from a mixture of methylene chloride and hexane hydrocarbons, melted at 167° to 170°C.

(b) Preparation of 9α-Bromo-11β-Hydroxy-17-Methyltestosterone: To a solution of 1 gram of 9(11)-dehydro-17-methyltestosteronein 50 ml of acetone was added dropwise, with stirring, at 15°C, 1 gram of N-bromoacetamide dissolved in 25 ml of water. A solution of 20 ml of 0.8 N perchloric acid was then slowly added at the same temperature. After 20 minutes, there was added a sufficient amount of a saturated aqueous solution of sodium sulfite to discharge the yellow color of the solution. The resulting mixture was then diluted with 100 ml of water thereby precipitating 1 gram of 9α-bromo-11β-hydroxy-17-methyltestosterone as needles melting at 153° to 155°C.

(c) Preparation of 9,11β-Epoxy-17-Methyltestosterone: A suspension of 1 gram of 9α-bromo-11β-hydroxy-17-methyltestosterone in 30 ml of methanol was titrated with 1 M equivalent of 0.1 N aqueous sodium hydroxide. The resulting mixture was diluted with 50 ml of water and then chilled to about 0°C thereby precipitating 0.64 gram of 9,11β-epoxy-17-methyltestosterone melting at 170° to 176°C which, after crystallization from dilute methanol, melted at 65° to 172°C (with sublimation).

(d) Preparation of 9α-Fluoro-11β-Hydroxy-17-Methyltestosterone: To a solution of 0.5 gram of 9,11β-epoxy-17-methyltestosterone in 10 ml of methylene chloride was added 2 ml of 48% aqueous hydrofluoric acid. The mixture was stirred at room temperature for 5 hours and then cautiously poured with stirring into a mixture of 6 grams of sodium bicarbonate in a mixture of ice and water. The precipitated steroid was extracted with methylene chloride, the extract washed with water and then dried. The solvent was distilled from the dried solution and the residue crystallized from methylene chloride to give 148 mg of 9α-fluoro-11β-hydroxy-17-methyltestosterone melting at 265°C with decomposition.

References

Merck Index 4091
Kleeman & Engel p. 420
PDR pp. 730, 1606, 1844
OCDS Vol. 1 p. 175 (1977)
I.N. p. 437
REM p. 998
Herr, M.E.; US Patent 2,793,218; May 21, 1957; assigned to The Upjohn Company
Herr, M.E.; US Patent 2,813,881; November 19, 1957; assigned to The Upjohn Company

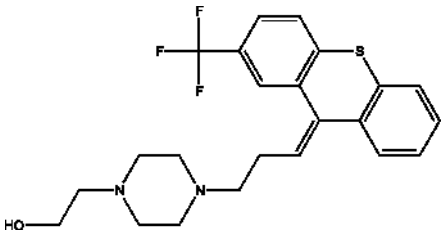
FLUPENTIXOL

Therapeutic Function: Tranquilizer

Chemical Name: 4-[3-[2-(Trifluoromethyl)-9H-thioxanthen-9-ylidene]propyl]-1-piperazineethanol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 2709-56-0; 2413-38-9 (Dihydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Emergil	Labaz	France	1971
Siplarol	Erba	Italy	1972
Metamin	Takeda	Japan	1973
Depixol	Lundbeck	UK	-
Fluanxol	Labaz	France	-

Raw Materials

2-Benzyloxyethanol p-Toluenesulfonyl chloride

3-Bromopropanol	N-Ethoxycarbonylpiperazine
Ethyl bromide	2-Trifluoromethyl-9-xanthenone
Magnesium	Hydrogen chloride
Thionyl chloride	Potassium hydroxide

Manufacturing Process

A mixture of 200 grams of 2-benzoyloxyethanol in 2 liters of pyridine at -5°C is treated with 275 grams of p-toluenesulfonyl chloride and the resulting mixture is stirred at 0°C for 2 hours. Water is added slowly at 0° to 5°C. Extracting with chloroform, washing the extract with dilute hydrochloric acid, water and potassium bicarbonate, and evaporating the solvent leaves benzyloxyethyl p-toluenesulfonate.

A mixture of 186 grams of the above prepared p-toluenesulfonate, 106 grams of N-ethoxycarbonylpiperazine, 44 grams of potassium carbonate and 800 ml of toluene is refluxed for 21 hours, then filtered and extracted with dilute hydrochloric acid. The extract is basified with sodium hydroxide and extracted into chloroform. Evaporation of the chloroform and distillation of the residue in vacuo gives 1-benzyloxyethyl-4-ethoxy-carbonylpiperazine, BP 153° to 156°C (0.15 mm).

Hydrolysis and decarboxylation of this ester (188 grams) is accomplished by refluxing with 155 grams of potassium hydroxide, 155 ml of water and 1,550 ml of ethanol for four days. Filtering, concentrating, adding water to the residue, acidifying with hydrochloric acid, heating to 90°C, saturating with potassium carbonate, extracting into chloroform, evaporating and distilling the chloroform gives N-benzoyloxyethylpiperazine.

A mixture of 50 grams of the above prepared piperazine, 30.1 grams of sodium carbonate and 200 ml of benzene is heated to reflux and treated with 39.5 grams of 3-bromopropanol over 1.5 hours. The resulting mixture is refluxed for 2 hours, then filtered, extracted with dilute hydrochloric acid, basified, extracted with benzene, and the extracts are concentrated and distilled to give l-benzyloxyethyl-4-(3-hydroxypropyl)-piperazine, BP 188° to 190°C (0.15 mm). The free base is converted to the dihydrochloride salt by treatment of an alcoholic solution with ethereal hydrogen chloride to separate the salt.

Thionyl chloride (67 grams) is added over 15 minutes to a mixture of 39.5 grams of the above prepared dihydrochloride salt and 400 ml of chloroform. Refluxing for 4 hours, cooling and filtering yields the dihydrochloride salt of l-benzyloxyethyl-4-(3-chloropropyl)-piperazine, MP 201° to 202°C. The salt in aqueous solution is basified. Extraction with ether and evaporation of the solvent yields the free base.

Magnesium (1.3 grams) in 8 ml of refluxing tetrahydrofuran is treated with 1 ml of ethyl bromide. A solution of 22.7 grams of l-benzyloxyethyl-4-(3-chloropropyl)-piperazine in 50 ml of tetrahydrofuran is added slowly and the mixture is refluxed for 1 hour.

A solution of 13.2 grams of 2-trifluoromethyl-9-xanthenone in tetrahydrofuran is added over 1 hour to 16.0 grams of 3-(4-benzyloxyethyl-1-piperazinyl) propylmagnesium chloride, prepared as above, in tetrahydrofuran while gently

refluxing. Refluxing is continued for 2 hours. Concentrating, pouring the residue into ammonium chloride, ice and water, extracting with ether, evaporating the extracts and treating the residue with concentrated hydrochloric acid at 95°C for 1 hour gives a mixture of cis and trans 9-[3-(4-hydroxyethyl-1-piperazinyl)propylidene]-2-trifluoromethylxanthene dihydrochloride. Fractional crystallization from ethanol-ether separates the isomers. The free bases are obtained by neutralizing an aqueous solution of the dihydrochloride, extracting into ether and evaporating the ether in vacuo.

References

Merck Index 4092
Kleeman & Engel p. 421
DOT 4 (4) 155 (1968) and 9 (6) 229 (1973)
I.N. p. 437
Smith Kline & French Laboratories; British Patent 925,538; May 8,1963
Craig, P.N. and Zirkle, C.L.; US Patent 3,282,930; November 1, 1966; assigned to Smith Kline and French Laboratories

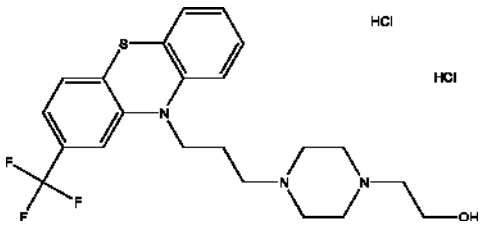
FLUPHENAZINE HYDROCHLORIDE

Therapeutic Function: Tranquilizer

Chemical Name: 4-[3-[2-(Trifluoromethyl)-10H-phenothiazin-10-yl]propyl]-1-piperazineethanol dihydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 146-56-5; 69-23-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Prolixin	Squibb	US	1959
Permitil	Schering	US	1959
Anatensol	Squibb	Italy	-
Anatensol	Showa	Japan	-
Calmansial	Squibb	-	-
Dapotum	Heyden	W. Germany	-

Trade Name	Manufacturer	Country	Year Introduced
Eutimox	Soc. Gen. De Farmacia	Spain	-
Flumezine	Yoshitomi	Japan	-
Lyogen	Byk Gulden	W. Germany	-
Lyorodin	Deutsches Hydrierwerk	E. Germany	-
Modecate	Squibb	France	-
Moditen	Squibb	France	-
Motipress	Squibb	UK	-
Qmca	Heyden	W. Germany	-
Pacinol	Schering	-	-
Seditin	Taro	Israel	-
Selecten	Unipharm	Israel	-
Sevinol	Schering-Shionogi	Japan	-
Siqualine	Iquinosa	Spain	-
Siqualone	Astra	Sweden	-
Trancin	Schering	-	-

Raw Materials

Sodium amide	2-Trifluoromethylphenothiazine
Thionyl chloride	1-(3-Hydroxypropyl)piperazine
Methyl formate	β-Bromoethyl acetate
Sodium hydroxide	Hydrogen chloride

Manufacturing Process

A suspension of 69.0 grams of 2-trifluoromethylphenothiazine in 1 liter of toluene with 10.9 grams of sodium amide is heated at reflux with high speed stirring for 15 minutes. A solution of 54.1 grams of 1-formyl-4-(3'-chloropropyl)-piperazine, [prepared by formylating 1-(3'-hydroxypropyl)-piperazine by refluxing in an excess of methyl formate, purifying the 1-formyl-4-(3'-hydroxypropyl)-piperazine by vacuum distillation, reacting this compound with an excess of thionyl chloride at reflux and isolating the desired 1-formyl-4(3'-chloropropyl)-piperazine by neutralization with sodium carbonate solution followed by distillation] in 200 ml of toluene is added. The reflux period is continued for 4 hours. The cooled reaction mixture is treated with 200 ml of water. The organic layer is extracted twice with dilute hydrochloric acid. The acid extracts are made basic with ammonia and extracted with benzene. The volatiles are taken off in vacuo at the steam bath to leave a dark brown oil which is 10-[3'-(N-formylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine. It can be distilled at 260°C at 10 microns, or used directly without distillation if desired.

A solution of 103.5 grams of 10-[3'-(N-formylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine in 400 ml of ethanol and 218 ml of water containing 26 ml of 40% sodium hydroxide solution is heated at reflux for 2 hours. The alcohol is taken off in vacuo on the steam bath. The residue is swirled with benzene and water. The dried benzene layer is evaporated in vacuo. The residue is vacuum distilled to give a viscous, yellow oil, 10-(3'piperazinylpropyl)-2-trifluoromethylphenothiazine, distilling at 210° to

235°C at 0.5 to 0.6 mm.

A suspension of 14.0 grams of 10-(3'-piperazinylpropyl)-2-trifluoromethylphenothiazine, 6.4 grams of β-bromoethyl acetate and 2.6 grams of potassium carbonate in 100 ml of toluene is stirred at reflux for 16 hours. Water (50 ml) is added to the cooled mixture. The organic layer is extracted into dilute hydrochloric acid. After neutralizing the extracts and taking the separated base up in benzene, a viscous, yellow residue is obtained by evaporating the organic solvent in vacuo. This oil is chromatographed on alumina. The purified fraction of 7.7 grams of 10-[3'-(N-acetoxyethylpiperazinyl)-propyl] -2-trifluoromethylphenothiazine is taken up in ethyl acetate and mixed with 25 ml of alcoholic hydrogen chloride. Concentration in vacuo separates white crystals of the dihydrochloride salt, MP 225° to 227°C.

A solution of 1.0 gram of 10-[3'-(N-acetoxyethylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine in 25 ml of 1 N hydrochloric acid is heated at reflux briefly. Neutralization with dilute sodium carbonate solution and extraction with benzene gives the oily base, 10-[3'-(N-β-hydroxyethylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine. The base is reacted with an excess of an alcoholic hydrogen chloride solution. Trituration with ether separates crystals of the dihydrochloride salt, MP 224° to 226°C, (from US Patent 3,058,979).

References

Merck Index 4094
Kleeman & Engel p. 423
PDR pp. 1646, 1759
OCDS Vol. 1 p. 383 (1977)
DOT 3 (1) 60 (1967) and 9 (6) 228 (1973)
I.N. p. 438
REM p. 1088
Ullyot, G.E.; US Patent 3,058,979; October 16, 1962; assigned to Smith Kline & French Laboratories

FLUPREDNIDENE ACETATE

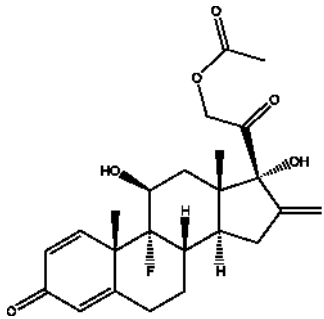
Therapeutic Function: Topical antiinflammatory

Chemical Name: 21-(Acetyloxy)-9-fluoro-11β,17-dihydroxy-16-methylenepregna-1,4-diene-3,20-dione

Common Name: 16-Methylene-9α-fluoroprednisolone 21-acetate

Chemical Abstracts Registry No.: 1255-35-2

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Etacortin	Hermal	W. Germany	1968
Decoderm	Bracco	Italy	1972
Decoderme	Merck Clevenot	France	1974
Decoderm	Merck	UK	-
Candio-Hermal	Hermal	W. Germany	-
Corticoderm	Merck	W. Germany	-
Crino-Hermal	Hermal	W. Germany	-
Emcortina	Merck	US	-

Raw Materials

Semicarbazide
t-Butyl hydroperoxide
9α-Fluoro-11β,17α,21-trihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione
Acetic anhydride
Hydrogen bromide

Manufacturing Process

Preparation of 3,20-Disemicarbazone of 9α-Fluoro-11β,17α,21-Trihydroxy-16α-Methyl-1,4-Pregnadiene-3,20-Dione: A mixture of 1.00 gram of 9α-fluoro-11β,17α,21-trihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione, 750 mg of semicarbazide base, 280 mg of semicarbazide hydrochloride in 20 ml of methanol and 10 ml of dimethylformamide is refluxed for 20 hours under nitrogen. The mixture is cooled to 20°C and 100 ml of water is added with stirring. The precipitated 3,20-disemicarbazone of 9α-fluoro-11β,17α,21-trihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione is filtered, washed with water, and dried in air; MP over 300°C.

Preparation of 9α-Fluoro-11β,21-Dihydroxy-16-Methyl-1,4,16-Pregnatriene-3,20-Dione 21-Acetate: A solution of 500 mg of the 3,20-disemicarbazone of 9α-fluoro-11β,17α,21-trhydroxy-16α-methyl-1,4-pregnadiene-3,20-dione in 10 ml of acetic acid and 0.5 ml acetic anhydride is refluxed under nitrogen for one hour to produce the corresponding 3,20-disemicarbazone of 11β,21-dihydroxy-16-methyl-1,4,16-pregnatriene-3,20-dione 21-acetate. The reaction mixture is cooled, 13 ml of water is added and the mixture heated on the

steam bath for 5 hours. It is then concentrated in vacuo nearly to dryness and water and chloroform added. The mixture is thoroughly extracted with chloroform, and the chloroform extract washed with excess aqueous potassium bicarbonate and saturated salt solution and dried over magnesium sulfate. Chromatography of the residue on neutral alumina and crystallization of pertinent benzene-chloroform fractions gives 9α-fluoro-11β,21-dihydroxy-16-methyl-1,4,16-pregnatriene-3,20-dione 21-acetate; MP 228° to 233°C.

Preparation of 9α-Fluoro-11β,21-Dihydroxy-16β-Methyl-16α,17β-Oxido-1,4-Pregnadiene-3,20-Dione 21-Acetate: To a stirred solution of 500 mg of 9α-fluoro-11β,21-dihydroxy-16-methyl-1,4,16-pregnatriene-3,20-dione 21-acetate in 5 ml of benzene and 5 ml of chloroform are added 0.50 ml of t-butyl hydroperoxide and 0.1 ml of a 35% methanolic solution of benzyl-trimethyl ammonium hydroxide. After 18 hours at room temperature, water is added and the mixture thoroughly extracted with chloroform. The chloroform extract is washed with saturated aqueous sodium chloride and dried over magnesium sulfate. Evaporation of the solvent and crystallization of the residue from acetone-ether gives 9α-fluoro-11β,21-dihydroxy-16β-methyl-16α,17α-oxido-1,4-pregnadiene-3,20-dione 21-acetate.

Preparation of 9α-Fluoro-11β,17α,21-Trihydroxy-16-Methylene-1,4-Pregnadiene-3,20-Dione 21-Acetate: To a stirred solution of 600 mg of 9α-fluoro-11β,21-dihydroxy-16β-methyl-16α,17α-oxido-1,4-pregnadiene-3,20-dione21 acetate in 10 ml of acetic acid maintained at 10° to 15°C is added 3 ml of cold 10% hydrogen bromide in acetic acid. After 30 minutes the mixture is concentrated to dryness in vacuo (temperature 15°C) and the residue chromatographed on neutral alumina. Combination of pertinent benzene-chloroform fractions and crystallization leads to the desired 9α-fluoro-11β,17α,21-trihydroxy-16-methylene-1,4-pregnadiene-3,20-dione 21-acetate.

References

Merck Index 4095
Kleeman & Engel p. 423
DOT 4 (2) 80 (1968)
I.N. p. 439
Wendler, N.L. and Taub, D.; US Patent 3,065,239; November 20, 1962; assigned to Merck & Co.,Inc.
Taub, D. and Wendler, N.L.; US Patent 3,068,224; December 11, 1962; assigned to Merck & Co., Inc.
Taub, D., Wendler, N.L. and Hoffsommer, R.D. Jr.; US Patent 3,068,226; December 11, 1962; assigned to Merck & Co., Inc.
Wendler, N.L., Taub, D.and Hoffsommer, R.D. Jr.; US Patent 3,136,760; June 9, 1964; assigned to Merck & Co., Inc.

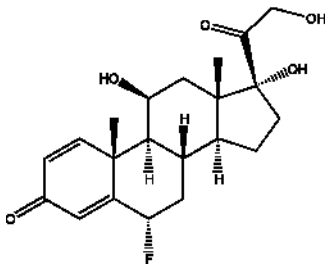
FLUPREDNISOLONE

Therapeutic Function: Glucocorticoid, Antiinflammatory

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

Common Name: 6α-Fluoroprednisolone

Structural Formula:



Chemical Abstracts Registry No.: 53-34-9

Trade Name	Manufacturer	Country	Year Introduced
Alphadrol	Upjohn	US	1961
Decoderme	Merck Clevenot	France	-
Etadrol	Farmitalia	Italy	-
Isopredon	Hoechst	W. Germany	-
Selectren	Albert Pharma	Spain	-

Raw Materials

Sulfuric acid
Acetic acid
Acetic anhydride
5α,11β,17α-Trihydroxy-6β-fluoro-21-acetoxyallopregnane-3,20-dione-3-ethyleneketal
Sodium bicarbonate
Bacterium *Sepromyxa affinis*
Hydrogen chloride

Manufacturing Process

5α,11β,17α-Trihydroxy-6β-Fluoro-21-Acetoxyallopregnane-3,20-Dione:A solution of 0.47 gram of 5α,11β,17α-trihydroxy-6β-fluoro-21-acetoxyallopregnane-3,20-dione-3-ethylene ketal in 35 ml of acetone and 4 ml of 1 N sulfuric acid solution was gently boiled on the steam bath for 10 minutes, cooled and neutralized with dilute sodium bicarbonate solution. Addition of water and cooling gave 0.33 gram of 5α,11β,17α-trihydroxy-6β-fluoro-21-acetoxyallopregnane-3,20-dione, MP 230° to 240°C.

6β-Fluoro-11β,17α-Dihydroxy-21-Acetoxy-4-Pregnene-3,20-Dione(6β-Fluorohydrocortisone Acetate): A solution of 100 mg of 5α,11β,17α-trihydroxy-6β-fluoro-21-acetoxyallopregnane-3,20-dione in 4.9 ml of acetic acid and 0.1 ml of water was refluxed for a period of 1 hour, cooled, diluted with 50 ml of water and evaporated to dryness under reduced pressure. The residue was chromatographed over Florisil (synthetic magnesium silicate) to give one fraction (77 mg) eluted with methylene chloride plus 10% acetone. Crystallization from acetone-Skellysolve B-hexanes gave 38 mg of 6β-fluoro-11β,17α-dihydroxy-21-acetoxy-4pregnene-3,20-dione (6β-fluorohydrocortisone

acetate), MP 210° to 218°C.

6β-Fluoro-11β,17α-Dihydroxy-21-Acetoxy-1,4-Pregnadiene-3,20-Dione: A medium consisting of 1% dextrose hydrate, 2% cornsteep liquor of 60% solids and Kalamazoo tap water was adjusted to pH 4.9 with sodium hydroxide. The medium was steam sterilized at 15 pounds pressure for 30 minutes, cooled, and then inoculated with a 24-hour growth, from spores, of *Septomyxa affinis*, ATCC 6737. The medium was agitated, sparged with sterile air at the rate of one-tenth volume of air per volume of medium per minute. At the end of 24 hours of fermentation at room temperature, the pH was about 7.4.

To this culture there was added a solution of 6β-fluoro-11β,17α-dihydroxy-21-acetoxy-4-pregnene-3,20-dione (6β-fluorohydrocortisone acetate), dissolved in diethylformamide. The solution was prepared by dissolving five parts of the steroid in 100 parts of the solid and adding about 10 cm of the solution per liter of the medium. Fermentation was continued for a period of 48 hours whereupon the mycelium and beer were extracted thoroughly with methylene chloride. The extract was washed with sodium bicarbonate solution and then with water, dried and concentrated in vacuo to a slightly viscous residue. The residue, after reacetylation with acetic anhydride in pyridine, was fractionated chromatographically and 6β-fluoro-11β,17α-dihydroxy-21-acetoxy-1,4-pregnadiene-3,20-dione was recovered as a light-colored crystalline solid. Isomerization to the 6β-fluoro product is effected by streaming dry HCl into a cold chloroform/ethanol solution of the 6α-epimer.

References

Merck Index 4096
Kleeman & Engel p. 425
I.N. p. 439
REM p. 972
Hogg, J.A. and Spero, G.B.; US Patent 2,841,600; July 1, 1958; assigned to The Upjohn Company

FLURANDRENOLIDE

Therapeutic Function: Glucocorticoid, Antiinflammatory

Chemical Name: 6α-Fluoro-11β,21-dihydroxy-16α,17-[(1-methylethylidene) bis(oxy)]pregn-4-ene-3,20-dione

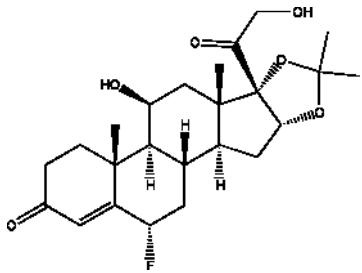
Common Name: Flurandrenolone; Fludroxycortide

Chemical Abstracts Registry No.: 1524-88-5

Raw Materials

6α-Fluoro-16α-hydroxycortisol
Acetone
Perchloric acid

Structural Formula:



Manufacturing Process

Trade Name	Manufacturer	Country	Year Introduced
Haelan	Lilly	UK	1962
Sermaka	Lilly	W. Germany	1964
Haelan	Lilly	Italy	1964
Haelan	Lilly	France	1966
Cortide Tape	Nichiban	Japan	1981
Cordran	Lilly	US	-
Drenison	Dainippon	Japan	-
Drenison	Lilly	UK	-
Drocort	Lilly	-	-
Sermaform	Lilly	W. Germany	-

6α-Fluoro-16α-hydroxycortisol is condensed with acetone by treating the solution in acetone with 70% perchloric acid.

References

Merck Index 4099
Kleeman & Engel p. 408
PDR p. 837
OCDS Vol. 2 p. 180 (1980)
I.N. p. 430
REM p. 967
Casas-Campillo, C.; US Patent 3,119,748; January 28, 1964; assigned to Syntex Corporation, Panama
Ringold, H.J., Zderic, J.A., Djerassi, C. and Bowers, A.; US Patent 3,126,375; March 24, 1964; assigned to Syntex Corporation, Panama

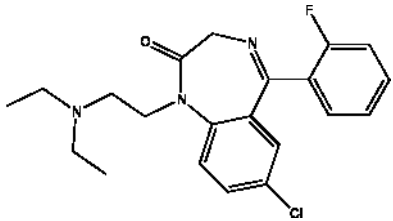
FLURAZEPAM

Therapeutic Function: Hypnotic

Chemical Name: 7-Chloro-1-[2-(diethylamino)ethyl]-5-(o-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 17617-23-1; 1172-18-5 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Dalmane	Roche	US	1970
Flunox	Boehringer Biochem.	Italy	1973
Dalmadorm	Roche	W. Germany	1974
Dalmane	Roche	UK	1974
Dalmadorm	Roche	Italy	1974
Dalmate	Roche	Japan	1975
Benozil	Kyowa Hakko	Japan	1975
Flunox	Robin	Italy	1975
Insumin	Kyorin	Japan	1979
Benodil	Kyowa	Japan	-
Felison	Sigurta	Italy	-
Fluzepam	Krka	Yugoslavia	-
Lunipax	Beecham	-	-
Natam	Unifa	Argentina	-
Novoflupam	Novopharm	Canada	-
Remdue	Biomedica Foscama	Italy	-
Somlan	Sintyal	Argentina	-
Sompan	I.C.N.	Canada	-
Valdorm	Valeas	Italy	-

Raw Materials

5-(2-Fluorophenyl)-7-chloro-2,3-dihydro-1H-benzodiazepinone-(2)
Sodium methoxide
Diethylaminoethyl chloride

Manufacturing Process

13 grams of 5-(2-fluorophenyl)-7-chloro-2,3-dihydro-1H-1,4-benzodiazepinone-(2) were dissolved in 100 ml of N,N-dimethylformamide and

treated with 10.3 ml of a solution of sodium methoxide in methanol containing 54 mmol or 2.95 grams of sodium methoxide. The resulting solution was stirred at about 20°C for 1 hour and then cooled in an ice-salt mixture to 0°C. A solution of diethylamino-ethyl chloride was prepared by dissolving 13.8 grams of diethylamino-ethyl chloride hydrochloride in cold dilute sodium hydroxide solution and extracting the base four times with 50 ml of toluene each time. The toluene extracts were combined, dried over anhydrous sodium sulfate, filtered and added to the reaction mixture.

The mixture was allowed to stand for 70 hours and then concentrated to a small volume under reduced pressure. The residue was dissolved in 100 ml of methylene chloride, washed with 75 ml of water, three times with 50 ml of saturated brine solution each time and filtered over neutral alumina (grade 1). The filtrate was evaporated to dryness and the resulting colorless oil taken up in ether, which was then saturated with hydrogen chloride. The pale yellow precipitate was filtered off and recrystallized from methanol/ether yielding 1-[2-(diethylamino)ethyl]-5-(2-fluorophenyl)-7-chloro-2,3-dihydro-1H-1,4-benzodiazepinone-(2) dihydrochloride as pale yellow rods melting at 190° to 220°C with decomposition, (from British Patent 1,040,548).

References

Merck Index 4100
Kleeman & Engel p. 426
PDR p. 1509
DOT 9 (6) 237 (1973) and 6 (6) 217 (1970)
I.N. p. 440
REM p. 1062
F. Hoffmann-La Roche and Co., AG, Switzerland; British Patent 1,040,547; Sept. 1,1966
F. Hoffmann-La Roche and Co., AG, Switzerland; British Patent 1,040,548; Sept. 1, 1966
Fryer, R. and Sternbach, L.H.; US Patent 3,567,710; March 2, 1971; assigned to Hoffrnan-La Roche, Inc.

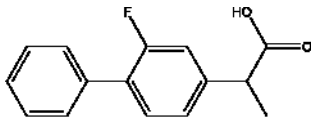
FLURBIPROFEN

Therapeutic Function: Antiinflammatory

Chemical Name: 2-(2-Fluoro-4-biphenylyl)propionic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 5104-49-4

Trade Name	Manufacturer	Country	Year Introduced
Froben	Boots	UK	1977
Froben	Boots	Switz.	1978
Froben	Kakenyaku Kako	Japan	1979
Froben	Boots	France	1979
Froben	Thomae	W. Germany	1980
Froben	Formenti	Italy	1981
Ansaid	Upjohn	-	-
Cebutid	Boots-Dacour	France	-
Flugalin	Galenika	Yugoslavia	-

Raw Materials

Morpholine
Sulfur
Ethanol
3-Acetyl-2-fluorobiphenyl
Diethyl carbonate
Dimethyl sulfate

Manufacturing Process

A mixture of 3-acetyl-2-fluorobiphenyl, MP 95°C to 96°C, (73.5 g) [prepared from 4.bromo-3-nitroacetophenone (Oelschlage, Ann., 1961, 641, 81) via-4-acetyl-2-nitrobiphenyl, MP 106°C to 108°C (Ullman reaction), 4-acetyl-2-aminobiphenyl, MP 124°C to 125°C (reduction), and finally the Schiemann reaction], sulfur (17.4 g) and morpholine (87 ml) was refluxed for 16.5 hr, and then the resulting thiomorpholide was hydrolyzed by refluxing with glacial acetic acid (340 ml) concentrated sulfuric acid (54 ml) and water (78 ml) for 24 hr. The cooled solution was diluted with water, and the precipitated crude 2-fluoro-4-biphenylylacetic acid was collected. (A sample was purified by recrystallization to give MP 143°C to 144.5°C; Found (%): C, 73.2; H, 4.8. $C_{14}H_{11}FO_2$ requires C, 73.1; H, 4.8.)

A sodium carbonate solution of the crude acetic acid was washed with ether and then acidified with hydrochloric acid; the required acid was isolated via an ether extraction and was esterified by refluxing for 6 hr with ethanol (370 ml) and concentrated sulfuric acid (15 ml). Excess alcohol was distilled, the residue diluted with water and the required ester isolated in ether. Distillation finally gave ethyl 2-fluoro-4-biphenylacetate, BP 134°C to 136°C/0.25 mm.

This ester (70g) and diethyl carbonate (250 mg) were stirred at 90°C to 100°C while a solution of sodium ethoxide [from sodium (7.8 g) and ethanol (154 ml)] was added over 1 hr. During addition, ethanol was allowed to distill and after addition distillation was continued until the column heat temperature reached 124°C. After cooling the solution to 90°C, dimethyl sulfate (33 ml) was followed by a further 85 ml of diethyl carbonate. This solution was stirred and refluxed for 1 hr and then, when ice cool, was diluted with water and acetic acid (10 ml). The malonate was isolated in ether and fractionally distilled to yield a fraction boiling at 148°C to 153°C/0.075 mm, identified as the alpha-methyl malonate. This was hydrolyzed by refluxing for 1 hr at 2.5 N sodium hydroxide (350 ml) and alcohol (175 ml), excess alcohol was distilled and the residual suspension of sodium salt was acidified with hydrochloric acid

to give a precipitate of the alpha-methyl malonic acid. This was decarboxylated by heating at 180°C to 200°C for 30 minutes and recrystallized from petroleum ether (BP 80°C to 100°C) to give 2-(2-fluoro-4-biphenylyl)propionic acid, MP 110°C to 111°C.

References

Merck Index 4101
DFU 1 (7) 323 (1976)
Kleeman & Engel p. 427
DOT 9 (9) 377 (1973) and 14 (9) 407 (1978)
I.N.p.440
Adams, S.S., Bernard, J., Nicholson, J.S. and Blancafort, A.R.; US Patent 3,755,427; Aug. 28, 1973; assigned to The Boots Company Ltd.

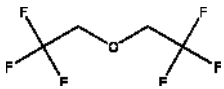
FLUROTHYL

Therapeutic Function: Central stimulant, Convulsant

Chemical Name: 1,1'-Oxybis[2,2,2-trifluoroethane]

Common Name: Hexafluorodiethyl ether; Bis(trifluoroethyl) ether

Structural Formula:



Chemical Abstracts Registry No.: 333-36-8

Trade Name	Manufacturer	Country	Year Introduced
Indoklon	Ohio Medical	US	1964

Raw Materials

2,2,2-Trifluoroethanol
Sodium
p-Toluenesulfonyl chloride

Manufacturing Process

23 parts of sodium metal were placed in 300 parts of dry dioxane in a reactor equipped with an agitator and reflux condenser. The dioxane was heated to reflux while stirring.150 parts of 2,2,2-trifluoroethanol were added very slowly in the period of about 1 hour, or until the sodium was all reacted, to form sodium 2,2,2-trifluoroethylate. 250 parts of 2,2,2-trifluoroethyl p-toluenesulfonate prepared by reacting 2,2,2-trifluoroethanol with p-

toluenesulfonyl chloride were placed in another reactor and heated to about 160° to 185°C. The solution of sodium 2,2,2-trifluoroethylate in dioxane was added very slowly over a period of about 1½ hours. Bis(2,2,2-trifluoroethyl) ether formed continuously and distilled from the reactor with the dioxane into a cooled receiving vessel. The condensed effluent from the reactor was fractionally distilled, yielding 46.5 parts of products boiling at 55° to 73°C.

The crude product was washed successively with concentrated HCl, 62% H_2SO_4,concentrated H_2SO_4 and 5% NaOH solution. It was dehydrated over a drying agent and then refractionated in a still. 20 parts of bis(2,2,2-trifluoroethyl) ether were recovered (BP 62.5° to 63.5°C).

References

Merck Index 4103
Kleeman & Engel p. 428
I.N. p. 440
REM p. 1138
Olin, J.F.; US Patent 3,363,006; January 9,1968; assigned to Pennsalt Chemicals Corp.

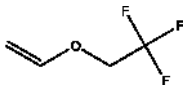
FLUROXENE

Therapeutic Function: Inhalation anesthetic

Chemical Name: (2,2,2-Trifluoroethoxy)ethene

Common Name: 2,2,2-Trifluoroethyl vinyl ether

Structural Formula:



Chemical Abstracts Registry No.: 406-90-6

Trade Name	Manufacturer	Country	Year Introduced
Fluoromar	Ohio Medical	US	1961

Raw Materials

2,2,2-Trifluoroethanol
Potassium
Acetylene

Manufacturing Process

The following process description is taken from US Patent 2,830,007.

270 grams 2,2,2-trifluoroethanol was added slowly to 15 grams of a cooled suspension of potassium metal in 250 ml of ethyl ether with stirring. When all the potassium metal had reacted, the resulting solution was fractionally distilled in order to remove the ethyl ether. The residue was placed in a bomb and the air was removed from the bomb by flushing with acetylene. The bomb was sealed and heated to 150°C. Acetylene was then introduced at 245 to 260 psi and the gas pressure was maintained for a period of 5 hours under mechanical agitation throughout the reaction. At the end of this time, heating was discontinued, the flow of acetylene was shut off and the bomb was allowed to cool to room temperature. The excess pressure in the bomb was reduced to atmospheric pressure by venting any gases through a dry ice cooled trap.

The reaction mixture comprising 2,2,2-trifluoroethyl vinyl ether, 2.2.2-trifluoroethanol and potassium 2,2,2-trifluoroethylate was fractionally distilled, whereupon crude 2,2,2-trifluoroethyl vinyl ether was obtained which boiled at 42° to 45°C at 760 mm. More 2,2,2-trifluoroethyl vinyl ether was obtained when the distillation residue was returned to the bomb and reacted with acetylene in the same manner as hereinabove described.

The alkali metal hydroxides, instead of the alkali metals per se, can be employed to produce the alkali metal 2,2,2-trifluoroethanolate. However, this introduces water in the reaction mixture which requires removal prior to vinylation with acetylene. The crude products, on further distillation, yielded 2,2,2-trifluoroethyl vinyl ether having a boiling point of 43.1°C at 759 mm.

References

Merck Index 4104
Kleeman & Engel p. 428
I.N. p. 440
REM p. 1042
Shukys, J.G.; US Patent 2,830,007; April 8, 1958; assigned to Air Reduction Company
Townsend, P.W.; US Patent 2,870,218; January 20, 1959; assigned to Air Reduction Co.

FLUSPIRILENE

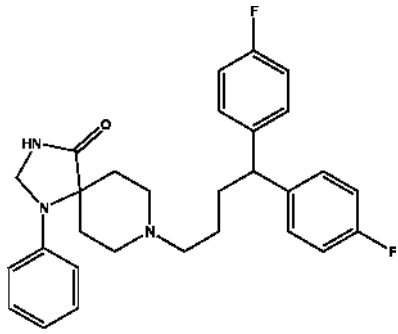
Therapeutic Function: Tranquilizer

Chemical Name: 8-[4,4-Bis(p-fluorophenyl)butyl]-1-phenyl-1,3,8-triazaspiro [4.5]decan-4-one

Common Name: -

Chemical Abstracts Registry No.: 1841-19-6

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Imap	Janssen	W. Germany	1972
Redeptin	SKF	UK	1975
Imap	McNeil	US	-

Raw Materials

Thionyl chloride
Hydrogen
Cyclopropyl di-(4-fluorophenyl)carbinol
1-Phenyl-4-oxo-1,3,8-triazaspiro(4,5)decane

Manufacturing Process

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

A solution of 61 parts 4-chloro-1,1-di-(4-fluorophenyl)-1-butene in 400 parts 2-propanol is hydrogenated at normal pressure and at room temperature in the presence of 5.5 parts palladium-on-charcoal catalyst 10% (exothermic reaction, temperature rises to about 30°C). After the calculated amount of hydrogen is taken up, hydrogenation is stopped. The catalyst is filtered off and the filtrate is evaporated. The oily residue is distilled in vacuo, yielding 1-chloro-4,4-di-(4-fluorophenyl)-butane, boiling point 166° to 168°C at 6 mm pressure; n_D^{20}= 1.5425; d_{20}^{20}= 1,2039.

A mixture of 7.3 parts 1-chloro-4,4-di-(4-fluorophenyl)-butane, 5.1 parts 1-phenyl-4-oxo-1,3,8-triaza-spiro[4,5]decane, 4 parts sodium carbonate, a few crystals of potassium iodide in 200 parts 4-methyl-2-pentanone is stirred and refluxed for 60 hours. After cooling the reaction mixture is treated with water. The organic layer is separated, dried, filtered and evaporated. The solid residue is recrystallized from 80 parts 4-methyl-2-pentanone, yielding 1-phenyl-4-oxo-8-[4,4-di-(4-fluorophenyl)]butyl-1,3,8-triaza-spiro[4,5]decane, melting point 187.5° to 190°C.

References

Merck Index 4105
Kleeman & Engel p. 428
OCDS Vol. 2 p. 292 (1980)
DOT 9 (6) 235 (1973)
I.N. p.441
Janssen, P.A.J.; US Patent 3,238,216; March 1,1966; assigned to Research Laboratorium Dr. C. Janssen NV, Belgium

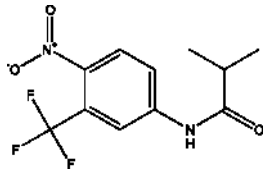
FLUTAMIDE

Therapeutic Function: Antiandrogen

Chemical Name: 2-Methyl-N-[4-nitro-3-(trifluoromethyl)phenyl]-propanamide

Common Name: Niftolid

Structural Formula:



Chemical Abstracts Registry No.: 13311-84-7

Trade Name	Manufacturer	Country	Year Introduced
Flugerel	Byk-Essex	W. Germany	1983
Drogenil	Schering	Chile	1983

Raw Materials

4-Nitro-3-trifluoromethylaniline
Isobutyryl chloride

Manu**facturing Process**

To a stirred, cooled solution of 100 g of 4-nitro-3-trifluoromethylaniline in 400 ml of pyridine, slowly and in a dropwise fashion, add 54 g of isobutyrylchloride and then heat the reaction mixture on a steam bath for 1.5 hours. Cool and pour the resulting mixture into ice water, filter and water-wash the crude anilide and crystallize the product of this example from benzene to obtain analytically pure material, MP 111.5°C to 112.5°C.

References

Merck Index 4106
DFU 1 (3) 108 (1976)
OCDS Vol. 3 p. 57 (1984)
I.N. p. 441
Gold, E.H.; US Patent 3,847,988; November 12, 1974; assigned to Schering Corp.

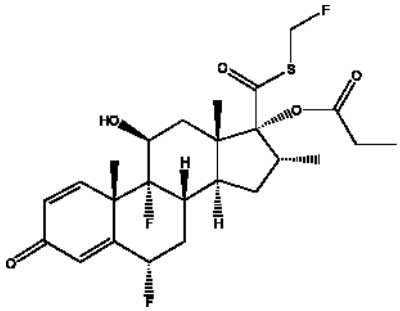
FLUTICASONE PROPIONATE

Therapeutic Function: Glucocorticoid

Chemical Name: Androsta-1,4-diene-17-carbothioic acid, 6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-(1-oxopropoxy)-, S-(fluoromethyl) ester, (6α,11β,16α,17α)-

Common Name: Fluticasone propionate

Structural Formula:



Chemical Abstracts Registry No.: 80474-14-2

Trade Name	Manufacturer	Country	Year Introduced
Cutivate	Glaxo Wellcome	UK	-
Flixonase	GlaxoSmithKline	UK	-
Flixotide	GlaxoWellcome	UK	-
Fluticare	Lyka Hetro Labs. Ltd.	India	-
Zoflut	Cipla Limited	India	-
Flutivate	Glaxo Smithkline	-	-
Flutopic	Systopic Laboratories (P) Ltd.	India	-
Lutica Cream	Ochoa Laboratories (P) Ltd.	India	-

Raw Materials

6α,9α-Difluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid
Propionyl chloride
Sodium iodide
Silver fluoride

Manufacturing Process

A solution of 6α,9α-difluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-7β-carboxylic acid (2.113 g) and triethylamine (2.5 ml) in dichloromethane (60 ml) was treated at 0°C with propionyl chloride (1.85 ml). After 1 h the mixture was diluted with more solvent (50 ml) and washed successively with 3% sodium hydrogen carbonate, water, 2 N hydrochloric acid, water, saturated brine, then dried and evaporated. The solid was dissolved in acetone (50 ml) and diethylamine (2.5 ml) was added. After 1 h at 22°C the solvent was removed in vacuo and the residual gum was dissolved in water (30 ml). Acidification to pH 1 with 2 N hydrochloric acid precipitated a solid, which was collected, washed with water, and dried to give the 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carboxylic acid (2.230 g), melting point 220-225°C, $[\alpha]_D$ =+4° (c 0.70).

A solution of the 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carboxylic acid (500 mg) and sodium iodide (1.874 g) in acetone (15 ml) was stirred and heated under reflux for 6.5 h. Ethyl acetate (75 ml) was then added and the solution was washed successively with water, 10% sodium thiosulfate solution, 5% sodium hydrogen carbonate solution and water, dried and evaporated to give an off-white foam (525 mg). PLC in chloroform-acetone (6:1) to give an off-white foam (478 mg) which was crystallised from acetone without being heated above room temperature to give colourless crystals of the S-iodomethyl-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate (241 mg); m.p. 196-197°C, $[\alpha]_D$ = -32° (c 1.01).

A solution of S-iodomethyl-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate (310 mg) in acetonitrile (10 ml) was stirred with silver fluoride (947 mg) for 3 days at room temperature in the dark. Ethyl acetate (100 ml) was added and the mixture was filtered through kieselguhr. The filtrate was washed successively with 2 N hydrochloric acid, water, saturated brine, then dried. The solvent was removed and the residue was subjected to column chromatography in chloroform then chloroform-acetone (19:1). The product was eluted with ethyl acetate and crystallised on concentration of the solution to give S-fluoromethyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate (0.075 g); melting point 272-273°C (dec.), $[\alpha]_D$= +30° (c 0.35).

References

Phillipps G.H. et al.; US Patent No. 4,335,121; June 15, 1982; Assigned to Glaxo Group Limited (London, GB2)

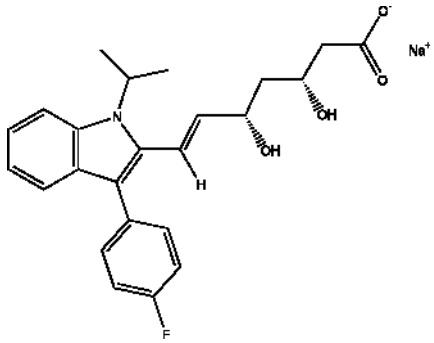
FLUVASTATIN SODIUM

Therapeutic Function: Antihyperlipidemic

Chemical Name: 6-Heptenoic acid, 7-(3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl)- 3,5-dihydroxy-, (3R,5S,6E)-rel-, monosodium salt

Common Name: Fluindostatin sodium; Fluvastatin sodium

Structural Formula:



Chemical Abstracts Registry No.: 93957-54-1 (Base); 93957-55-2

Trade Name	Manufacturer	Country	Year Introduced
Lipaxan	Italfarmaco spa	-	-
Primesin	SCHWARZ PHARMA spa	-	-
Locol	Novartis Pharma	-	-
Fluvastatin sodium	ZYF Pharm Chemical	-	-

Raw Materials

Fluorobenzene
Hydrochloric acid
N-Isopropylaniline
Chloroacetyl chloride
Aluminum chloride
Sodium hydroxide

Manufacturing Process

164 ml (235.1 g, 2.04 moles) of chloroacetyl chloride is added over a 50 min period to a mixture of 400 ml (410 g, 4.22 moles) of fluorobenzene and 300.0 g (2.25 moles) of anhydrous aluminum chloride stirred at 75°C under nitrogen. The reaction mixture is stirred at 80°C under nitrogen for 1 h, cooled to 50°C, 500 ml of fluorobenzene is added, and the reaction mixture is cooled to 0°C and gradually (over a 30 min period) siphoned into 1 L of 6 N hydrochloric acid stirred at 0°C. (The temperature of the aqueous acid is maintained at or below 25°C throughout the addition). The quenched, acidified reaction mixture is stirred for 15 min, and the aqueous phase is separated and extracted with 350 ml of fluorobenzene. The two organic

phases are combined and washed twice with 500 ml portions of 3 N hydrochloric acid and once with 500 ml of water. The fluorobenzene is distilled at 30 mm. Hg and 60°C and, upon cooling, the obtained 4-chloroacetyl-1-fluorobenzene oily residue solidifies.

562.9 g (4.08 moles) of N-isopropylaniline is rapidly added to a solution of the 4-chloroacetyl-1-fluorobenzene in 500 ml of dimethylformamide stirred at 50°C under nitrogen. The reaction mixture is stirred at 100°C under nitrogen for 10 h and allowed to cool to room temperature overnight. The reaction mixture is heated to 60°C, 2 L of water is added, and the mixture is cooled to 10°C. The obtained solids are collected, washed twice with 500 ml portions of water and dissolved in 550 ml of 95% ethanol at 75°C. The solution is cooled to 0°C, and the obtained solids are collected, washed three times with 100 ml portions of 95% ethanol and vacuum dried at 35°-40°C for 4 h to obtain the 95.3% pure yellow product: N-(4-fluorobenzoylmethyl)-N-(1-methylethyl) aniline (466.0 g, 84.2%, melting point 78° -81°C).

4.5 ml of 1 N sodium hydroxide solution (4.5 mmol) and 2.0 g (4.7 mmol) of N-(4-fluorobenzoylmethyl)-N-(1-methylethyl)aniline are stirred in 150 ml of ethanol at room temperature for 2 h, the solvent is evaporated at reduced pressure, and the residue is dissolved in 50 ml of water. The aqueous solution is gently extracted with diethyl ether, the traces of ether in the aqueous layer are removed at reduced pressure, and the aqueous layer is freeze dried to obtain racemic sodium threo-(+/-)-(E)-3,5-dihydroxy-7-[3'-(4"-fluorophenyl)-1'-(1"-methylethyl)indol-2'-yl]hept-6-enoate (1.8 g (88%)), melting point 194°-197°C.

The crude sodium threo-(+/-)-(E)-3,5-dihydroxy-7-[3'-(4"-fluorophenyl)-1'-(1"-methylethyl)indol-2'-yl]hept-6-enoate is dissolved in water, and the solution is acidified to pH 2 with 2 N hydrochloric acid and extracted with diethyl ether. The diethyl ether extract is washed three times with saturated sodium chloride solution, dried over anhydrous magnesium sulfate and evaporated at reduced pressure to obtain the crude solid racemic erythro-(+/-)-(E)-3,5-dihydroxy-7-[3'-(4"-fluorophenyl)-1'-(1"-methylethyl)indol-2'-yl] hept-6-enoic acid (6.9 g).

The racemic erythro-(+/-)-(E)-3,5-dihydroxy-7-[3'-(4"-fluorophenyl)-1'-(1"-methylethyl)indol-2'-yl]hept-6-enoic acid may both be resolved into two optically pure enantiomers, the 3R, 5S and 3S, 5R isomers by chromatography on silica gel column using organic solutions as the eluent.

References

Kathawala; Faizulla G.; US Patent No. 4,739,073; April 19, 1988; Assigned: Sandoz Pharmaceuticals Corp. (E. Hanover, NJ)

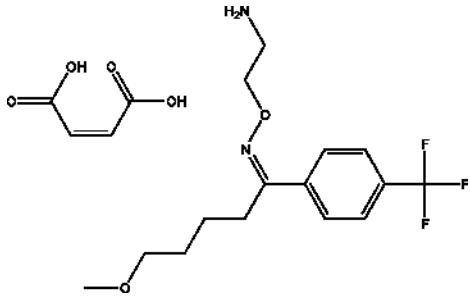
FLUVOXAMINE MALEATE

Therapeutic Function: Antidepressant

Chemical Name: 5-Methoxy-4'-trifluoromethylvalerophenone O-(2-aminoethyl)oxime maleate (1:1)

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 54739-18-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Floxyfral	Kali-Duphar	Switz.	1983
Solvay	Kali-Duphar	W. Germany	1983
Floxyfral	Duphar	UK	-

Raw Materials

5-Methoxy-4'-trifluoromethylvalerophenone
2-Aminooxyethylamine dihydrochloride
Maleic anhydride

Manufacturing Process

20.4 mmol (5.3 g) of 5-methoxy-4'-trifluoromethylvalerophenone (MP 43°C to 44°C), 20.5 mmol (3.1 g) of 2-aminooxyethylamine dihydrochloride and 10 ml of pyridine were refluxed for 15 hr in 20 ml of absolute ethanol. After evaporating the pyridine and the ethanol in vacuo, the residue was dissolved in water. This solution was washed with petroleum ether and 10 ml of 50% sodium hydroxide solution were then added. Then three extractions with 40 ml of ether were carried out. The ether extract was washed successively with 20 ml of 5% sodium bicarbonate solution and 20 ml of water. After drying on sodium sulfate, the ether layer was evaporated in vacuo. Toluene was then evaporated another three times (to remove the pyridine) and the oil thus obtained was dissolved in 15 ml of absolute ethanol. An equimolar quantity of maleic acid was added to the solution and the solution was then heated until a clear solution was obtained. The ethanol was then removed in vacuo and the residue was crystallized from 10 ml of acetonitrile at +5°C. After sucking off and washing with cold acetonitrile, it was dried in air. The MP of the resulting compound was 120°C to 121.5°C.

References

Merck Index 4108
DFU 3 (4) 288 (1978)
I.N. p. 441
Welle, H.B.A. and Claassen, V.; US Patent 4,085,225; April 18, 1978; assigned to US Phillips Corp.

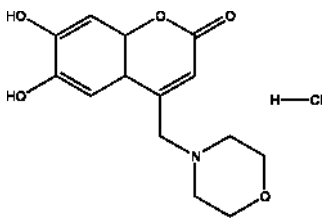
FOLESCUTOL HYDROCHLORIDE

Therapeutic Function: Capillary protective

Chemical Name: 6,7-Dihydroxy-4-(morpholinomethyl)coumarin hydrochloride

Common Name: Folescutol hydrochloride; Pholescutol hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 15687-22-6 (Base); 36002-19-4

Trade Name	Manufacturer	Country	Year Introduced
Folescutol hydrochloride	ZYF Pharm Chemical	-	-

Raw Materials

4-Chlormethyl-6,7-dihydroxycoumarin
Morpholine

Manufacturing Process

A solution 35.6 g of 4-chlormethyl-6,7-dihydroxycoumarin and 27.3 g of morpholine in 4.5 L methyl ethyl ketone was refluxed for 9 hours. On cooling the morpholine hydrochloride was deleted. Methyl ethyl ketone was evaporated in vacuum. The solid product was mixed with 500 ml of water and dried in vacuum with P_2O_5. Yield of crude 6,7-dihydroxy-4-(morpholinomethyl)coumarin is 41.5 g. After recrystallization from ethanol was obtained 6,7-dihydroxy-4-(morpholinomethyl)coumarin with M.P. 232°C.

In practice it is usually used as hydrochloride.

References

Merck Index, Monograph number: 4252, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
FR Patent No. 2,035M; Sept. 23, 1963; Assigned to Les Laboratoir Dausse, France

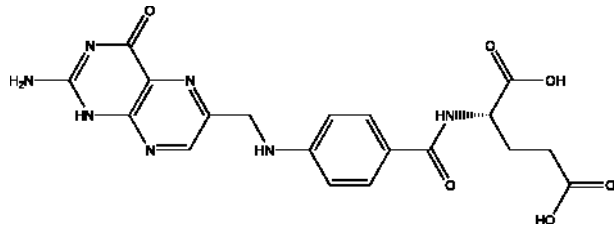
FOLIC ACID

Therapeutic Function: Treatment of B vitamin (folacin) deficiency

Chemical Name: N-[4-[[(2-Amino-1,4-dihydro-4-oxo-6-pteridinyl)methyl] amino]benzoyl]-L-glutamic acid

Common Name: Pteroylglutamic acid

Structural Formula:



Chemical Abstracts Registry No.: 59-30-3

Trade Name	Manufacturer	Country	Year Introduced
Folvite	Lederle	US	1946
Foldine	Specia	France	1947
Follcet	Mission	US	1981
Acfol	Torlan	Spain	-
Cefol	Abbott	US	-
Cevi-Fer	Geriatric	US	-
Cytofol	Lappe	W. Germany	-
Eldec	Parke Davis	US	-
Eldercaps	Mayrand	US	-
Enviro-Stress	Vitaline	US	-
Fefol	SKF	UK	-
Feosol	Menley and James	US	-
Fero-Folic	Abbott	US	-
Ferrocap	Consolidated	UK	-
Ferrograd	Abbott	UK	-
Ferromyn	Calmic	UK	-
Filibon	Lederle	US	-

Trade Name	Manufacturer	Country	Year Introduced
Folacid	U.C.B.	-	-
Folacin	Kabi Vitrum	Sweden	-
Folaemin	O.P.G.	Netherlands	-
Folamin	Becker	Austria	-
Folan	Farmakos	Yugoslavia	-
Folasic	Adams	Australia	-
Folbiol	I.E. Kimya Evi	Turkey	-
Folettes	Fawns and McAllan	Australia	-
Folex	Rybar	UK	-
Folical	Shionogi	Japan	-
Foliamin	Takeda	Japan	-
Folicet	Mission	US	-
Folico	Mitim	Italy	-
Folina	Tosi	Italy	-
Folirivo	Rivopharm	Switz.	-
Hemocyte	US Pharm.	US	-
Hemostyl	Roussel	-	-
Iberet	Abbott	US	-
Ircon	Key	US	-
Irofol	Abbott	UK	-
Iromin	Mission	US	-
Lipo	Legere	US	-
May-Vita	Mayrand	US	-
Mega-B	Arco	US	-
Megadose	Arco	US	-
Methiofoline	Hepatrol	France	-
Mevanin	Beutlich	US	-
Niferex	Central	US	-
Nifolin	Ferrosan	Denmark	-
Novofolac	Novopharm	Canada	-
Nu-Iron	Mayrand	US	-
Pramet	Ross	US	-
Pramilet	Ross	US	-
Pregaday	Glaxo	UK	-
Prenate	Bock	US	-
Pronemia	Lederle	US	-
Stuartnatal	Stuart	US	-
Trinsicon	Glaxo	US	-
Vicon	Glaxo	US	-
Vitafol	Everett	US	-
Zenate	Reid-Rowell	US	-
Zincvit	R.A.M. Labs	US	-

Raw Materials

Bromine
Sodium bisulfite
1,3,3-Trichloroacetone
p-Aminobenzoylglutamic acid
2,4,5-Triamino-6-hydroxypyrimidine HCl

Manufacturing Process

The following description is taken from US Patent 2,956,057.

100 grams of 1,3,3-trichloroacetone are heated on a boiling water bath and 95 grams of bromine are added thereto in drops while being stirred and the stirring is continued for about 1 hour. The resulting reaction solution is distilled under reduced pressure. 115 grams of 1-bromo-1,3,3-trichloroacetone are obtained having a boiling point of 85° to 95°C/17 mm (Hg).

For the preparation of the hydrate, 100 grams of water are added to 100 grams of 1bromo-1,3,3-trichloroacetone, which is agitated and cooled. A white scaly crystal of hydrate of 1-bromo-1,3,3-trichloroacetone is obtained (100 grams), having a melting point of 52° to 53°C.

8.9 grams of 2,4,5-triamino-6-hydroxypyrimidine hydrochloride and 8 grams of p-aminobenzoylglutamic acid are dissolved in 400 cc warm water, which is cooled at 35° to 27°C and adjusted to pH 4 by using 20% caustic soda solution. To this solution was simultaneously added dropwise a solution obtained by dissolving 13.4 grams of 1-bromo-1,3,3-trichloroacetone hydrate in 90 cc of 50% methanol and 24 grams of 35% aqueous sodium bisulfite solution over a period of approximately 2 hours. During this period, in order to maintain the pH value of the reaction solution at 4 to 5, 20% caustic soda solution is added from time to time. The precipitate, formed by stirring for 5 hours after dropping was finished, is filtered, and the filtrated precipitate is refined; 5.6 grams of pure pteroylglutamic acid is obtained.

References

Merck Index 4110
Kleeman & Engel p. 430
PDR pp. 508, 524, 581, 673, 785, 830, 875, 905, 916, 969, 1010, 1033, 1050, 1083, 1131, 1264, 1344, 1441, 1449, 1559, 1786, 1808, 1869
I.N. p. 24
REM pp. 1014, 1023
Sletzinger, M. and Tishler, M.; US Patent 2,786,056; March 19, 1957; assigned to Merck and Co.,Inc.
Sletzinger, M. and Tishler, M.; US Patent 2,816,109; December 10, 1957; assigned to Merck and Co., Inc.
Sletzinger, M. and Tishler, M.; US Patent 2,821,527; January 28, 1958; assigned to Merck and Co., Inc.
Sletzinger, M. and Tishler, M.; US Patent 2,821,528; January 28, 1958; assigned to Merck and Co., Inc.
Kawanishi, S.; US Patent 2,956,057; October 11, 1960; assigned to Kongo Kagaku KK, Japan

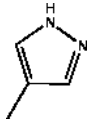
FOMEPIZOLE

Therapeutic Function: Antidote

Chemical Name: 4-Methylpyrazole

Common Name: Fomepizole; 4-Methylpyrazole

Structural Formula:



Chemical Abstracts Registry No.: 7554-65-6

Trade Name	Manufacturer	Country	Year Introduced
Antizol	Enzon, Inc.	-	-
Antizol	Orphan Medical, Inc.	-	-

Raw Materials

Sodium iodide
Hydrazine hydrate
Sulfuric acid
Isobutyraldehyde

Manufacturing Process

Preparation of 4-methylpyrazole

1.0 g (6.67 mmol) of sodium iodide is added to a suspension of 560 g (4.0 mol) of 70% strength sulfuric acid and 62.5 g (1.0 mol) of 80% strength hydrazine hydrate and, at 125°C, 86.4 g (1.2 mol) of isobutyraldehyde are pumped under the surface of the suspension over the course of 2 hours using a metering pump. During and up to 100 min after the addition of isobutyraldehyde, a total of 175 g of water was distilled out, with the temperature of the mixture rising to 135°C. The solution is cooled and adjusted to pH 8.6 with 820 g (5.125 mol) of 25% strength sodium isobutyraldehyde hydroxide solution and is extracted with isobutanol. The combined extracts are concentrated to 82 g in a rotary evaporator and then distilled. The main fraction (boiling point 82°C/7 mbar; 49 g) consists of 82% 4-methylpyrazole. Yield: 49% of theory.

References

Merkle H.R., Fretschner E.; US Panent No. 6,229,022; May 8, 2001; Assigned to BASF Aktiengesellschaft (Ludwigshafen, DE)

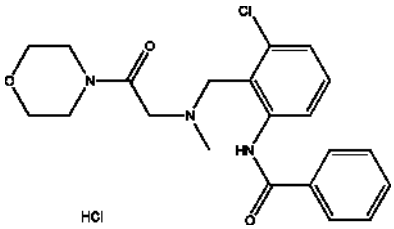
FOMINOBEN HYDROCHLORIDE

Therapeutic Function: Antitussive, Respiratory stimulant

Chemical Name: 3'-Chloro-α-[methyl[(morpholinocarbonyl)methyl]amino]-o-benzotoluidide hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 18053-32-2; 18053-31-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Noleptan	Thomae	W. Germany	1973
Terion	Lusofarmaco	Italy	1979
Noleptan	TANABE SEIYAKU	Japan	1983
Deronyl	Arzneimittelwerk Dresden	E. Germany	-
Finaten	Finadiet	Argentina	-
Oleptan	Bender	Austria	-
Tussirama	Serpero	Italy	-

Raw Materials

Morpholine
Hydrogen chloride
6-Chloro-2-dibenzoylaminobenzyl bromide
Sarcosine methyl ester
Ethyl chloroformate

Manufacturing Process

(a) A mixture consisting of 9.75 g of 6-chloro-2-dibenzoylamino-benzyl bromide, 2.34 g of sarcosine methyl ester, 3.18 ml of triethylamine and 250 ml of chloroform was refluxed for five hours. Thereafter, an addition 0.5 g of sarcosine methyl ester was added, and the mixture was again refluxed for five hours. Subsequently, the chloroform was evaporated in vacuo, the residue was taken up in ethylacetate, the insoluble matter was separated by filtration, and the filtrate was again evaporated in vacuo. The residual oil was dissolved in methanol, the solution was admixed with 25 ml of 2 N sodium hydroxide, and the mixture was allowed to stand overnight at about 20°C. Thereafter, the methanol was evaporated in vacuo, and the residual aqueous solution was adjusted to pH 2 with 2 N hydrochloric acid, then extracted with ethyl acetate and then adjusted to pH 6 with 2N sodium hydroxide. The crystalline product precipitated thereby was collected by vacuum filtration and recrystallized from water, yielding N-(2-benzoylamino-6-chloro-benzyl)-N-methyl-glycine, MP 150°C to 152°C.

(b) 80.7 g of N-(2-benzoylamino-6-chlorobenzyl)-N-methyl-glycine and 38 ml of triethylamine were dissolved in 1 liter of dry chloroform. While stirring the resulting solution at -15°C to -5°C, 23.4 ml of ethyl chloroformate were rapidly added dropwise, and the mixture was stirred for 40 minutes more at -15°C to -5°C. Thereafter, 50 ml of morpholine were added all at once, and the mixture was allowed to stand at 20°C for 20 hours. Subsequently, the chloroformic reaction solution was washed three times with brine, dried over magnesium sulfate and evaporated in vacuo, and the oily residue was taken up in ether, whereupon it crystallized. The crystalline product was recrystallized from methanol, yielding N-(2-benzoyl-amino-6-chloro-benzyl)-N-methyl-glycine-morpholide, MP 122.5°C to 123°C.

The product was dissolved in isopropanol, and the solution was acidified with anhydrous hydrochloric acid, yielding the hydrochloride, MP 206°C to 208°C (decomp.).

References

Merck Index 4124
Kleeman and Engel p.432
DOT 9 (7) 288 (1973)
I.N. p. 442
Kruger, G., Zipp, O.,Keck, J., Nickl, J., Machleidt, H., Ohnacker, G., Engelhorn, R. and Puschmann, S.; US Patent 3,661,903; May 9,1972; assigned to Boehringer Ingelheim G.m.b.H. (W. Germany)

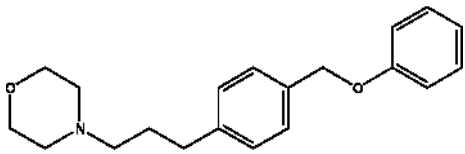
FOMOCAINE

Therapeutic Function: Local anesthetic

Chemical Name: 4-[3-[4-(Phenoxymethyl)phenyl]propyl]morpholine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 17692-39-6

Trade Name	Manufacturer	Country	Year Introduced
Erbocain	Heilit	W. Germany	1967
Panacain	Hemal	W. Germany	-

Raw Materials

Morpholine
Sodium phenolate
γ-(4-Chloromethylphenyl)propyl chloride

Manufacturing Process

64 parts of dry sodium phenolate are dissolved in 300 parts of methylisobutyl ketone by heating at 110°C. 103 parts of γ-(4-chloromethylphenyl)propyl chloride are added dropwise with agitation, and the mixture is maintained at 110°C for a period of 4 hours with constant agitation. After cooling, the reaction mixture is washed 2 or 3 times with 100 parts of water and the methylisobutyl ketone is distilled off under reduced pressure. The residue is taken up in 200 parts of petroleum ether and γ-(4-phenoxymethylphenyl) propyl chloride is crystallized by addition of ice water. The crystals are filtered off employing a suction pump and dried at 100°C in vacuo (10 mm Hg) for 1 to 2 hours. The γ-(4-phenoxymethylphenyl)propyl chloride melts at 55°C to 56°C after recrystallization from petroleum ether.

130 parts of γ-(4-phenoxymethylphenyl)propyl chloride are heated under reflux at 140°C for 24 hours with 130 parts of morpholine. The reaction mixture is treated to give N-[(γ-phenoxymethylphenyl)propyl]-morpholine, which forms colorless crystals melting at 52°C to 53°C when crystallized from n-heptane.

References

Merck Index 4115
I.N. p. 442
Chemische Fabrik Promonta G.m.b.H.; British Patent 786,128; November 13,1957

FONAZINE MESYLATE

Therapeutic Function: Analgesic

Chemical Name: 10-[2-Dimethylamino)propyl]-N,N-dimethylphenothiazine-2-sulfonamide methane sulfonate

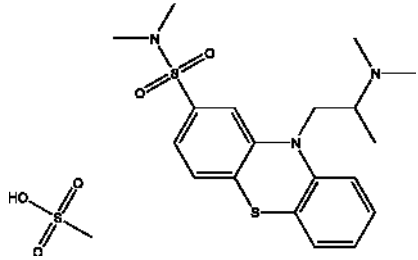
Common Name: Dimethothiazine

Chemical Abstracts Registry No.: 7455-39-2; 7456-24-8 (Base)

Raw Materials

Sodium amide
Hydrogen chloride
3-Dimethylsulfamoylphenothiazine
1-Dimethylamino-2-chloropropane
Methanesulfonic acid

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Migristene	Rhone Poulenc	France	1965
Migristene	Rhone Poulenc	W. Germany	1967
Migristene	Rhone Poulenc	UK	1968
Migristene	Rhone Poulenc	Italy	1972
Migristen	Shionogi	Japan	1973
Alius	Scharper	Italy	-
Banistyl	May and Baker	UK	-
Bistermin	Toyo Shinyaku	Japan	-
Calsekin	Kanto	Japan	-
Demethotiazine	Mohan	Japan	-
Normelin	Sawai	Japan	-
Serevirol	Fuji Zoki	Japan	-

Manufacturing Process

A solution of 3-dimethylsulfamoylphenthiazine (10 grams) in xylene (100 cc) is heated under reflux for 3 hours with sodium amide (1.5 grams). A solution of 1-dimethylamino-2-chloropropane (4.4 grams) in anhydrous xylene (30 cc) is then added and heating under reflux continued for 4 hours. After cooling the suspension obtained is agitated with water (50 cc) and ether (30 cc). The aqueous layer is separated and the basic products are extracted from the organic phase with 10% hydrochloric acid. The xylene layer is discarded and, after the combined acid solutions have been made alkaline with sodium carbonate, the base is extracted with chloroform. The chloroform solutions are then washed with water and dried over anhydrous potassium carbonate. After evaporation of the solvent under reduced pressure there is obtained a crude resinous base (9.7 grams).

On the addition of ethereal hydrogen chloride to a solution of the base in isopropanol and recrystallization from anhydrous ethanol of the salt formed, there is obtained 3-dimethylsulfamoyl-10-(2-dimethylaminopropyl) phenthiazine hydrochloride (2.1 grams), MP 214°C with decomposition. After dissolving the product in anhydrous ethanol and adding methanesulfonic acid there is obtained fonazine mesylate.

References

Merck Index 4116

Kleeman & Engel p. 320
DOT 3 (2) 57 (1967) and 9 (6) 226 (1973)
I.N. p. 341
Societe des Usines Chimiques Rhone-Poulenc, France: British Patent 814,512; June 3, 1959

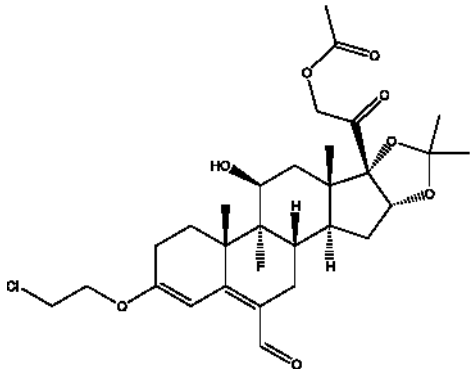
FORMOCORTAL ACETATE

Therapeutic Function: Glucocorticoid, Antiinflammatory

Chemical Name: 3-(2-Chloroethoxy)-9-fluoro-11β,16α,17,21-tetrahydroxy-20-oxopregna-3,5-diene-6-carboxaldehyde, cyclic 16,17-acetal-21-acetate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 2825-60-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Fluderma	Farmitalia	Italy	1970
Deflamene	Pharmitalia	UK	1971
Deidral	Montedison	W. Germany	-
Formaftil	Farmigea	Italy	-

Raw Materials

Ethylene glycol
Ethyl orthoformate
Trichloroethylene
Phosphorus oxychloride
9α-Fluoro-4-pregnene-11β,16α,17α,21-tetrol-3,20-dione-21-acetate-16α,17α-acetonide

Manufacturing Process

4.8 grams of 9α-fluoro-4-pregnene-11β,16α,17α,21-tetrol-3,20-dione-21-acetate-16α,17α-acetonide, melting at 248° to 250°C and prepared by acetylation of the corresponding 21-alcohol (J. Amer. Chem. Soc., 1959, 81, page 1689), were refluxed for 20 hours with 80 cc of dioxane, 5.2 cc of ethylene glycol, 4.8 cc of ethyl orthoformate and 60 mg of p-toluenesulfonic acid. After cooling, 0.6 cc of pyridine were added and the mixture was concentrated in vacuo, diluted with ethyl acetate, poured into a separatory funnel, and washed with water, with a solution of 5% aqueous sodium bicarbonate and then with water to neutrality. After distilling off the solvent, a residue of 5.5 grams remained, which was dissolved in benzene and chromatographed over 100 grams of Florisil (chromatographic adsorbent). 3 grams of 9α-fluoro-5-pregnene-11β,16α,17α,21-tetrol-3,20-dione-21-acetate-3-ethyleneketal-16α,17α-acetonide, melting at 145° to 147°C, were collected from the fractions eluted with benzene-ether 9:1.

1 gram of this 9α-fluoro-5-pregnene-11β,16α,17α,21-tetrol-3,20-dione-21-acetate-3-ethyleneketal-16α,17α-acetonide in 2 cc of dimethylformamide and 2 cc of trichloroethylene was heated for 3 hours on an oil bath at 70°C with the reagent obtained from 0.5 cc of dimethylformamide in 4 cc of trichloroethylene with 0.5 cc phosphorus oxychloride. After cooling to 0°C, 1 gram of sodium acetate dissolved in 3 cc of water were slowly added with stirring. The mixture was extracted with ethyl acetate and the extracts were washed with water, with a 5% aqueous solution of sodium bicarbonate and then with water to neutrality. On distillation of the solvent 1.1 grams of a residue was obtained from which, after dissolution in ether and precipitation with petroleum ether, 0.500 gram of 3-(2'-chloroethoxy)-6-formyl-9α-fluoro-3,5-pregnadien-11β,16α,17α,21-tetrol-20-one-21-acetate-16α,17α-acetonide, melting at 180° to 182°C were obtained.

References

Merck Index 4126
Kleeman & Engel p. 433
OCDS Vol. 2 p. 189 (1980)
DOT 7 (1) 21 (1971)
I.N. p. 443
Camerino, B., Patelli, B. and Sciaky, R.; US Patent 3,314,945; April 18,1967; assigned to Societa Farmaceutici Italia, Italy

FOSCARNET SODIUM

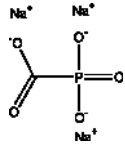
Therapeutic Function: Antiviral

Chemical Name: Phosphinecarboxylic acid, dihydroxy-, oxide, trisodium salt

Common Name: Foscarnet sodium; Foscarnetum natricum; Trisodium phosphonoformate

Chemical Abstracts Registry No.: 63585-09-1; 4428-95-9 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Foscarnet Sodium	AstraZeneca	USA	-
Foscavir	AstraZeneca	USA	-

Raw Materials

Sodium hydroxide
Triethyl phosphonoformate

Manufacturing Process

423 g (4.77 mol) of sodium hydroxide is added to 400 ml of water. The solution is heated to about 50°C and 167 g (0.795 mol) of triethyl phosphonoformate is added. The reaction mixture is then heated to about 90°C and ethanol formed is distilled off. After about 1 hour at 90-95°C the reaction mixture is cooled to about 20°C and the product is filtered off. The yield of trisodium phosphonoformate hexahydrate wet is 248 g.

The wet substance is recrystallized in 570 ml of water by heating to 423 g (4.77 mol) of sodium hydroxide liquid conc. is added to 400 ml of water. The solution is heated to about 50°C and 167 g (0.795 mol) of triethyl phosphonoformate is added at this temperature. The reaction mixture is then heated to about 90°C and ethanol formed is distilled off. After about 1 hour at 90-95°C the reaction mixture is cooled to about 20°C and the product is filtered off. The yield of trisodium phosphonoformate hexahydrate wet is 248 g.

The wet substance is recrystallized in 570 ml of water by heating to 90°C in order to obtain a clear solution and then cooling to about 20°C. After filtration and washing with 50 ml of water at 18-22°C 187 g (74% of theoretical yield) of trisodium phosphonoformate hexahydrate is obtained. This substance contains about 2% free water, which can be eliminated by drying.

References

Jakupovic E., Stenhede J.; US Patent No. 5,591,889; Jan. 7, 1997; Assigned to Aktiebolaget Astra (Sodertalje, SE)

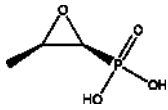
FOSFOMYCIN

Therapeutic Function: Antibiotic

Chemical Name: (cis-1,2-Epoxypropyl)phosphonic acid

Common Name: Phosphonomycin

Structural Formula:



Chemical Abstracts Registry No.: 23155-02-4

Trade Name	Manufacturer	Country	Year Introduced
Fosfocin	Crinos	Italy	1977
Fosfocine	Clin Midy	France	1980
Fosfocin	Boehringer Mannheim	W. Germany	1980
Fosmicin	Meiji Seika	Japan	1981
Fosfocine	Boehringer Mannheim	Switz.	1983
Biocin	Ibirn	Italy	-
Faremicin	Lafare	Italy	-
Fonofos	Pulitzer	Italy	-
Fosfogram	Firma	Italy	-
Fosfotricina	Italfarmaco	Italy	-
Francital	Francia	Italy	-
Lancetina	Lancet	Italy	-
Lofoxin	Locatelli	Italy	-
Palmofen	Zambon	Italy	-
Priomicina	San Carlo	Italy	-
Selemicina	Italchemi	Italy	-
Valemicina	Valeas	Italy	-

Raw Materials

Acetaldehyde
t-Butyl hypochlorite
Hydroxymethylphosphonic acid
Zinc-copper couple

Manufacturing Process

(A) The preparation of [(1-chloroethoxy)chloromethyl]phosphonic acid: Acetaldehyde (1.1 mol) and hydroxymethylphosphonic acid (1 mol) in 500 ml of benzene are saturated with hydrogen chloride gas at 10°C to 15°C. The mixture is aged at 25°C for 24 hr, the solvent distilled out in vacuo and the residue flushed three times with benzene to remove all traces of hydrogen

chloride. The residue is taken up in benzene (500 ml), treated with tert-butyl hypochlorite (0.8 mol) and azobisisobutyronitrile (0.8 mm) at 40°C until titration shows the absence of hypochlorite and the solution is then evaporated to yield [(1-chloroethoxy)chloromethyl] phosphonic acid in the form of an oil.

(B) The preparation of (cis-1,2-epoxypropyl)phosphonic acid: [(1-chloroethoxy)chloromethyl] phosphonic acid (1.0 g) is added with stirring to tetrahydrofuran (50 ml) to which has been added a crystal of iodine and a zinc-copper couple (15.0 g). The mixture is then heated under reflux for 24 hr and the resulting solution filtered to yield (cis-1,2-epoxypropyl)-phosphonic acid.

There is also a fermentation route to Fosfomycin as noted by Kleeman and Engel.

References

Merck Index 4137
Kleeman & Engel p. 434
DOT 9 (7) 294 (1973)
I.N. p. 444
REM p. 1212
Christensen, B.G. and Firestone, R.A.; US Patent 3,632,691; January 4, 1972; assigned to Merck & Co., Inc.
Firestone, R.A. and Sletzinger, M.; US Patent 3,584,014; June 8, 1971; assigned to Merck & Co., Inc.
Firestone, R.A. and Glamkowski, E.J.; US Patent 3,632,609; January 4, 1972; assigned to Merck & Co., Inc.
Firestone, R.A.; US Patent 3,637,765; January 25, 1972; assigned to Merck & Co., Inc.
Glamkowski, E.J. and Sletzinger, M.; US Patent 3,637,766; January 25, 1972; assigned to Merck & Co., Inc.
Poliak, P.I., Wendler, N.L. and Christensen, B.G.; US Patent 3,649,619; March 14, 1972; assigned to Merck & Co., Inc.

FOSINOPRIL SODIUM

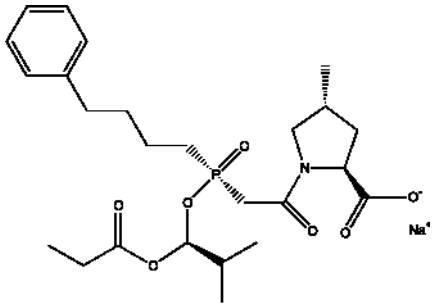
Therapeutic Function: Antihypertensive

Chemical Name: L-Proline, 4-cyclohexyl-1-(((R)-((1S)-2-methyl-1-(1-oxopropoxy)propoxy)(4-phenylbutyl)phosphinyl)acetyl)-, sodium salt, (4S)-

Common Name: Fosenopril sodium; Fosfenopril sodium; Fosinopril sodium

Chemical Abstracts Registry No.: 88889-14-9; 98048-97-6 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Fosinopril Sodium	Bristol-Myers Squibb	-	-
Fosinopril Sodium	Eon Labs, Inc.	-	-
Fosinopril Sodium	Ranbaxy	India	-
Lin-fosinopril	Linson Pharma Inc.	-	-
Monopril	Bristol-Myers Squibb	USA	-
Monopril	Teva Pharmaceuticals	USA	-

Raw Materials

Triethylamine
Trimethylsilyl chloride
Sodium iodide
Palladium on carbon
L-Cinchonidine
Benzyl bromoacetate
(trans)-4-Cyclohexyl-L-proline, hydrochloride
4-Phenylbutyl phosphinic acid
2-Ethylhexanoic acid, sodium salt
1-Chloroisobutyl propionate
Ammonium n-butyl sulfate
Hydroxybenzotriazole hydrate
N,N'-Dicyclohexylcarbodiimide

Manufacturing Process

To a solution of 4-phenylbutyl phosphinic acid (2.0 g, 0.01 mole) in chloroform (40 ml) was added triethylamine (3.2 ml, 0.022 mole) and the mixture was cooled in an ice bath to 0°C. Trimethylsilyl chloride (2.8 ml, 0.022 mole) was added to the above solution dropwise, followed by benzyl bromoacetate (1.6 ml, 0.011 mole). The ice bath was removed and the mixture stirred at room temperature for 5 hours and poured into 10% aqueous HCl (30 ml) and crushed ice (20 g). After shaking the mixture in a separatory funnel, the chloroform layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic phase was washed with brine, dried over anhydrous sodium sulfate and the solvents removed in vacuum. The resulting crude thick oil (3.5 g) was dissolved in 30 ml ether, hexane was added dropwise to get a turbid solution and the mixture was left at room temperature overnight to complete the crystallization. It was cooled in the freezer for 2 hours, filtered and the solid was washed very thoroughly with hexane (50 ml), ether (50 ml) and again hexane (50 ml), ether (50 ml) in that order. The solid was vacuum dried to get 2.48 g (71%) of [hydroxy-(4-

phenylbutyl)-phosphinyl]acetic acid, phenylmethyl ester, m.p. 68-70°C. TLC (Silica gel, CH_2Cl_2:MeOH:HOAc (20:1:1)) shows a single spot.

A solution of 50 g (0.14 mole) of [hydroxy-(4-phenylbutyl)-phosphinyl]acetic acid, phenylmethyl ester in 300 ml of dry $CHCl_3$ was treated with 28.6 g (0.28 mole) of Et_3N, 35.6 g (0.21 mole) of 1-chloroisobutyl propionate, 12.0 g (0.035 mole) of (n-Bu)4$NHSO_4$ and 5.3 g (0.035 mole) of NaI. The above mixture was stirred and heated to mild reflux for 20 hours, then cooled and the solvent evaporated in vacuo. The oil residue was dissolved in 150 ml of ether and washed with 150 ml of water. The aqueous wash was extracted with 150 ml of ether. The combined ether solutions were washed with 5% $NaHCO_3$, 10% $NaHSO_3$ and brine. After drying ($MgSO_4$) the ether was evaporated in vacuo to give 57.0 g (83%) of crude [[2-methyl-1-(1-oxopropoxy)propoxy](4-phenylbutyl)phosphinyl]acetic acid, phenyl methyl ester as an oil product.

A solution of 57.0 g (0.12 mole) of [[2-methyl-1-(1-oxopropoxy)propoxy](4-phenylbutyl)phosphinyl]acetic acid, phenyl methyl ester in 300 ml of ethyl acetate was treated with 3.0 g of 10% Pd/C and hydrogenated on the Parr apparatus (45 psi) for 4 hours. The mixture was filtered through Hyflo and the solution was extracted with 5% $NaHCO_3$. The aqueous extracts were washed with ether, cooled to 5°C and treated with 36 ml of HOAc. The product was extracted into ethyl acetate, dried ($MgSO_4$) and the solvent was evaporated in vacuo. The residue was dissolved in 300 ml of toluene and the solvent was evaporated in vacuo to remove last traces of acetic acid. The oil residue became semi-solid on standing at room temperature. The yield of the product of debenzoylation - 2-[carboxymethyl)-(4-phenylbutyl)-phosphinoyloxy]-2-methylpropionic acid ethyl ester (racemic mixtures) was 39.8 g (72%).

A suspension of 10.0 g (0.026 mole) of [[2-methyl-1-(1-oxopropoxy)propoxy](4-phenylbutyl)phosphinyl]acetic acid in 50 ml of isopropyl ether was stirred vigorously for 15 min, then kept at 5°C for 20 hours. The colorless product was filtered, washed with a small amount of cold isopropyl ether to give 5.0 g of [[2-methyl-1-(1-oxopropoxy)propoxy](4-phenylbutyl)phosphinyl]acetic acid (A/B isomer, racemic mixture) , m.p. 87-89°C. The filtrate was evaporated in vacuo and retained for isolation of isomer C/D. A solution of the above material in 110 ml of hot isopropyl ether was filtered through a hot glass funnel (glass wool). The cooled solution gave 4.6 g (92%) of desired product, m.p. 90-92°C.

To a vigorously stirred suspension of 980 g (3.33 mol) of l-cinchonidine in 6 L of ethyl acetate maintained at 45°C was gradually added 1275.5 g (3.33 mol) of A/B isomer mixture and stirring then continued for an additional 2.5 hours while the resulting suspension of salt was gradually heated to 70°C when complete solution was obtained. After filtration (Hyflo) from a small amount of insoluble material, the solution was seeded and cooled. The crystalline product which separated was then filtered, washed with 1200 ml of 1:1 ethyl acetate/isopropyl ether, and dried in vacuo to give 1897.2 g of cinchonidine salt enriched in the B-isomer, m.p. 106-109°C, $[\alpha]_D$ = -59.3° (c = 1, methanol). This material was combined with 136.8 g of similarly prepared material (from 0.412 mol of A/B isomer) and the total quantity (2014 g) recrystallized from 10.18 L of boiling ethyl acetate to afford after filtration, washing with 1500 ml of the same solvent mixture used before, and drying in vacuo 1162 g (92%) of [[2-methyl-1-(1-oxopropoxy)propoxy](4-phenylbutyl)

phosphinyl]acetic acid (Resolution; isomer B), cinchonidine salt (1:1), m.p. 120-122°C (dec.), $[\alpha]_D$= -45° (c = 1, methanol), $[\alpha]_{365}$ = -185.5° (c = 1, methanol). A sample (10 g) was recrystallized twice from acetonitirle and three times from ethyl acetate additionally to give salt of m.p. 125-126°C (dec.), $[\alpha]_D$= -42.2°.

A slurry of methyl-1-(1-oxopropoxy)propoxy](4-phenylbutyl)phosphinyl]acetic acid (B-isomer), dried in vacuo at room temperature for 72 hours, (230.4 g, 0.6 moles) and hydroxybenzotriazole hydrate, dried, in vacuo at 80°C for 24 hours, (101.1 g, 0.66 mole) dichloromethane (sieved dried) (6 L) was chilled in an ice/acetone bath and treated with N,N-dicyclohexylcarbodiimide (136 g, 0.66 mole). The mixture was warmed to room temperature and stirred for 3 hours. The mixture was then chilled in ice/acetone and treated with (trans)-4-cyclohexyl-L-proline, hydrochloride (154.2 g, 0.66 mole) followed by diisopropylethylamine (170.7 g, 1.32 mole). The reaction mixture was stirred at room temperature for 18 hours. The mixture was then chilled, treated with water (1 L) and concentrated in vacuo to remove dichloromethane. The residue was diluted with ether (3600 ml) and water (3600 ml) and filtered. The filtrate was brought to pH = 1.8 with 10% hydrochloric acid. The ether layer was separated and the aqueous layer washed with ethyl acetate (3 x 2 L). The combined organic layers were washed with 5% $KHSO_4$ (3 x 1 L), water (3 x 1 L) and brine (1 L), dried over magnesium sulfate and concentrated in vacuo to yield 398.9 g of crude [R,1S,4S]-4-Cyclohexyl-1-[[[2-methyl-1-(1-oxopropoxy)propoxy](4-phenylbutyl)phosphinyl]acetyl]-L-proline, monosodium salt (isomer B). The crude product was dissolved in acetone (4393 ml), treated with a solution of 2-ethyl hexanoic acid, sodium salt (117.3 g) in acetone (1468 ml), then stirred at room temperature overnight. The resultant precipitate was collected by filtration, washed with acetone (3 x 400 ml) and hexane (1 L) then dried in vacuo. Yield 277 g, m.p. 195-196°C, $[\alpha]_D$= -5.1° (MeOH, c = 2), HI = 99.8%. Isomer "A" was not detectable.

References

Petrillo Jr. E.W.; US Patent No. 4,873,356; Oct. 10, 1989; Assigned to E.R. Squibb and Sons, Inc. (Princeton, NJ)

FOSPHENYTOIN SODIUM

Therapeutic Function: Antiepileptic, Anticonvulsant

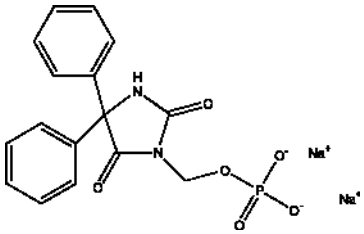
Chemical Name: 2,4-Imidazolidinedione, 5,5-diphenyl-3-((phosphonooxy) methyl)-, disodium salt

Common Name: Fosphenytoin sodium; Phosphenytoin sodium

Chemical Abstracts Registry No.: 92134-98-0; 93390-81-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Cerebyx	Pfizer	-	-
Fosphenytoin Sodium	Cilag	-	-

Structural Formula:



Raw Materials

Formaldehyde	5,5-Diphenylhydantoin
Hydrochloric acid	Phosphorus trichloride
Hydrogen	Argentum salt of phosphoric acid dibenzyl ester

Manufacturing Process

By action of formaldehyde and hydrochloric acid on 5,5-diphenylhydantoin was prepared 3-hydroxymethyl-5,5-diphenyl-imidazolidine-2,4-dione which was converted by action PCl_3 to 3-chloromethyl-5,5-diphenyl-imidazolidine-2,4-dione by action PCl_3. Then the chlorine atom was substituted on P(O)(OBz)O-group by action of argentum salt of phosphoric acid dibenzyl ester. Removal of the protecting groups by hydrogenolysis gives the 2,4-imidazolidinedione, 5,5-diphenyl-3-((phosphonooxy)methyl)- (fosphenytoin).

In practice it is usually used as sodium salt.

References

Varia S.A. et al.; J Pharm. Sci.; m 1984, 73, 1068

FROVATRIPTAN SUCCINATE

Therapeutic Function: Migraine therapy

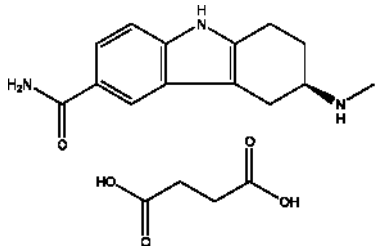
Chemical Name: 1H-Carbazole-6-carboxamide, 2,3,4,9-tetrahydro-3-(methylamino)-, (3R)-, butanedioate (1:1)

Common Name: Frovatriptan succinate

Chemical Abstracts Registry No.: 158930-09-7; 158747-02-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Frova	Elan Corporation	-	-
Frova	UCB Pharma	-	-
Frovatriptan Succinate	SmithKline Beecham	-	-

Structural Formula:



Raw Materials

Acetic acid	4-Carboxamidophenylhydrazine hydrochloride
Benzaldehyde	4-Phthalimidocyclohexanone
Formaldehyde	Potassium carbonate
Succinic acid	Hydrazine hydrate
	Sodium cyanoborohydride

Manufacturing Process

4-Carboxamidophenylhydrazine hydrochloride (2.87 g) and 4-phthalimidocyclohexanone (3.00 g) were mixed in acetic acid and the mixture was heated under reflux for 2 h. After cooling, the mixture was neutralized using aq. potassium carbonate solution, and the yellow solid thus obtained was filtered, washed with water, and dried. Purification by column chromatography (SiO_2; $CHCl_3/CH_3OH$) gave 6-carboxamido-3-phthalimido-1,2,3,4-tetrahydrocarbazole (2.8 g).

The 6-carboxamido-3-phthalimido-1,2,3,4-tetrahydrocarbazole (1.0 g) was suspended in ethanol (10 ml) and hydrazine hydrate (5 ml) was added. A clear solution was obtained, and the mixture was left to stir overnight, to yield a precipitate. The whole mixture was evaporated to dryness, washed with aq. K_2CO_3 solution, and water, to leave the (+/-)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (0.44 g), melting point 146°-148°C.

Separation of diastereoisomers of a chiral derivative of a 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole e.g. by crystallisation, or by chromatography.

Benzaldehyde (10.6 g) was added to a suspension of (+)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (12.35 g) in methanol (100 ml). The mixture was stirred for 1 h, sodium cyanoborohydride (9.3 g) added over 1 h and the clear solution stirred for 24 h. The solution was cooled (ice bath) and formaldehyde (37% aqueous methanolic, 9:1 solution, 5.5 ml) added. After 30 min stirring at room temperature water (100 ml) was added, stirring continued for 30 min followed by extraction with dichloromethane (3 times 150 ml). The combined organic extracts were washed with water (2 times 200 ml), dried (Na_2SO_4), filtered and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, dichloromethane-10% ethanol/dichloromethane) to give 3-N-benzyl-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (9.4 g) as a foam. The succinate

salt (1:1) was recrystallised from methanol, melting point 175°-182°C.

To a solution of 3-N-benzyl-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (1.0 g) in ethanol (100 ml) containing succinic acid (0.39 g), Pearlmans catalyst (1.0 g) was added and the mixture shaken under an atmosphere of hydrogen at 45 psi and 50°C for 2 h. The mixture was filtered (celite pad) and the pad washed thoroughly with ethanol. The combined flitrate and washings were evaporated to dryness, coevaporated with ethanol (3 times 100 ml) and recrystallised from methanol to give the (+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole succinate (1:1) salt, melting point 148°-155°C.

References

Borrett G.T. et al.; US Patent No. 5,618,947; April 8, 1997; Assigned: SmithKline Beecham, p.l.c., England

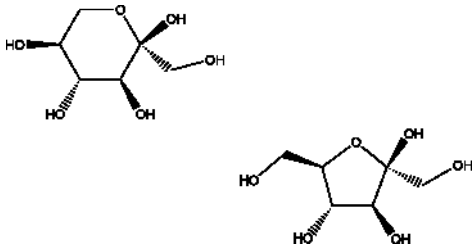
FRUCTOSE

Therapeutic Function: Fluid replenisher, Pharmaceutic aid

Chemical Name: Fructose

Common Name: Levulose and fruit sugar

Structural Formula:



Chemical Abstracts Registry No.: 57-48-7

Trade Name	Manufacturer	Country	Year Introduced
Levugen	Baxter	US	1953
Fructosteril	Fresenius	W. Germany	-
Inulon	Boehringer Mannheim	W. Germany	-
Laevoral	Laevosan	Austria	-
Laevosan	Laevosan	Austria	-
Laevuflex	Geistlich	UK	-
Levulose	Biosedra	France	-
Levupan	Sirt-B.B.P.	Italy	-

Raw Materials

Bacterium *Leuconostoc mesenteroides*
Sucrose
Corn steep liquor

Manufacturing Process

200 gal of medium containing 2% sucrose, 2% corn steep liquor solids, 0.1% potassium dihydrogen phosphate, and traces of mineral salts, was inoculated with *Leuconostoc mesenteroides* NRRL B-512 and incubated at 25°C. During growth, alkali was added automatically as needed to maintain the pH between 6.6 and 7.0. Fermentation was completed in 11 hours and the culture was immediately adjusted to pH 5 to maintain enzyme stability. Bacterial cells were removed by filtration and yielded a culture filtrate containing 40 dextransucrase units per ml, where one unit is the amount of dextransucrase which will convert 1 mg of sucrose to dextran, as determined by the amount of fructose liberated, measured as reducing power in 1 hour.

10 gal of the above culture filtrate was diluted to 40 gal with water, 33.3 lb of sucrose was added to give a 10% solution, and toluene was added as a preservative. Dextran synthesis was complete before 22 hours, and dextran was harvested at 24 hours by the addition of alcohol to be 40% on a volume basis.

The alcoholic supernatant liquor obtained was evaporated to recover the alcohol and yielded a thick syrup, rich in fructose. Analysis showed the syrup to contain 50.1% of reducing sugar, calculated as monosaccharide and to have an optical rotation equivalent to 35.1% fructose. The percentages are expressed on a weight/volume basis, and reducing power was determined by the method of Somogyi, Jour. Biol. Chem. 160, 61 (1945). A portion (4.3 liters) of the syrup was cooled to 3°C. One-tenth of this volume was treated by slow regular addition, with rapid stirring, of a 6-fold volume of cold 20% calcium oxide suspension. A second portion was treated in the same manner, and this process was continued until the entire volume of crude fructose syrup had been utilized. The reaction mixture became thick with a white sediment containing a profusion of microscopic needlelike crystals of calcium levulate. Stirring was continued for 2 hours.

The calcium levulate precipitate was separated from the reaction mixture by filtration and washed with cold water. The precipitate was suspended in water to give a thick slurry, and solid carbon dioxide added until the solution was colorless to phenolphthalein. A heavy precipitate of calcium carbonate was now present and free fructose remained in the solution. The calcium carbonate precipitate was removed by filtration, and the filtered solution was found to contain 1,436 g of fructose as determined by optical rotation. A small amount of calcium bicarbonate was present as an impurity in solution and was removed by the addition of oxalic acid solution until a test for both calcium and oxalic acid was negative. The insoluble calcium oxalate precipitate was removed by filtration.

The fructose solution was decolorized by treatment with activated charcoal and concentrated under vacuum to a thick syrup. Two volumes of hot 95% ethyl alcohol were added, and the solution was heated to a boil and filtered to

remove a small amount of insoluble material. After cooling, three volumes of ethyl ether were added, and the solution was allowed to stand overnight in the refrigerator. Fructose separated from the solution as a thick syrup and was separated from the supernatant liquid by decantation. The syrup was seeded with fructose crystals and after standing in the cold for 4 days, became a crystalline mass of fructose. The yield of dry fructose was 928 g. Additional recoverable quantities of fructose are present in the crystallization mother liquor. In continuous operation this mother liquor may be recycled for addition to subsequent quantities of fructose syrup and the combined liquors crystallized as in the foregoing example.

References

Merck Index 4149
I.N. p. 445
REM p. 1029
Koepsell, H.J., Jackson, R.W. and Hoffman, C.A.; US Patent 2,729,587; January 3, 1956; assigned to the Secretary of Agriculture
Cantor, S.M. and Hobbs, K.C.; US Patent 2,354,664; August 1, 1944; assigned to Corn Products Refining Co.

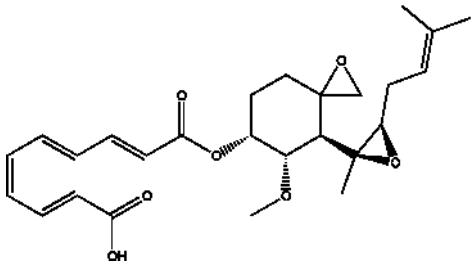
FUMAGILLIN

Therapeutic Function: Antibiotic

Chemical Name: 2,4,6,8-Decatetraenedioic acid mono[5-methoxy-4-[2-methyl-3-(methyl-2-butenyl)oxiranyl]-1-oxaspiro[2.5]oct-6-yl] ester

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 23110-15-8

Trade Name	Manufacturer	Country	Year Introduced
Fugillin	Upjohn	US	1953
Fumidil	Abbott	US	1953

Raw Materials

Corn steep liquor
Bacterium *Aspergillus fumigatus*

Manufacturing Process

A fermentation medium comprising 4,600 gal of sterile corn steep-glucose-calcium carbonate medium in a 6,000-gal fermentation tank is adjusted to pH 6.0 with sodium carbonate prior to sterilization and thereafter inoculated with 200 gal of vegetative inoculum of *Aspergillus fumigatus* NRRL 2436. The inoculated medium is incubated for approximately 108 hours at a temperature of 26°C and agitated by an impeller rotating at 114 rpm and aerated at a rate of 500 cfm. An antifoam agent of the type used in penicillin fermentation is used as required.

The clarified liquid obtained from the fermentation medium (beer) by filtration in any of the usual apparatus for removing mycelia and suspended solids from fermentation beers, after first adjusting the pH of the contents of the fermentation tank to above about pH 7.0 and preferably to between pH 7.5 and pH 8.5 with, for example, the addition of an alkaline material such as sodium carbonate, is intimately mixed with hexane with a Podbielniak extractor and the hexane layer containing undesirable fatty material discarded. The pH of the defatted liquid is adjusted to about pH 3 by the addition of H_2SO_4, and the defatted liquid is extracted with chloroform. The chloroform is removed under reduced pressure without external heating. After the removal of all of the chloroform the residual syrup is dissolved in acetone. The acetone solution is cooled to 5°C whereupon a small quantity of brown precipitate separates which is removed by filtration. The precipitate is washed with acetone and the washings added to the original filtrate. A portion of the above acetone solution is concentrated under reduced pressure at room temperature under an atmosphere of nitrogen. The resulting thick suspension is placed in a 1-liter centrifuge cup, under nitrogen, and cooled at 30°C for 18 hours. The suspension is centrifuged for 1 hour at 1,500 to 1,700 rpm. The supernatant liquid is decanted from the residual solids which are washed 5 times at room temperature with several portions of tert-butanol. A residual solid material remains after the wash and after drying at room temperature. This material, after recrystallization from a mixture of equal parts of water and of methanol has a MP of 190°C to 192°C.

References

Merck Index 4164
Kleeman & Engel p. 434
I.N. p. 447
Peterson, M.H., Goldstein, A.W. and Denison, F.W. Jr.; US Patent 2,803,586; August 20, 1957; assigned to Abbott Laboratories

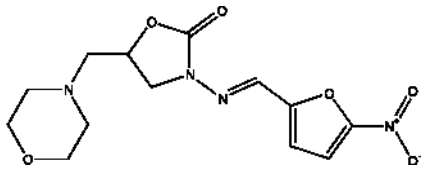
FURALTADONE

Therapeutic Function: Antibacterial

Chemical Name: 5-(4-Morpholinylmethyl)-3-[[(5-nitro-2-furanyl)methylene] amino]-2-oxazolidinone

Common Name: Furmethanol, Nitrofurmethone

Structural Formula:



Chemical Abstracts Registry No.: 139-91-3

Trade Name	Manufacturer	Country	Year Introduced
Altafur	Norwich Eaton	US	1959
Altabactina	Esteve	Spain	-
Darifur	Norwich Eaton	US	-
Furasol	SKF	US	-
Medifuran	Hess and Clark	US	-
Valsyn	Pharmacia	Sweden	-

Raw Materials

Sodium
Hydrazine hydrate
5-Nitro-2-furaldehyde
3-(N-Morpholinyl)-1,2-epoxypropane
Diethyl carbonate
Hydrogen chloride

Manufacturing Process

11.17 g (0.78 mol) 3-(N-morpholinyl)-1,2-epoxypropane, BP 76.5°C to 78°C. 3.9 mm, prepared by Eisleb's method for 3-(1-piperidyl)-1,2-epoxypropane (US Patent 1,790,042) is added dropwise in 12 minutes to 19.5 g (0.39 mol) 100% hydrazine hydrate, which has been warmed to 85% on the steam bath, and is being mechanically stirred. The heat of the reaction maintains the internal temperature at 90°C to 100°C without further external heating. The reaction mixture is then warmed on the steam bath for an additional two hours (90°C to 95°C). The excess hydrazine hydrate is removed in vacuo. The residue of viscous 1-hydrazino-3-morpholinyl-2-propanol is not distilled, but is mixed with 10.16 g (0.086 mol) diethyl carbonate and a solution of 0.3 g sodium metal in 15 ml methyl alcohol. The mixture is refluxed about 2 hours under a 15 cm Widmer column, the alcohol being removed leaving a thick, green liquid residue, which is cooled and the precipitate which forms is removed by filtration and washed well with ether. Yield 82%. MP 114°C to 116°C. Recrystallization from isopropanol gives purified 3-amino-5-(N-morpholinyl)-methyl-2-oxazolidone, MP 120°C as the intermediate.

It is not necessary that the intermediate be separated from the reaction medium in the preparation of the end product. Instead, the reaction mixture, after cooling, is treated with 200 ml of water acidified with 42 ml 10%

hydrochloric acid solution, and filtered. To the clear, light yellow filtrate is added dropwise a solution of 9.8 g (0.07 mol) 5-nitro-2-furaldehyde in 100 ml ethyl alcohol. An orange solution of the hydrochloride results. The free base is precipitated as yellow plates by making the solution basic with saturated sodium carbonate solution. 14 g of the compound is filtered off by suction, washed with alcohol, and dried. The yield, MP 204°C to 205°C (dec.), is 53% of theoretical based on 3-(N-morpholinyl)-1,2-epoxy-propane. Recrystallization from 95% alcohol (75%recovery) raises the melting point to 206°C (dec.).

The hydrochloride salt is isolated quantitatively by suspending the base in alcohol and adding sufficient aqueous concentrated HCl solution. The precipitate becomes pale yellow, is filtered off, and recrystallized from 80% alcohol. The MP range is about 223°C to 228°C (dec.).

References

Merck Index 4170
OCDS Vol. 1 p. 229 (1977)
I.N. p.448
Gever, G.; US Patent 2,802,002; August 6, 1957; assigned to The Norwich Pharmacal Co.

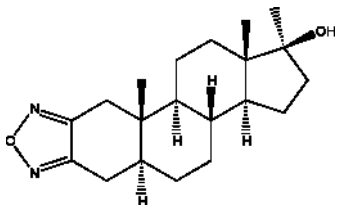
FURAZABOL

Therapeutic Function: Anticholesteremic

Chemical Name: 17α-Methyl-5α-androstano[2,3-c][1,2,5]oxadiazol-17β-ol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 1239-29-8

Trade Name	Manufacturer	Country	Year Introduced
Miotolon	Daiichi	Japan	1969

Raw Materials

2,3-Dihydroxyimino-17α-methyl-5α-androstan-17β-ol
Ethylene glycol

Manufacturing Process

A mixture of 2.0 grams of 2,3-dihydroxyimino-17α-methyl-5cα-androstan-17β-ol, 5 ml of piperidine and 10 ml of ethylene glycol was heated at a temperature between 180° and 190°C for 30 minutes. After the resulting product was cooled, water was added thereto, and the separated product was filtered, washed with water and dried. The product was dissolved in benzene and passed through a column of alumina. The column was washed with ether, and the eluted fractions were collected and condensed. Subsequently, the residue was recrystallized from ether or aqueous methanol to produce 1.53 grams of 17β-hydroxy-17α-methyl-5α-androstano[2,3-c]furazan which has a melting point of 152°C.

References

Merck Index 4174
Kleeman & Engel p. 435
I.N. p. 448
Ohta, G., Takegoshi, T., Onodera, T., Kasahara, A., Oshima, Y., Shimizu, M. and Ueno, K.; US Patent 3,245,988; April 12, 1966; assigned to Daiichi Seiyaku KK, Japan

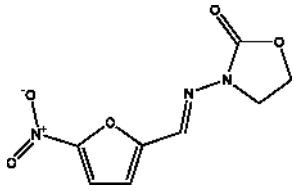
FURAZOLIDONE

Therapeutic Function: Topical antiinfective

Chemical Name: 3-[[(5-Nitro-2-furanyl)methylene]-amino]-2-oxazolidinone

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 67-45-8

Trade Name	Manufacturer	Country	Year Introduced
Tricofuron	Norwich Eaton	US	1955
Furoxone	Norwich Eaton	US	1958
Furoxane	Oberval	France	1963
Colivan	Croce Bianca	Italy	-
Diafuron	Arnaldi	Italy	-
Dialidene	S.A.M.	Italy	-

Trade Name	Manufacturer	Country	Year Introduced
Enteroxon	Bieffe	Italy	-
Furall	Farnam	US	-
Furazon	Daiko Seiyaku	Japan	-
Giarlam	Laquifa	Portugal	-
Ginvel	Fujita	Japan	-
Intefuran	Crosara	Italy	-
Medaron	Yamanouchi	Japan	-
Nifulidone	Abic	Israel	-
Nifuran	Pharmamed	E. Germany	-
Sclaventerol	Sclavo	US	-
Trifurox	Pharmacia	Sweden	-
Viofuragyn	Violani-Farmavigor	Italy	-

Raw Materials

N-(Benzylidene)-3-amino-2-oxazolidone
5-Nitro-2-furaldehyde diacetate

Manufacturing Process

In 212 cc of water are mixed 21.2 grams (0,112 mol) of N-(benzylidene)-3-amino-2-oxazolidone, 8.93 grams of concentrated sulfuric acid, and 30.1 grams (0.124 mol) of 5-nitro-2-furaldehyde diacetate. This mixture is heated to effect the hydrolysis of N-(benzylidene)-3-amino-2-oxazolidone, steam distillation of the benzaldehyde and hydrolysis of 5-nitro-2-furaldehyde diacetate. Approximately 1½ hours are required for this reaction to take place. When the bulk of the benzaldehyde has been removed, 50 cc of 99% isopropanol are added, the reaction mixture is refluxed a short time, and the crystals of N(5-nitro-2-furfurylidene)-3-amino-2-oxazolidone are filtered from the hot suspension. The product is washed with water and isopropanol and dried; a yield of 23.3 grams, 92.8% based on N-(benzylidene)-3-amino-2-oxazolidone of MP 254° to 256°C is obtained, according to US Patent 2,759,931.

References

Merck Index 4175
Kleeman & Engel p. 435
PDR p. 1279
OCDS Vol. 1 p. 229 (1977)
I.N.p.448
Drake, G.D., Gever, G. and Hayes, K.J.; US Patent 2,759,931; August 21, 1956; assigned to The Norwich Pharmacal Company
Gever, G. and O'Keefe, C.J.; US Patent 2,927,110; March 1, 1960; assigned to The Norwich Pharmacal Company

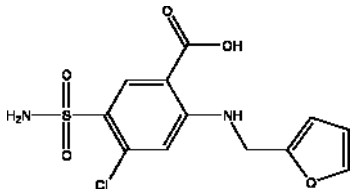
FUROSEMIDE

Therapeutic Function: Diuretic

Chemical Name: 5-(Aminosulfonyl)-4-chloro-2-[(2-furanylmethyl)amino] benzoic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 54-31-9

Trade Name	Manufacturer	Country	Year Introduced
Lasix	Hoechst	W. Germany	1964
Lasix	Hoechst	UK	1964
Lasilix	Hoechst	France	1965
Lasix	Hoechst	Italy	1965
Lasix	Hoechst	US	1966
Eutensin	Hoechst	Japan	1981
Aisemide	Hotta	Japan	-
Accent	Toyama	Japan	-
Arasemide	Arakawa	Japan	-
Beronald	Kowa	Japan	-
Desal	Biofarma	Turkey	-
Desdemin	Vitacain	Japan	-
Disal	Med-Tech	US	-
Diumide	Napp	UK	-
Diural	A.L.	Norway	-
Diuresal	Lagap	Switz.	-
Diurix	Helvepharm	Switz.	-
Diurolasa	Lasa	Spain	-
Diusemide	Nakataki	Japan	-
Diuzol	Wakamoto	Japan	-
Dryptal	Berk	UK	-
Errolon	Disprovent	Argentina	-
Franyl	Seiko Eiyo	Japan	-
Frusemin	Toho	Japan	-
Frusetic	Unimed	US	-
Frusid	D.D.S.A.	UK	-

Trade Name	Manufacturer	Country	Year Introduced
Fulsix	Tatsumi	Japan	-
Fuluvamide	Kanto	Japan	-
Furantral	Polfa	Poland	-
Furantril	Farmakhim	Bulgaria	-
Furesis	Farmos	Finland	-
Furetic	Script Intal	S. Africa	-
Furex	Siegfried	Switz.	-
Furfan	Nippon-Roussel-Chugai	Japan	-
Furix	Benzon	Denmark	-
Furix	Medica	Finland	-
Furomex	Orion	Finland	-
Furopuren	Klinge	W. Germany	-
Furosedon	Santen	Japan	-
Furoside	I.C.N.	Canada	-
Fusid	Teva	Israel	-
Hydro-Rapid	Sanorania	W. Germany	-
Impugan	Dumex	Denmark	-
Katlex	Iwaki	Japan	-
Kutrix	Kyowa	Japan	-
Lizik	Aksu	Turkey	-
Lowpston	Maruro	Japan	-
Macasirool	Hishiyama	Japan	-
Mirfat	Merckle	W. Germany	-
Moilarorin	Toho	Japan	-
Nephron	Alet	Argentina	-
Nicorol	Lundbeck	-	-
Oedemex	Mepha	Switz.	-
Panseman	Ono	Japan	-
Polysquall	Tokyo Hosei	Japan	-
Profemin	Toa Eiyo	Japan	-
Promedes	Fuso	Japan	-
Protargen	Ohta	Japan	-
Puresis	Lennon	S. Africa	-
Radiamin	Nippon Shinyaku	Japan	-
Radonna	Nippon Kayaku, Co.	Japan	-
Rasisemid	Kodama	Japan	-
Rosemid	Toyo	Japan	-
Sigasalur	Siegfried	Switz.	-
Transit	Inca	Argentina	-
Trofurit	Chinoin	Hungary	-
Uremide	Protea	Australia	-
Urex	Mochida	Japan	-
Urex	Fawns and McAllan	Australia	-

Raw Materials

3-Sulfamyl-4,6-dichlorobenzoic acid
Furfurylamine

Manufacturing Process

10.8 grams of 3-sulfamyl-4,6-dichlorobenzoic acid (0.04 mol) and 11.7 grams of furfurylamine (0.12 mol) are heated in 30 cc of diethyleneglycol-dimethylether for 6 hours under reflux. When pouring the reaction mixture into 300 cc of 1 N hydrochloric acid, the reaction product is immediately separated off in the form of crystals. The light-yellow crude product is purified by dissolving it in 100 cc of warm 1 N sodium bicarbonate solution, precipitation by means of hydrochloric acid and subsequent recrystallization from ethanol/water, with addition of charcoal. Colorless prisms are obtained which decompose at 206°C while adopting a brown coloration, and with evolution of gas.

References

Merck index 4186
Kleeman & Engel p. 436
PDR pp.592, 872, 939, 993, 1349, 1606, 1723, 1999
OCDS Vol. 1 p. 134 (1977) and 2, 87 (1980)
DOT 1 (1) 5 (1965)
I.N. p.450
REM p. 943
Sturm, K., Siedel, W. and Weyer, R.; US Patent 3,058,882; October 16, 1962; assigned to Farbwerke Hoechst AG, Germany

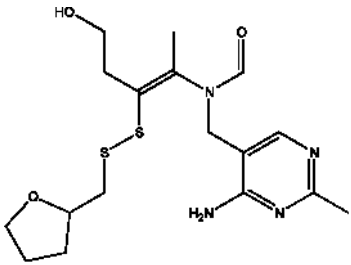
FURSULTIAMINE

Therapeutic Function: Enzyme cofactor vitamin

Chemical Name: N-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-N'-[4-hydroxy-1-methyl-2-[(tetrahydrofurfuryl)dithio]-1-butenyl] formamide

Common Name: Thiamine tetrahydrofurfuryl disulfide

Structural Formula:



Chemical Abstracts Registry No.: 804-30-8

Trade Name	Manufacturer	Country	Year Introduced
Alinamin F	Takeda	Japan	1961
Adventan	Abello	Spain	-
Benlipoid	Heilmittelwerke Wien	Austria	-
Bevitol Lipophil	Lanacher Heilmittel	Austria	-
Judolor	I.C.N.	W. Germany	-

Raw Materials

Thiamine hydrochloride
Sodium hydroxide
Sodium tetrahydrofurfuryl thiosulfate

Manufacturing Process

To a solution of 20 parts of thiamine hydrochloride in 30 parts of water is added an aqueous solution of sodium hydroxide (7.2 parts of NaOH in 30 parts of water), and the mixture is cooled with water. The mixture is allowed to stand for 30 minutes, 60 parts of chloroform is added, followed by a solution of 30 parts of crude sodium tetrahydrofurfurylthiosulfate in 30 parts of water, and the whole is stirred for 30 minutes. The chloroform layer is separated and the aqueous layer is extracted twice with 20 parts of chloroform. All the chloroform solutions are combined and shaken with 50 parts of 5% hydrochloric acid. The acid solution is decolorized and neutralized with alkali carbonate, whereupon thiamine tetrahydrofurfuryl disulfide separates out in the resinous state but soon solidifies [MP 129°C (decamp.)] . The yield is 16 parts. Recrystallization from ethyl acetate gives colorless prisms melting at 132°C (decomp.).

References

Merck Index 4188
Kleeman & Engel p. 436
I.N. p. 451
Yurugi, S. and Fushimi, T.; US Patent 3,016,380; January 9, 1962; assigned to Takeda Pharmaceutical Industries, Ltd. (Japan)

FURTRETHONIUM IODIDE

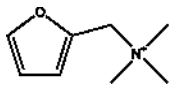
Therapeutic Function: Cholinergic

Chemical Name: N,N,N-Trimethyl-2-furamethaminium iodide

Common Name: -

Chemical Abstracts Registry No.: 7618-86-2 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Furmethide	SKF	US	1944

Raw Materials

Dimethyl amine
Formic acid
Furfural
Methyl iodide

Manufacturing Process

Furfuryl dimethyl amine is first produced, This may conveniently be accomplished by employing the Leuckart synthesis known to those skilled in the art, which involves the use of an aldehyde or a ketone, and formate of ammonia or an amine, or corresponding formamide derived by dehydration of formate of ammonia or an amine.

For example, 5 mols of dimethyl amine and 5 mols of formic acid and water are distilled to 135°C; distilling off most of the water. To the remaining liquid, consisting for the most part of the formyl derivative of dimethyl amine, 1 mol of furfural mixed with 1 mol of formic acid is slowly added with heating, the temperature being maintained at 150°C to 170°C, until the reaction is complete. The mixture is then distilled into a receiver. The course of this reaction may be illustrated as follows:

Part of the formic acid used in the above reaction functions to react with the dimethyl amine liberated in the reaction.

After the furfural has all been added and the reaction has subsided, the residue is cooled, diluted with water, made strongly alkaline and distilled until all volatile substances are removed, The distillate is then made acid with formic acid and distilled with steam as long as nonbasic substances are carried over by the steam. The residue is then made strongly basic with caustic soda and the volatile amines again distilled with steam. The distillate is then treated with strong alkali and then extracted with ether to extract the base. The extract is dried by the addition of caustic potash, the ether removed and the residual amine purified by distillation. Furfuryl dimethyl amine boils over the range 145°C to 150°C.

To obtain the quaternary salt, furfuryl dimethyl amine so prepared is dissolved in dry benzene and to the solution is added slightly more than one equivalent of methyl iodide. Inducement of crystallization of the quaternary salt which separates may be effected as, for example, by scratching the side of the vessel containing the mixture or seeding with a small quantity of the crystalline quaternary salt.

References

Merck Index 4190
I.N. p. 451
Nabenhauer, F.P.; US Patent 2,185,220; January 2, 1940; assigned to Smith Kline and French Laboratories

FUSAFUNGINE

Therapeutic Function: Antibacterial

Chemical Name: Fusafungine (complex antibotic)

Common Name: -

Structural Formula: Complex Antibotic

Chemical Abstracts Registry No.: 1393-87-9

Trade Name	Manufacturer	Country	Year Introduced
Locabiotal	Servier	France	1963
Locabiotal	Servier	UK	1964
Locabiotal	Stroder	Italy	1973
Locabiosol	Pharmacodex	W. Germany	1973
Fusaloyos	Servier	France	-
Fusarine	Couchoud	-	-

Raw Materials

Glucose
Bacterium *Fusarium lateritium*

Manufacturing Process

In a 5-liter round flask provided with two tubes, one of which is adapted for subsequent connection to a source of sterile air, 2 liters of fermentation medium are prepared according to the following formulation:

	Percentage
Peptone	1
Crude glucose	3
Sodium nitrate	0.1
Monohydrogen potassium phosphate	0.1
Magnesium sulfate	0.05
Potassium chloride	0.05
Water, balance to	100

Both openings of the flask are stopped with cotton wool and the medium is sterilized by placing it in an autoclave for 30 minutes at 120°C. The flask is

then cooled to 29°C to 30°C and a small sample is taken to check the sterility and the pH value which should be approximately 5.

The spores from an inclined culture of Fusarium lateritium Wr, CSB 119.63 on a gelose medium are extracted with sterilized distilled water to obtain a suspension containing about 600,000 spores per ml. This suspension is then used to seed the medium prepared as earlier described. The contents of the flask are left to incubate at 27°C. Sterile air is injected into the liquid to effect thorough agitation and uniform supply of oxygen into the medium.

After 55 hours of fermentation, the contents of the round flask is transferred under aseptic conditions into a metal reactor of about 100 liters capacity containing 60 liters of sterile medium prepared as follows:

	Percentage
Peptone	0.5
Saccharose	4
Ammonium nitrate	0.5
Dihydrogen potassium phosphate	0.1
Potassium chloride	0.5
Magnesium sulfate	0.5
Ferric sulfate	0.002
Water, balance to	100

The culture is incubated at a temperature of 28°C in the reactor for 60 hours with mechanical agitation and constant aeration. The resulting broth is seeded into 600 liters of a sterile culture medium contained in a metal fermenting vat 1,800 liters in capacity and prepared according to the following formulation:

	Percentage
Saccharose	5
Cerelose*	0.5
Ammonium nitrate	1
Sodium chloride	0.3
Magnesium sulfate	0.25
Potassium chloride	0.03
Bacon oil (axonge oil)	0.1
Water, balance to	100

*Trade Mark

The culture is incubated for 55 hours at 28°C with constant forced aeration and agitation, and the broth is seeded into the production medium. In a fermentation vat 12 cubic meters in capacity provided with suitable stirring means, a temperature control jacket, sterile air-injecting and dispersing means, and means for automatically injecting sterile antifoaming agent if required, there are prepared 6 cubic meters of a culture medium of the following formulation:

	Percentage
Saccharose	5.5
Cerelose*	0.5
Ammonium nitrate	1
Sodium chloride	0.3

	Percentage
Dihydrogen potassium phosphate	0.5
Magnesium sulfate	0.25
Water, balance to	100

*Trade Mark

The medium is sterilized by heating it at 120°C for 40 minutes and is then cooled to 30°C. After seeding, the medium is incubated for about 60 hours, the temperature being maintained at 30°C. Throughout the period of fermentation, agitation is maintained at a rate of 20-40 rpm and sterile air is injected into the bottom of the vat at a rate of 4.8 cubic meters per minute by means of the air dispersing device. Fermentation is arrested when about 90% of the carbohydrates have been consumed. The average Fusafungine content in the fermentation broth is then found to be about 0.5 to 0.8 grams per liter. The fermented broth is filtered under pressure and the content of the filter-press frames is washed with 2 cubic meters of water, then the filter cake is partially dried in a blast of compressed air. The mycelium is then dried in a ventilated oven at 70°C for 30 hours, dried and ground.

The yield obtained is 88 kilograms of dry product, containing 5.71% of Fusafungine. This is extracted from the crude product as follows: the dry powder is suspended in 836 liters of methanol, and 44 liters of an acetic buffer at pH 4.25 (0.05 M) is added. The mixture is agitated for one hour at ordinary temperature, then drained to separate the exhausted powder from the methanol solution. This solution is transferred into an evaporator in which its volume is reduced to 200 liters. 100 liters of hexane are added, followed by 200 liters of water with agitation. After 15 minutes agitation, the mixture is allowed to stand for 30 minutes and the underlying phase is drawn off. The hexane extract is exhausted with three 25-liter batches of a methanol/water mixture, 3/1 by volume. The methanol mixture is then concentrated to 12.5 liters under reduced pressure. In this concentration step, the methanol is evaporated so that the water content of the residue increases regularly end the Fusafungine precipitates.

The resulting suspension is placed in a round flask equipped with a scraper-agitator device, and agitation is effected for 48 hours in an ice water bath. The antibiotic is isolated from the mother liquor by filtration through a Buchner filter. The filter cake is washed with 5 liters of a methyl alcohol and water mixture (1/2.5 by volume) cooled to 4°C. After drying in an oven at reduced pressure, 2.805 kilograms of a greyish-yellow crude product is obtained.

This crude product is dissolved in 140 liters anhydrous undenatured methyl alcohol, then 100 grams of discoloring carbon black, and 100 grams of a filtering aid are added. The mixture is agitated 30 minutes. The carbon black, filtering agent and insoluble impurities are filtered out. The filter cake is washed with 14 liters of methyl alcohol. The filtrate is placed in a receiving vessel, and 280 liters of distilled water at 70°C temperature are poured in with agitation. While continuing to agitate slowly, the mixture is allowed to cool gradually to a temperature of about 35°C. Crystallization is then initiated by adding a few crystals of pure Fusafungine, and agitation is continued for another 12 hours. The crystallization is allowed to proceed for 48 hours at +4°C. The pure Fusafungine crystals are collected by filtration. The filter cake

is washed with 10 liters of methanol/water (1/2 by volume) mixture preliminarily cooled to +4°C and then with 20 liters of distilled water. The crystals are dried in an oven at 40°C under reduced pressure. A yield of 2.110 kilograms of pure Fusafungine antibiotics has thus been obtained.

References

Merck Index 4191
I.N. p. 451
Servier, J.; British Patent 1,018,626; January 26, 1966; assigned to Biofarma (France)