E

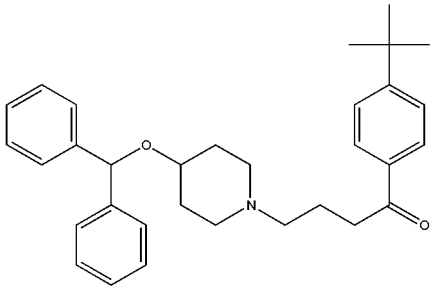
EBASTINE

Therapeutic Function: Antihistaminic, Antiallergic, Calcium entry blocker

Chemical Name: 1-[4-(1,1-Dimethylethyl)phenyl]-4-[4-(diphenylmethoxy)-1-piperidinyl]-1-butanone

Common Name: Ebastine; Ebastel; Evastel; Kestine

Structural Formula:



Chemical Abstracts Registry No.: 90729-43-4

Trade Name	Manufacturer	Country	Year Introduced
Ebastine	Almirall	-	-

Raw Materials

4-Hydroxypiperidine
Sodium bicarbonate
Diphenylmethyl bromide
p-tert-Butyl-ω-chlorobutyrophenone
Potassium iodide

Manufacturing Process

(a) A mixture of 4-hydroxypiperidine (40.4 g; 0.4 moles), p-tert-butyl-ω-chlorobutyrophenone (105 g, 0.44 moles), sodium bicarbonate (67.2 g; 0.8 moles) and a crystal of potassium iodide in methyl isobutyl ketone (1 liter) was boiled under reflux for 24 hours. After cooling, the reaction mixture was

washed with water, dried (Na_2SO_4) and the solvent removed in vacuum. The residue was salified with the stoichiometric amount of fumaric acid in a mixture of acetone and ethanol to give 1-[3-(4-tert-butylbenzoyl)propyl]-4-hydroxypiperidine fumarate (148 g), melting point 163-165°C. This compound was converted into the free base, and 1-[3-(4-tert-butylbenzoyl)propyl]-4-hydroxypiperidine was obtained and recrystallized from a mixture of diethyl ether and petroleum ether (boiling point 50-70°C). 102 g were obtained (yield 84%), melting point 63-65°C.

(b) A mixture of 1-[3-(tert-butylbenzoyl)propyl]-4-hydroxypiperidine (60.68 g; 0.2 moles) and sodium carbonate (42.4 g; 0.4 moles) in methyl isobutyl ketone (500 ml) was heated to the boiling point and a solution of diphenylmethyl bromide (49.42 g; 0.2 moles) in methyl isobutyl ketone (75 ml) was slowly added in 1.5 hours. The resulting mixture was boiled under reflux for another 12 hours, and then another solution of diphenylmethyl bromide (24.71 g; 0.1 moles) in methyl isobutyl ketone (50 ml) was added and the mixture boiled under reflux again for 12 hours. Another solution of diphenylmethyl bromide in the same quantity was added and after refluxing for 12 additional hours the reaction mixture was cooled, washed with water, dried (Na_2SO_4) and the solvent removed in vacuum.

The residual oil was treated with the stoichiometric amount of fumaric acid in ethanol and 4-diphenylmethoxy-1-[3-(4-tert-butylbenzoyl)propyl]piperidine fumarate crystallized. After recrystallisation from ethanol the pure compound was obtained (88 g; yield 75%), melting point 197-198°C.

References

Soto Jose M. P., Noverola Armando V., Mauri Jacinto M., Spickett Robert; US Patent No. 4,550,116; October 29, 1985; Assigned to Fordonal, S.A. (Madrid, ES)

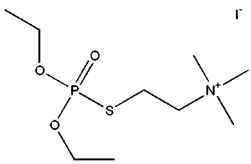
ECHOTHIOPATE IODIDE

Therapeutic Function: Cholinergic (ophthalmic)

Chemical Name: 2-[(Diethoxyphosphinyl)thio]-N,N,N-trimethylethanaminium iodide

Common Name: O,O-Diethyl-S-β-dimethylaminoethylthiophosphate methyl iodide

Structural Formula:



Chemical Abstracts Registry No.: 513-10-0

Trade Name	Manufacturer	Country	Year Introduced
Phospholine Iodide	Ayerst	US	1959
Phospholine Iodide	Promedica	France	1966
Echiodide	Alcon	US	1977
Phospholine Iodide	Santen	Japan	-
Phospholine Iodide	Ayerst	UK	-
Phospholine Iodide	Chinoin	Italy	-

Raw Materials

β-Dimethylaminoethyl mercaptan hydrochloride
Sodium
Diethylchlorophosphate
Methyl iodide

Manufacturing Process

The reaction is carried out in an atmosphere of nitrogen. To a solution of 4.60 grams sodium (0.20 mol) in 60 cc of methanol is added 14.17 grams β-dimethylaminoethyl mercaptan hydro chloride (0.10 mol), rinsed in with 10 cc methanol. Solvent is removed at a water-pump vacuum while blowing with a slow stream of nitrogen to 100°C/20 mm. To the residue suspended in 150 cc benzene and cooled in an ice bath is added 17.25 grams diethylchlorophosphate (0.10 mol) in 3 portions at 10-minute intervals. After each addition, the temperature increases from about 4° to about 14°C and then falls. The mixture is stirred in an ice bath for one-half hour and while warming to room temperature during 2 hours is washed with 35 and 5 cc portions of water with two 10 cc portions of saturated brine and is dried over calcium sulfate and filtered.

After removal of solvent by distillation under reduced pressure to 55°C/20 mm, the residue is 23.0 grams crude base (95% theory) as a pale yellow liquid. A sample of the crude base distills with some decomposition at 105° to 112°C/0.8 mm.

A sample of distilled base in cold isopropanol is treated with excess methyl iodide, left at room temperature overnight, diluted with 5 volumes of ethyl acetate and filtered from the methiodide salt. This is purified by crystallization from mixtures of isopropanol and ethyl acetate, filtering hot to remove an impurity of low solubility. The pure methiodide is obtained as a white solid, MP 124° to 124.5°C, containing 99 mol percent thiol isomer.

References

Merck Index 3481
Kleeman & Engel p. 345
PDR p. 632
I.N. p. 371
REM p. 898
Fitch, H.M.; US Patent 2,911,430; November 3, 1959; assigned to Campbell Pharmaceuticals, Inc.

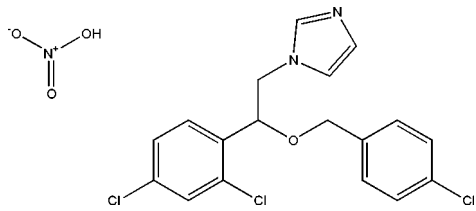
ECONAZOLE NITRATE

Therapeutic Function: Antifungal

Chemical Name: 1-(2-[(4-Chlorophenyl)methoxy]-2-(2,4-dichlorophenyl) ethyl)-1H-imidazole nitrate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 24169-02-6; 27220-47-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Pevaryl	Cilag Chemie	France	1976
Pevaryl	Cilag	Italy	1978
Ecostatin	Fair Labs	UK	1978
Pevaryl	Cilag Chemie	W. Germany	1978
Skilar	Italchemie	Italy	1979
Paravale	Otsuka	Japan	1981
Spectazole	Ortho	US	1983
Epi-Pevaryl	Cilag	W. Germany	-
Gyno-Pevaryl	Cilag	W. Germany	-
Ifenec	Italfarmaco	Italy	-
Micoespec	Centrum	Spain	-
Micofugal	Ion	Italy	-
Micogyn	Crosara	Italy	-
Mycopevaryl	Cilag	-	-

Raw Materials

α-(2,4-Dichlorophenyl)imidazole-1-ethanol
Sodium hydride
4-Chlorobenzyl chloride
Nitric acid

Manufacturing Process

A suspension of 10.3 parts of α-(2,4-dichlorophenyl)-imidazole-1-ethanol and 2.1 parts of sodium hydride in 50 parts of dry tetrahydrofuran is stirred and

refluxed for 2 hours. After this reaction-time, the evolution of hydrogen is ceased. Then there are added successively 60 parts dimethylformamide and 8 parts of p-chlorobenzylchloride and stirring and refluxing is continued for another two hours. The tetrahydrofuran is removed at atmospheric pressure. The dimethylformamide solution is poured onto water. The product, 1-[2,4-dichloro-β-(p-chlorobenzyloxy)phenethyl]imidazole, is extracted with benzene. The extract is washed with water, dried, filtered and evaporated in vacuo. From the residual oily free base, the nitrate salt is prepared in the usual manner in 2-propanol by treatment with concentrated nitric acid, yielding, after recrystallization of the crude solid salt from a mixture of 2-propanol, methanol and diisopropylether, 1-[2,4-dichloro-β-(p-chlorobenzyloxy)phenethyl]imidazole nitrate; MP 162°C.

References

Merck Index 3482
Kleeman & Engel p. 345
PDR p. 1309
OCDS Vol. 2 p. 249 (1980)
DOT 11 (8) 310 (1975)
I.N. p. 371
REM p. 1227
Godefroi, E.F. and Heeres, J.; US Patent 3,717,655; February 20, 1973; assigned to Janssen Pharmaceutica NV, Belgium

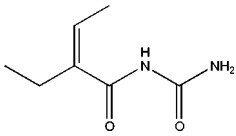
ECTYLUREA

Therapeutic Function: Sedative

Chemical Name: (Z)-N-(Aminocarbonyl)-2-ethyl-2-butenamide

Common Name: Ethylcrotonylurea

Structural Formula:



Chemical Abstracts Registry No.: 95-04-5

Trade Name	Manufacturer	Country	Year Introduced
Nostyn	Ames	US	1956
Levanil	Upjohn	US	1959
Cronil	Farmigea	Italy	-
Distasol	Locatelli	Italy	-

Trade Name	Manufacturer	Country	Year Introduced
Ektyl	A.C.O.	Sweden	-
Neuroprocin	Minerva-Chemie	Netherlands	-

Raw Materials

2-Bromo-2-ethylbutyryl urea (carbromal)
Silver oxide

Manufacturing Process

54 g of carbromal (2-bromo-2-ethylbutyryl-urea) in 600 cc of isopropanol was stirred and refluxed for 3 hours with 27.8 g of anhydrous silver oxide. The reaction mixture was filtered and the silver residue was extracted with 100 cc of boiling isopropanol. The filtered and dried solids which separated weighed 22.5 g and melted at 189°C to 190.5°C. Concentration of the filtrate yielded an additional 3.3 g of product which melted at 160°C to 170°C. These two crops were separately obtained as white needles by crystallization from alcohol and exhibited slight solubility in water. The first crop gave 21.7 g of 2-ethyl-cis-crotonyl urea with a melting point of 191°C to 193°C, and the second crop gave 0.9 g with a melting point of 191°C to 193°C for a total yield of 42.4 g or 63% of the theoretical.

References

Merck Index 3484
OCDS Vol. 1 p. 221 (1977)
I.N. p. 372
Faucher, O.E.; US Patents 2,854,379; September 30, 1958; and 2,931,832; April 5,1960; both assigned to Miles Laboratories, Inc.

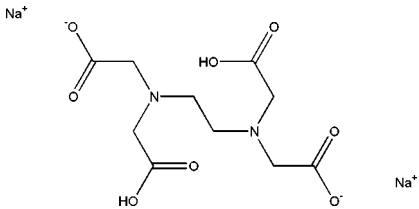
EDETATE DISODIUM

Therapeutic Function: Pharmaceutic aid (chelating agent)

Chemical Name: N,N'-1,2-Ethanediylbis[N-(carboxymethyl)glycine]-disodium salt

Common Name: EDTA disodium

Structural Formula:



Chemical Abstracts Registry No.: 139-33-3

Trade Name	Manufacturer	Country	Year Introduced
Endrate Disodium	Bersworth	US	1959
Cheladrate	PHARMEX	US	-
Diso-Tate	O'Neal Jones	US	-
Idranal	Riedel de Hahn	W. Germany	-
Komplexon III	Chemische Fabrik	Switz.	-
Uni Wash	United	US	-

Raw Materials

Ethylene diamine
Sodium cyanide
Formaldehyde
Sodium hydroxide

Manufacturing Process

10 mols of ethylene diamine as a 30% aqueous solution and 4 mols of solid caustic soda are placed in a steam heated kettle supplied with an agitator. 8 mols of sodium cyanide as a concentrated water solution (about 30%) are added and the solution heated to 60°C. About a 10 inch vacuum is applied to bring the liquid to incipient boiling. Formaldehyde (7.5 mols of 37% to 40% aqueous solution) is slowly added, the temperature being held at 60°C, and the solution vigorously stirred. Then, when the evolution of ammonia has substantially stopped, an additional 8 mols of sodium cyanide, followed by 8 mols of formaldehyde are added as before. This is continued until 40 mols of cyanide and 40 mols of formaldehyde have been added. Then at the end about 2 mols more of formaldehyde are added, making 42 mols in all, to remove any last traces of cyanide. About 8 to 10 hours are required to complete the reaction. The resulting product, referred to herein as the crude reaction product, is essentially an aqueous solution of the sodium salt of ethylene diamine tetracetic acid.

To 1,000 g of the crude reaction product are added 264 g of ethylene diamine tetracetic acid. The mixture is preferably heated to incipient boiling to increase the rate of reaction, and then the mixture is allowed to cool and crystallize. The crystals formed are filtered off, washed with the smallest possible amount of ice water, and dried to a constant weight, which is 452 g. A representative sample of the product so prepared showed, upon analysis, 13.26% sodium against a theoretical of 13.70% for the disodium salt. The dialkali salt has a pH of about 5.3 and behaves like a weak acid, displacing CO_2 from carbonates and reacting with metals to form hydrogen. It is a white crystalline solid.

References

Merck Index 3487
PDR p. 1826
I.N. p. 21
REM p. 838
Bersworth, F.C.; US Patent 2,407,645; September 17, 1946; assigned to The Martin Dennis Co.

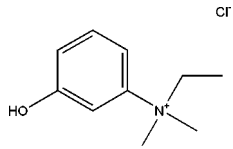
EDROPHONIUM CHLORIDE

Therapeutic Function: Cholinergic

Chemical Name: N-Ethyl-3-hydroxy-N,N-dimethylbenzeneaminium chloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 116-38-1

Trade Name	Manufacturer	Country	Year Introduced
Tensilon	Roche	US	1951
Tensilon	Roche	UK	-
Antirex	Kyorin	Japan	-

Raw Materials

m-Dimethylaminophenol
Sodium hydroxide
Hydrogen chloride
Ethyl iodide
Silver nitrate

Manufacturing Process

A solution made up of 10 grams of m-dimethylaminophenol, 50 cc of acetone and 13 grams of ethyl iodide was heated at 50°C for five hours. On addition of ether to the cooled solution, (3-hydroxyphenyl)ethyl dimethylammonium iodide precipitated as an oil which soon crystallized. Upon recrystallization from isopropanol the compound had a MP of 113° to 115°C.

A slight excess of a 10% sodium hydroxide solution was added to a solution of 23 grams of silver nitrate in 300 cc of water. The precipitated silver oxide was washed free of silver ion with distilled water. To a suspension of the silver oxide in 200 cc of water, a solution of 25 grams of (3-hydroxyphenyl)ethyl dimethylammonium iodide in 300 cc of water was added. The precipitate of silver iodide was removed by filtration and the filtrate concentrated to a volume of about 100 cc in vacuo. The remainder of the water was removed by lyophilization. (3-hydroxyphenyl)ethyl dimethylammonium hydroxide was obtained as a hygroscopic, amorphous solid.

A solution of 5 grams of (3-hydroxyphenyl)ethyl dimethylammonium hydroxide in about 200 cc of water was neutralized with dilute hydrochloric acid. On concentration to dry ness in vacuo, (3-hydroxyphenyl)ethyl dimethylammonium chloride crystallized. The compound was recrystallized

from isopropanol; MP 162° to 163°C (with decomposition).

References

Merck Index 3492
Kleeman & Engel p. 346
PDR pp. 1504, 2009
I.N. p. 372
REM p. 899
Terrell, R.C.; US Patents 3,469,011; September 23, 1969 and 3,527,813; September 8, 1970; both assigned to Air Reduction Company, Incorporated

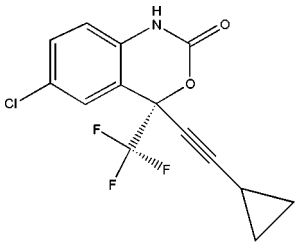
EFAVIRENZ

Therapeutic Function: Antiviral

Chemical Name: 2H-3,1-Benzoxazin-2-one, 6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-, (4S)-

Common Name: Efavirenz

Structural Formula:



Chemical Abstracts Registry No.: 154598-52-4

Trade Name	Manufacturer	Country	Year Introduced
DMP-266	DuPont Merck	-	-
Efavirenz	Bristol-Myers Squibb	USA	-
Stocrin	Merck Sharp and Dohme	Netherlands	-
Sustiva	Bristol-Myers Squibb	USA	-
Sustiva	DuPont Pharmaceuticals	-	-

Raw Materials

Ethylmagnesium bromide	Cyclopropylacetylene
1-(2-Amino-5-chlorophenyl)-2,2,2-trifluoromethylethanone	1,1'-Carbonyldiimidazole
	4-Dimethylaminopyridine
(-)-Camphanic acid chloride	Triethylamine

Manufacturing Process

(-)-6-Chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one and (+) 6-Chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one

The above products can be produced in the next steps:

Step A: 2-(2-Amino-5-chlorophenyl)-4-cyclopropyl-1,1,1-trifluoro-3-butyn-2-ol.

A solution, was prepared from 23 g of cyclopropylacetylene (0.348 mol) in 250 mL of THF by dropwise addition of 116 mL of a 3.0 M solution of ethylmagnesium bromide in ether (0.348 mol) over 1 h. This solution was maintained at 0°C for 1 h, then at 40°C for 3 h. To this solution, recooled to 0°C, 15.56 g of 1-(2-amino-5-chlorophenyl)-2,2,2-trifluoromethylethanone (0.0696 mol), was added as a solid, portionwise over 5 min. The reaction mixture was allowed to stir at 0°C for 1.5 hours. The reaction was quenched at 0°C by dropwise addition of 700 mL of saturated aqueous ammonium chloride solution. The mixture was extracted with 2 times 400 mL portions of ethyl acetate, the combined organic phases were washed with brine and dried over $MgSO_4$. Removal of the drying agent and solvents left a yellow solid. This material was recrystallized from boiling hexanes (100 mL final volume) to afford 14.67 g of 2-(2-amino-5-chlorophenyl)-4-cyclopropyl-1,1,1-trifluoro-3-butyn-2-ol. A second crop (2.1 g) was obtained from concentrating the mother liquors. M.p.: 153°-154°C.

Step B: ()-6-Chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one.

A solution of 2-(2-amino-5-chlorophenyl)-4-cyclopropyl-1,1,1-trifluoro-3-butyn-2-ol (15.00 g, 0.0518 mol) and 41.98 g (0.259 mol) of 1,1'-carbonyldiimidazole in 250 mL of dry THF was stirred under argon at 55°C for 24 hours. The solvent was removed on a rotary evaporator and the residue was partitioned between 500 mL of ethyl acetate and 400 mL of water. The layers were separated and the aqueous phase was extracted once more with ethyl acetate. The combined ethyl acetate extracts were washed with 2 times 200 mL of 2% aqueous HCl, saturated aqueous $NaHCO_3$, and brine. Drying over $MgSO_4$, filtration, and removal of the solvent in vacuo provided 16.42 g of the title compound as a solid. Recrystallization from ethyl acetate/hexane afforded 12.97 g of analytically pure ()-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one as a white crystals. Melting point: 178°-180°C.

Step C: 6-Chloro-1-(1S)-camphanoyl-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one.

To a solution containing (+)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one (12.97 g, 0.041 mol), 4-dimethylaminopyridine (1.02 g, 0.0083 mol), and (-)-camphanic acid chloride (14.22 g, 0.06556 mol) in 350 mL of dry dichloromethane, stirred under argon in an ice bath, was added triethylamine (22.84 mL, 0.164 mol). The cooling bath was removed and the reaction was allowed to proceed at room temperature. After 75 min. the reaction was judged complete by thin layer chromatography (SiO_2, 4% EtOAc in $CHCl_3$), and the solution was diluted with 500 mL of $CHCl_3$ then washed with 10% citric acid (2X), water (1X), and brine (1X). Drying ($MgSO_4$), filtration, and removal of the solvent in vacuo left a colorless foam. This material was triturated with 200 mL of boiling hexane. On cooling to room temperature the desired diastereomeric camphanate imide precipitated. The solid was collected on a frit, washed with a little cold hexanes and dried in vacuo to give 7.79 g of 6-chloro-1-(1S)-camphanoyl-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one as white crystals. Melting point: 164°-165°C. HPLC purity: 99.2% γ 254 nm.

Step D: (-)-6-Chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one.

6-Chloro-1-(1S)-camphanoyl-4-cyclopropylethynyl-4-trifluoromethyl-1,2-dihydro-4(H)-3,1-benzoxazin-2-one(7.50 g, 0.01512 mol) was dissolved in 150 mL of n-butanol at 60°C under an atmosphere of argon. To this solution was added 10 mL of 1 N HCl. This solution was maintained at 60°C for 72 h. The mixture was neutralized with aqueous $NaHCO_3$ and the n-butanol was removed in vacuo. The residue was dissolved in 150 mL of THF and treated with 50 mL of 2 N LiOH for 3 h at room temperature. This mixture was diluted with ethyl acetate and washed with two portions of water and one of brine. Drying ($MgSO_4$), filtration and removal of the solvent in vacuo gave a white solid. This material was recrystallized from hot hexane to give 3.43 g of (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one as white crystals, melting point 131°-132°C, $[\alpha]_D^{20}$ = - 84.7° ($CHCl_3$, c=0.005 g /mL).

Step E: (+)-6-Chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one.

The mother liquors from Step C above were purified by column chromatography on silica gel using 10% ethyl acetate in hexanes as eluant. The pure, undesired diastereomer (a colorless foam) was hydroylzed according to Step D. The enantiomeric benzoxazinone, (+)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one, was obtained as white crystals. Melting point 131°-132°C; $[\alpha]_D^{20}$ =+84.4° ($CHCl_3$, c=0.005 g/mL).

References

Young S.D. et al.; US Patent No. 5,519,021; May 21, 1996; Assignee: Merck and Co., Inc. (Rahway, NJ)

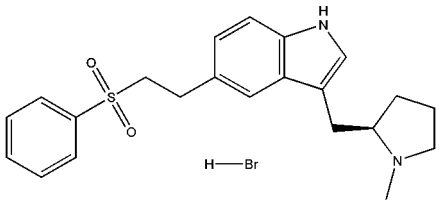
ELETRIPTAN HYDROBROMIDE

Therapeutic Function: Serotonin agonist

Chemical Name: 1H-Indole, 3-(((2R)-1-methyl-2-pyrrolidinyl)methyl)-5-(2-(phenylsulfonyl)ethyl)ethyl)-, monohydrobromide

Common Name: Eletriptan hydrocbromide; Relpax

Structural Formula:



Chemical Abstracts Registry No.: 143322-58-1 (Base); 177834-92-3

Trade Name	Manufacturer	Country	Year Introduced
Relpax	Pfizer	-	-

Raw Materials

Phenyl vinyl sulfone
Palladium (II) acetate
Palladium on carbon
Hydrobromic acid
Hydrogen chloride
Phosphine, tri-o-tolyl-
Triethylamine
(R)-5-Bromo-3-(N-methylpyrrolidinyl-methyl)-1H-indole

Manufacturing Process

A mixture of the appropriate phenyl vinyl sulfone, tri-o-tolylphosphine, palladium (II) acetate, triethlamine and (R)-5-bromo-3-(N-methylpyrrolidinylmethyl)-1H-indole in anhydrous acetonitrle was heated at reflux under nitrogen. The resultant reaction mixture was evaporated under reduced pressure, and the residue was column chromatographed using silica gel and elution with methylene chloride/absolute ethanol/ammonia to afford the (R)-5-trans-(2-phenylsulfonylethenyl)-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole.

A solution of (R)-5-trans-(2-phenylsulfonylethenyl)-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole and 10% Pd/C in ethanolic hydrogen chloride (prepared from absolute ethanol and acetyl chloride and N,N-dimethylformamide was shaken under a hydrogen atmosphere at room temperature). The resultant reaction mixture was filtered through diatomaceous earth (Celite trademark), washed with absolute ethanol, and the combined filtrates were evaporated under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic phase was separated, washed with water, brine, dried

(Na_2SO_4), and evaporated under reduced pressure to afford a oil product. Column chromatography of this product using silica gel and elution with methylene chloride/absolute ethanol/ammonia afforded the appropriate (R)-5-(2-phenylsulfonylethyl)-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole.

The salt eletriptan hydrobromide may be produced by reaction of the (R)-5-(2-phenylsulfonylethyl)-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole with hydrobromic acid.

References

Macor J.E , Wythes M.J.; Patent cooperation treaty (PCT) WO 92/06973; April 30, 1992

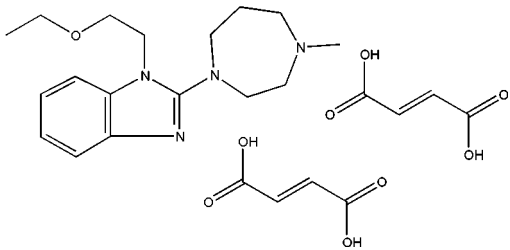
EMEDASTINE FUMARATE

Therapeutic Function: Antiallergic, Antihistaminic

Chemical Name: 1H-Benzimidazole, 1-(2-ethoxyethyl)-2-(hexahydro-4-methyl-1H-1,4-diazepin-1-yl)-, (E)-2-butenedioate (1:2)

Common Name: Emedastine fumarate

Structural Formula:



Chemical Abstracts Registry No.: 87233-62-3

Trade Name	Manufacturer	Country	Year Introduced
Daren	Kanebo, Ltd.	Japan	-
Emedastine	Alcon	-	-
Emadine	Alcon	UK	-

Raw Materials

2-Chlorobenzimidazole
N-Methylpiperazine
2-Bromoethyl ethyl ether

2-Chlorobenzimidazole
Fumaric acid

Manufacturing Process

Preparation of 2-(4-methyl-1-piperazinyl)benzimidazole. A mixture of 2-chlorobenzimidazole (10.00 g) and N-mehylpiperazine (20.00 g) is stirred at 125°C for 5 hours. A 10% aqueous sodium hydroxide (100 ml) is added to the reaction mixture, and the precipitated crystals are separated by filtration. The filtrate is extracted with chloroform, and the chloroform extract is evaporated to dryness to give the same crystals. The crystals are combined and recrystallized from water-methanol to give 2-(4-methyl-1-piperazinyl)benzimidazole (7.02 g) as colorless needles, m.p. 225°-226°C.

2-(4-Methyl-1-piperazinyl)benzimididazole (5.00 g) prepared as above is dissolved in N,N-dimethylformamide (50 ml) and thereto is added sodium hydride (concentration: 50%) (1.50 g) at room temperature, and the mixture is stirred for 30 minutes. To the mixture is added 2-bromoethyl ethyl ether (4.00 g), and the mixture is stirred at 70°C for 10 hours. To the reaction mixture is added water (150 ml), and the mixture is extracted with ethyl acetate. The extract is washed with water, dried over anhydrous magnesium sulfate and then concentrated to give a brown oily substance (5.40 g). The brown oily substance is treated with fumaric acid (3.26 g) in hot ethanol. The crude crystals thus obtained are recrystallized from ethyl acetate-ethanol to give 1-[2-(ethoxy)ethyl]-2-(4-methyl-1-piperazinyl)benzimidazole 3/2 fumarate (6.31 g) as colorless plates, melting point 167.5°-168.5°C. Elementary analysis for $C_{22}H_{30}N_4O_7$: Calcd. (%): C, 57.13; H, 6.54; N, 12.11; Found (%): C, 57.04; H, 6.44; N, 12.02.

1-[2-(Ethoxy)ethyl]-2-(4-methyl-1-piperazinyl)benzimidazole can be prepared using 2-chloro-(1-[2-(ethoxy)ethyl]benzimidazole), (last one can be produced from 2-bromoethyl ethyl ether 2-chlorobenzimidazole) and N-methylpiperazine and fumaric acid there are obtained crude crystals, which are recrystallized from ethanol to give 1-[2-(ethoxy)ethyl]-2-(4-methyl-1-piperazinyl)benzimidazole 3/2 fumarate. This product has the same physical properties as those of the product above described.

References

Iemura R. et al.; US Patent No. 4,430,343; Feb. 7, 1984; Assigned: Kanebo, Ltd. (Tokyo, JP)

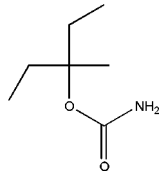
EMYLCAMATE

Therapeutic Function: Tranquilizer

Chemical Name: 3-Methyl-3-pentanol carbamate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 78-28-4

Trade Name	Manufacturer	Country	Year Introduced
Striatin	MSD	US	1960

Raw Materials

3-Methyl-3-pentanol
Potassium cyanate
Trichloroacetic acid
Sodium carbonate

Manufacturing Process

30.5 g of 3-methyl-3-pentanol, 8.1 g of potassium cyanate and 16.3 g of trichloroacetic acid are heated while stirring at 45°C to 50°C for 24 hours, neutralized by successive addition of anhydrous sodium carbonate. The precipitate is removed from the reaction mixture. Unreacted 3-methyl-3-pentanol is distilled off and the residue is added to a small volume of distilled water. After precipitation and filtration the resulting 3-methyl-3-pentanol carbamate is dried and recrystallized from petroleum ether. MP 54°C to 55°C.

References

Merck Index 3528
I.N. p. 376
Melander, B.O. and Hanshoff, G.; US Patent 2,972,564; February 21, 1961; assigned to A/B Kabi (Sweden)

ENALAPRIL MALEATE

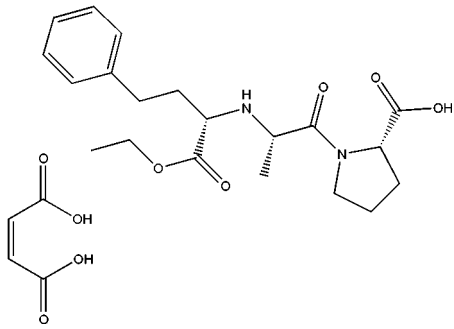
Therapeutic Function: Antihypertensive

Chemical Name: L-Proline, 1-(N-(1-(ethoxycarbonyl)-3-phenylpropyl)-L-alanyl)-, (1S)-, (2Z)-2-butenedioate (1:1)

Common Name: Enalapril maleate

Chemical Abstracts Registry No.: 76095-16-4; 77549-59-8

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Calpiren	Medochemie Ltd.	-	-
Cardiovet	Intervet Ltd.	UK	-
Converten	Khandelwal Laboratories Ltd.	India	-
Crinoren	Uriach	Spain	-
Ena	Menarini Raunaq Pharma Limited	India	-
Enace	Nicholas Piramal India Ltd. (Npil)	India	-
Enalapril Maleate	Teva Pharmaceuticals	Israel	-
Enam	Dr. Reddy's Laboratories Ltd.	India	-
Enamate	Glenmark Pharmaceuticals Ltd.	India	-
Enapril	Intas Pharmaceuticals Pvt. Ltd.	India	-
Enaten	Globus	India	-
Encardil	Medley Pharmaceuticals Pvt. Ltd.	India	-
Enpril	Wockhardt Ltd.	India	-
Envas	Cadila Pharmaceuticals Ltd.	India	-
Hytrol	Sun Pharmaceuticals Industries Ltd.	India	-
Invoril	Rextar	India	-
Mapryl	Polfa Warszawa	Poland	-
Minipril	Alembic Ltd.	India	-
Myoace	E. Merck (India) Ltd.	India	-
Normace	Unisearch	India	-
Nuril	USV-Corvette (A Div of USV Ltd.)	India	-
Vasonorm	Kopran Limited	India	-
Viviril	Sarabhai Chemicals	-	-

Raw Materials

L-Alanyl-L-proline
Molecular sieves
Maleic acid
Ethyl 2-oxo-4-phenyl-butanoate
Nickel Raney

Manufacturing Process

N-[1(S)-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl-L-proline maleic acid salt

A mixture of 3 g of L-alanyl-L-proline, 5 g of ethyl 2-oxo-4-phenyl-butanoate, 13 g of 3A molecular sieves, and 3.6 g of Raney nickel in 85 ml of ethanol is hydrogenated at 25°C and at 40 psig of hydrogen until uptake of hydrogen ceases. The solids are filtered, washed with 80 ml of ethanol and the filtrates are combined. Assay by high pressure liquid chromatography shows an 87:13 ratio of diastereoisomers in favor of the desired product. Ethanol is removed under vacuum to afford an oil which is dissolved in 60 ml of water and 20 ml of ethyl acetate. The pH of the stirred two-phase mixture is adjusted to 8.6 with 50% NaOH. The layers are separated and the water phase is extracted with 2x20 ml of ethyl acetate. The water phase is adjusted to pH 4.25 with hydrochloric acid, 12 g of NaCl is dissolved in the water, and product is extracted with 5x12 ml of ethyl acetate. The extracts are combined and dried with Na_2SO_4. The desired product, N-[1-(S)-ethoxycarbonyl-3-phenylpropyl]-L-alanyl-L-proline, is crystallized as its maleate salt by addition of 1.86 g of maleic acid. After stirring for 4 hours, the salt is filtered, washed with ethyl acetate and dried to afford 5.2 g of pure product, melting point 150°-151°C.

References

Harris E. et al.; US Patent No. 4,374,829; Feb. 22, 1983; Assigned Merk and Co., Inc., Rahway, N.J.

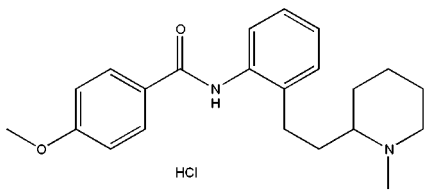
ENCAINIDE HYDROCHLORIDE

Therapeutic Function: Antiarrhythmic

Chemical Name: Benzamide, 4-methoxy-N-(2-(2-(1-methyl-2-piperidinyl) ethyl)phenyl)-, monohydrochloride

Common Name: Encainide hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 66794-74-9

Trade Name	Manufacturer	Country	Year Introduced
Enkaid	Bristol-Myers Squibb	USA	-

Raw Materials

Methyl anthranilate
Diisopropylamine
2-Picoline
Formaldehyde
p-Anisoyl chloride
Butyl lithium
Palladium on carbon

Manufacturing Process

Encainide was prepared in three steps starting with methylantranylate.

A solution of 529.8 g (3.505 mole) methyl anthranilate and 294.4 g 50 weight percent NaOH (3.68 mole) in 3.6 L CH_2Cl_2 and 1.8 L water was stirred in an ice-bath as 627.8 g (3.680 mole) p-anisoyl chloride was added at such rate that the temperature did not exceed 10°C (time required was 1.25 hr). The mixture was allowed to warm to 23°C. Acetic acid (50 mL) was added to adjust the pH to 5. The layers were separated and the organic layer was washed with 10% aqueous $NaHCO_3$ (1 times 0.8 L) and brine (1 times 0.8 L). The residual white solid was recrystallized from 7.0 L boiling material. The product was dried in vacuo at 70°C for 24 hr to yield 959.7 g (96.0%) white crystalline solid, melting point 122.5°C-124.5°C.

2-(2-Pyridylacetyl)-p-anilsanilide. A dry, nitrogen purged flask was charged with 1.875 ml 1.6 N (3.0 mole) n-butyl lithium in hexane. The solution was stirred under nitrogen and chilled to -45° to -40°C, and 1.5 L THF (dried over molecular sieve 4 A) was added slowly. Diisopropylamine (303.6 g; 3.0 mole) was added at such a rate that the temperature did not exceed -30°C. Then 307.3 g (3.3 mole) 2-picoline was added with stirring, keeping the temperature below -30°C. The cooling was interrupted, and the mixture was slowly warmed to 10°C by which time the conversion to anion was complete and all the 2-picolyl lithium had redissolved. The solution was recooled to -45°C to -40°C (the orange solid reprecipitated), and a solution of 285.3 g (1.0 mole) methyl N-p-anisoylanthranilate in 1.9 L dry THF was added at a rate so the temperature did not exceed -30°C. After the addition, the mixture was slowly warmed to 25°C. The solution was adjusted to pH 6 with 500 mL acetic acid; 5.0 H_2O was added with stirring. Then the organic solvents were distilled in vacuo and the residual yellow semi-solid product was extracted with CH_2Cl_2 (1 times 2.5 L). The extract was washed with H_2O (1 times 1.0 L) and stripped to dryness in vacuo. The residue was dissolved in 6.7 L boiling isopropanol. The solution was chilled with stirring to 5°C, and the resulting yellow solid was collected on a filter, rinsed with isopropanol and dried in vacuo at 80°C for six hours. The filtrate was concentrated and chilled to yield a second crop of product. Both crops of intensely yellow material exhibited single spots in the TLC (7.5 cm silica gel with indicator, 9 CH_2Cl_2/1 methanol, UV). The total yield was 306.7 g (88.5%) of material, m.p 145°-148.5°C.

2-(2-Pyridylacetyl)-p-anisanilide (25.0 g, 0.0722 mole) was dissolved with

gentle warming in 500 ml THF. The bright yellow solution was chilled in an ice bath, and 6.5 ml (0.078 mole) 12 N HCl was added. The yellow color disappeared and a white precipitate formed immediately. The solid was collected on a filter; rinsed with THF and air-dried to give 27.4 g white solid 2-(2-pyridylacetyl)-p-anisanilide hydrochloride (99.3%), m.p. 190.5°-191.5°C. (dec.).

4-Methoxy-2'-[2-(1-methyl-2-piperidyl)-ethyl]benzanilide, Encainide. A mixture of 53.5 (0.1397 mole) 2-(2-pyridylacetyl)-p-anisanilide hydrochloride, 1.0 g platinum catalyst (2.5-5% Pt/C or PtO_2) and 1.0 L glacial acetic acid was stirred vigorously under a slight positive pressure of H_2 at 23°-25°C for 20 hr, by which time 0.43 mole (3.08 equivalents) of H_2O had been absorbed. The catalyst was removed by filtration through a celite bed. The filtrate was returned to the flask, and 10.0 g 10% Pd/C was added under nitrogen. The mixture was stirred vigorously under H_2 as it was heated to 60°C. After an additional 6.5 hr the total H_2 uptake equaled 0.71 mole (5.08 equivalents, 101.6% of theory). The mixture was cooled to 25°C, and 22.7 g formalin (37 weight percent formaldehyde, 8.4 g, 0.28 mole) was injected into the reaction mixture. The mixture was stirred vigorously under H_2 at 23°-25°C for 20 hr; during that time 0.1452 mole (1.04 equivalents) H_2 was absorbed. The catalyst was removed by filtration, and the filtrate concentrated in vacuo to a thick oil. Twice the oil was mixed with 200 mL isopropanol and stripped in vacuo at 90°C to a thick oil. The oil was dissolved in 200 mL boiling isopropanol. The solution was stirred, seeded with, and chilled to 10°C for 1 hr. The solid was collected on a filter, rinsed with cold isopropanol (2 times 2.0 mL) to give 36.6 g (67.4%) product, m.p. 181.5°-184.5°C. Additional product was obtained from isopropanol filtrate to give a total yield of 76.1% encainide.

References

Madding G.D.; US Patent No.: 4,394,507; July 19, 1983; Assignee: Mead Johnson and Company (Evansville, IN)

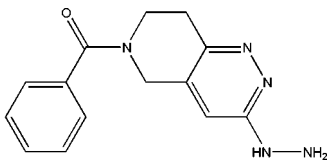
ENDRALAZINE

Therapeutic Function: Hypotensive

Chemical Name: 6-Benzoyl-3-hydrazino-5,6,7,8-tetrahydropyridol[4,3-c]pyridezine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 39715-02-1

Trade Name	Manufacturer	Country	Year Introduced
Miretilan	Sandoz	Switz.	1981
Miretilan	Sandoz	W. Germany	1982

Raw Materials

2,3,4,4a,5,6,7,8-Octahydro-3-oxo-6-pyrido[4,3-c]pyridazine-carboxylic acid ethyl ester
Bromine
Hydrogen chloride
Phosphorus oxychloride
Benzoyl chloride
Maleic acid
Hydrazine

Manufacturing Process

(a) 6-Carbethoxy-5,6,7,8-tetrahydro-3(2H)pyrido[4,3-c]pyridazinone: Produced from 450.5 g of 2,3,4,4a,5,6,7,8-octahydro-3-oxo-6-pyrido[4,3c]pyridazinecarboxylic acid ethyl ester and 320 g of bromine. The bromine is added dropwise to a boiling solution of the ester in 200 cc of chloroform over one hour and the mixture is stirred for another hour at the same temperature. 1 kg of ice water is added to the mixture, the chloroform portion is separated, and the acid aqueous phase is again extracted with 500 cc of chloroform. The semicrystalline crude product obtained after concentrating the chloroform phase, is recrystallized with 250 cc of absolute ethanol, melting point 165°C to 168°C (decomp.).

A solution of 223.2 g of 6-carbethoxy-5,6,7,8-tetrahydro-3(2H)pyrido[4,3-c]pyridazinone in 1 liter of concentrated hydrochloric acid is heated to the boil at reflux for 22 hours while stirring. The mixture is concentrated in a vacuum, and the resulting crude crystalline hydrochloride of 5,6,7,8-tetrahydro-3(2H)pyrido[4,3-c]pyridazinone, having a melting point of 307°C to 310°C (decomposed from methanol), is suspended in 0.75 liter of methanol, and 0.4 liter of triethylamine is slowly added to the suspension. After stirring for 15 minutes and cooling the violet suspension, the crude base is obtained. 25 g of the crude base are recrystallized from 300 cc of methanol, mixed with 10 cc of concentrated ammonia and 40 cc of water, with the addition of a small amount of coal. 5,6,7,8-Tetrahydro-3(2H)pyrido[4,3-c]pyridazinone has a melting point of 223°C to 225°C (decomp.).

(b) 3-Chloro-5,6,7,8-tethydropyrido[4,3-c]pyridazine: Produced from 30.3 g of 5,6,7,8-tetrahydro3(2H)pyrido[4,3-c]pyridazinone suspended in 250 cc of phosphorus oxychloride. The suspension is heated to the boil while stirring. The resulting solution is stirred for 1 hour at the boil and then concentrated to an oil in a vacuum. 150 cc of ice water and 40 cc of concentrated ammonia solution are added to this oil, and the mixture is extracted twice with a total of 300 cc of chloroform. The chloroform phase is concentrated in a vacuum.

(c) The crude unstable base is converted into the maleate for working up. This is effected by boiling 24.8 g of the base in 150 cc of methanol with 17.5 g of

maleic acid. Upon cooling the solution, the crude maleate is obtained, which is recrystallized from methanol with the addition of a small amount of coal. 3-Chloro-5,6,7,8-tetrahydropyrido[4,3-c]pyridazine maleate has a melting point of 162°C to 164°C (decomp.).

A mixture of 12.6 g of benzoyl chloride in 100 cc of ethylene chloride is added dropwise to a suspension of 25.6 g of 3-chloro-5,6,7,8-tetrahydropyrido[4,3-c]pyridazine maleate in 250 cc of ethylene chloride and 21.8 g of triethylamine within 18 minutes at room temperature while stirring. The mixture is stirred at room temperature for a further 14 hours, 200 cc of water are added, the organic phase is separated and concentrated to an oil in a vacuum. Upon adding ether/dimethoxyethane to this oil, crude 6-benzoyl-3-chloro-5,6,7,8-tetrahydropyrido[4,3-c]pyridazine is obtained. After recrystallization from absolute ethanol with the addition of a small amount of coal, the compound has a melting point of 125°C to 127°C (decomp.). Displacement of the halogen with hydrazine leads to the formation of endralazine.

References

Merck Index 3538
DFU 3 (5) 375 (1978)
OCDS Vol. 3 p. 232 (1984)
I.N. p. 378
Schenker, E.; US Patent 3,838,125; September 24, 1974; assigned to Sandoz Ltd.
Schenker, E.; US Patent 3,954,754; May 4, 1978; assigned to Sandoz, Ltd.

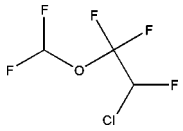
ENFLURANE

Therapeutic Function: Anesthetic

Chemical Name: 2-Chloro-1-(difluoromethoxy)-1,1,2-trifluoroethane

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 13838-16-9

Trade Name	Manufacturer	Country	Year Introduced
Ethrane	Ohio Medical	US	1972
Ethrane	Abbott	Italy	1974

Trade Name	Manufacturer	Country	Year Introduced
Ethrane	Deutsche Abbott	W. Germany	1975
Ethrane	Abbott	UK	1977
Ethrane	Abbott	France	1978
Ethrane	Dainippon	Japan	1981
Aerrane	Ohio Medical	UK	1983
Alyrane	Ohio Medical	-	-
Efrane	Abbott	-	-
Inheltran	Abbott	-	-

Raw Materials

2-Methoxy-2,2-difluoro-1-chloro-1-fluoroethane
Chlorine
Hydrogen fluoride

Manufacturing Process

Preparation of the Intermediate $CHCl_2OCF_2CHFCl$: To a 3-necked round-bottomed flask fitted with a Dry Ice condenser, a fritted glass gas inlet tube, a thermometer and a stirrer, was charged 1,180 grams (8 mols) of CH_3OCF_2CHFCl.After flushing the system with nitrogen, chlorine gas was added via the inlet tube while the reaction was stirred and illuminated with a 300 watt incandescent lamp. The chlorination was rapid and exothermic and the reactor was cooled to hold the temperature between 30° and 35°C. The effluent gases were led from the top of the condenser to a water scrubber which was titrated at intervals with standard base. When a total of 1.45 mols of HCl per mol of ether was titrated the reaction was stopped. The crude product obtained weighed 1,566 grams which corresponded to the addition of 1.41 mols of chlorine per mol of the starting ether. The product was flash distilled to yield 1,480 grams of product which had the following composition as determined by vapor phase chromatography: 45.3% CH_2ClOCF_2CHFCl; 50.5% $CHCl_2OCF_2CHFCl$, plus a small amount of $CH_2ClOCF_2CFCl_2$; 1.8% $CHCl_2OCF_2CFCl_2$ and 2.1% CCl_3OCF_2CHFCl.

Fractional distillation of this mixture using a 5 x 120 cm column packed with ¼" Penn State packing yielded 670 grams of product containing 95% CH_2ClOCF_2CHFCl and 5% $CHCl_2OCF_2CHFCl$; BP 55° to 60°C at 100 mm, n_D^{20} = 1.3748 to 1.3795; and 670 grams of $CHCl_2OCF_2CHFCl$ (95% pure, containing 5% $CH_2ClOCF_2CFCl_2$); BP 60°C at 100 mm, n_D^{20} = 1.3870 to 1.3875. The still bottoms were comprised mostly of CCl_3OCF_2CHFCl and $CHCl_2OCF_2CFCl_2$.

Preparation of CHF_2OCF_2CHFCl: To a mixture of 2,172 grams (10 mols) $CHCl_2OCF_2CHFCl$ prepared as described above (containing approximately 5% $CH_2ClOCF_2CFCl_2$) and 40 grams (2% by weight) $SbCl_5$ was added anhydrous hydrogen fluoride while the temperature was maintained at 0-5°C. The reaction was carried out in a 3-necked stainless steel flask fitted with a stainless steel stirrer, a thermocouple well and a copper Dry Ice condenser.

The amount of hydrogen fluoride added was measured by titration of the HCl given off. At the end of the reaction (total HCl evolved: 1.98 mols per mol of starting ether) the mixture was poured into water and the organic layer (1,803 grams, n_D^{20} = 1.3080) recovered. The crude product was flash distilled in a 60 x 2 cm column packed with ¼" Penn State packing giving 1,594 grams of substantially pure CHF_2OCF_2CHFCl, BP 56° to 57°C. By further distillation 1,450 grams of the pure ether were obtained, BP 56.5°C, n_D^{20} = 1.3030 as described in each of the patents cited as references.

References

Merck Index 3541
Kleeman & Engel p. 346
DOT 9 (5) 173 (1973) & 11 (9) 347 (1975)
I.N. p. 378
REM p. 1041
Terrell, R.C.; US Patents 3,469,011; September 23, 1969 and 3,527,813; September 8, 1970; both assigned to Air Reduction Company, Incorporated

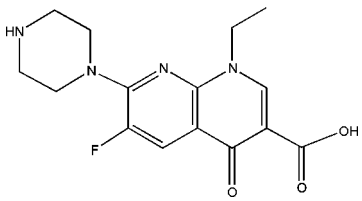
ENOXACIN

Therapeutic Function: Antibacterial, Antiinfective

Chemical Name: 1,8-Naphthyridine-3-carboxylic acid, 1,4-dihydro-1-ethyl-6-fluoro-4-oxo-7-(1-piperazinyl)-

Common Name: Enoxacin

Structural Formula:



Chemical Abstracts Registry No.: 74011-58-8

Trade Name	Manufacturer	Country	Year Introduced
Arox	Hikma	-	-
Enoxacin	LKT Laboratories, Inc.	-	-
Enoxor	Pierre Fabre Medicament	France	-
Flumark	Dainippon	Japan	-

Trade Name	Manufacturer	Country	Year Introduced
Comprecin	Parke-Davis	-	-
Gyramid	Reynolds	-	-
Penetrex	Rhone-Poulenc Rorer	-	-

Raw Materials

2,6-Dichloro-3-nitropyridine
Acetic anhydride
Tetrafluoroboric acid
Diethyl ethoxymethylenemalonate
Thionyl chloride
Ethyl iodide
N-Ethoxycarbonylpiperazine
Palladium on carbon
Isoamyl nitrite
Ethylene bromohydrin
Methanesulfonic acid

Manufacturing Process

2,6-Dichloro-3-nitropyridine was reacted with N-ethoxycarbonylpiperazine to give 6-chloro-2-(4-ethoxycarbonyl-1-piperazinyl)-3-nitropyridine. The product, without purification, was heated with ethanolic ammonia in a sealed tube at 120°-125°C to give 6-amino-2-(4-ethoxycarbonyl-1-piperazinyl)-3-nitropyridine (mp 132°-134°C), which was treated with acetic anhydride in acetic acid to give 6-acetylamino-2-(4-ethoxycarbonyl-1-piperazinyl)-3-nitropyridine (mp 168°-169°C). This compound was catalytically hydrogenated in the presence of 5% palladium-carbon in acetic acid to yield 3-amino-6-acetylamino-2-(4-ethoxycarbonyl-1-piperazinyl)pyridine. The obtained 3-amino derivative, without further purification, was dissolved in a mixture of ethanol and 42% tetrafluoroboric acid, and to this solution was added a solution of isoamyl nitrite in ethanol at below 0°C with stirring 20 minutes later, ether was added to the solution. The resulting precipitate was collected by filtration and washed with a mixture of methanol and ether and then with chloroform to yield 6-acetylamino-2-(4-ethoxycarbonyl-1-piperazinyl)-3-pyridine diazonium tetrafluoroborate; mp 117°-117.5°C (dec.).

A suspension of the diazonium salt in toluene was gradually heated and kept at 120°C (bath temp.) for 30 minutes with stirring. After evaporation of the solvent under reduced pressure, the residue was made alkaline with 10% sodium carbonate and then extracted with chloroform. The chloroform extract was dried over anhydrous potassium carbonate. After evaporation of the solvent, the crystalline residue was recrystallized from ethyl acetate to give 6-acetylamino-2-(4-ethoxycarbonyl-1-piperazinyl)-3-fluoropyridine (mp 132°-133°C). The 3-fluoro derivative was hydrolyzed with a mixture of 15% hydrochloric acid and methanol (1:2 v/v) to give 6-amino-2-(4-ethoxycarbonyl-1-piperazinyl)-3-fluoropyridine. This compound was treated with diethyl ethoxymethylenemalonate at 130°-140°C to give N-[2-(4-ethoxycarbonyl-1-piperazinyl)-3-fluoro-6-pyridinyl]aminomethylenemalonate (mp 144°-145°C) and then the product was cyclized by heating at 255°C to give ethyl 7-(4-ethoxycarbonyl-1-piperazinyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (mp 279°-281°C).

Preparation of 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1,8-naphthyridine-3-carboxylic acid and acid addition salts thereof.

Ethyl 7-(4-ethoxycarbonyl-1-piperazinyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate was suspended in dimethylformamide (10 ml) and to the suspension was added potassium carbonate (0.53 g). After the mixture was kept at 60°C for 10 minutes with stirring, ethyl iodide (1.2 g) was added to the solution. The mixture was stirred for 2 hours at 60°-70°C. The reaction mixture was concentrated to dryness under reduced pressure, and water was added to the residue. After extraction with chloroform, the chloroform extract was dried over anhydrous potassium carbonate. After removal of the chloroform by distillation, the resulting precipitate was recrystallized from a mixture of dichloromethane and n-hexane to give 0.89 g of ethyl 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(4-ethoxycarbonyl-1-piperazinyl)-1,8-naphthyridine-3-carboxylate (mp 171°-173°C). A mixture of the above ethyl ester (0.8 g), 10% sodium hydroxide (6 ml) and ethanol (2 ml) was refluxed by heating for 3 hours. After cooling, the solution was adjusted to pH 7.0-7.5 with 10% acetic acid. The precipitate was collected by filtration, washed with ethanol and recrystallized from a mixture of dimethylformamide and ethanol to give 0.57 g of 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1,8-naphthyridine-3-carboxylic acid. Melting point 220°-224°C.

The above prepared carboxylic acid (0.2 g) thus obtained was dissolved in 5% hydrochloric acid, and the solution was concentrated to dryness under reduced pressure. The residue was crystallized from water to give a hydrochloride of the (0.21 g), m.p. above 300°C. On the other hand, the above free carboxylic acid (0.2 g) was dissolved in 7% methanesulfonic acid solution under heating. After cooling, the precipitate was recrystallized from diluted methanol to give a methanesulfonic acid salt of the carboxylic acid (0.22 g), mp above 300°C (dec.).

The free carboxylic acid (1.0 g) was heated to dissolve in ethanol and then to the solution was added acetic acid (1.0 ml). After the mixture was cooled, the resulting crystals were collected and recrystallized from ethanol to give acetic acid salt of the carboxylic acid (0.93 g), mp 228°-229°C.

References

Matsumoto et al.; US Patent No. 4,352,803; Oct. 5, 1982; Assigved Dainippon Pharmaceutical Co Ltd. (Osaka, Japan), Laboratorire Roger Bellon (Nouilly sur Seine, France)

ENTACAPONE

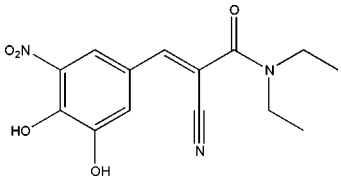
Therapeutic Function: Antiparkinsonian

Chemical Name: 2-Propenamide, 2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethyl-, (2E)-

Common Name: Entacapone

Chemical Abstracts Registry No.: 116314-67-1; 130929-57-6

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Comtan	Orion Corporation for Novartis Pharma	-	-
Comtess	Orion Corporation	-	-
Entacapone	Orion Pharma	-	-

Raw Materials

3,4-Dihydroxy-5-nitrobenzaldehyde
N,N-Diethylcyanoacetamide
Piperidine acetate

Manufacturing Process

N,N-Diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide (2-Propenamide, 2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethyl).

A solution containing 1.83 g of 3,4-dihydroxy-5-nitrobenzaldehyde, 1.5 g of N,N-diethylcyanoacetamide and catalytic amount of piperidine acetate in 40 ml of dry ethanol was refluxed over night. After cooling the solvent was evaporated in vacuo and the residue was recrystallized from water-dimethylformamide. Yield of desired product was 2.23 g (73%), melting point 153°-156°C.

References

Backstrom R.J. et al.; US Patent No. 5,446,194; Aug. 29, 1995; Assigned to Orion-yhtyma Oy, Espoo, Finland

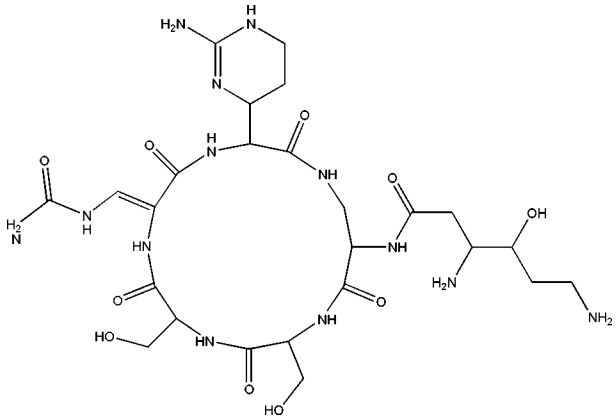
ENVIOMYCIN

Therapeutic Function: Antitubercular

Chemical Name: 1-(L-Threo-3,6-diamino-4-hydroxyhexanoic acid)-6-[L-2-(2-amino-1,4,5,6-tetrahydro-4-pyrimidinyl)glycine]viomycin

Common Name: Tuberactinomycin-N

Structural Formula:



Chemical Abstracts Registry No.: 33103-22-9

Trade Name	Manufacturer	Country	Year Introduced
Tuberactin	Toyo Jozo	Japan	1975
TUM	Toyo Jozo	Japan	-

Raw Materials

Bacterium Streptomyces griseoverticillatus var. tuberacticus
Glucose

Manufacturing Process

Two liters of an aqueous medium consisting of glucose 3%, starch 2%, soybean meal 3% and sodium chloride 1.5% were equally divided and introduced into twenty 500-ml Erlenmeyer flasks, adjusted to pH 6, sterilized at 120°C for 30 minutes, inoculated with Streptomyces griseoverticillatus var. tuberacticus N6-130 and then rotatively shake-cultured (radius 2.5 cm, 330 rpm) at 30°C for 7 days, obtaining 1.5 liter of cultured broth containing 2,360 mcg/ml of tuberactinomycin-N.

Filtered broth was passed at 2.5 ml/min through a resin column (2.5 cm diameter, 28 cm length) packed with 150 ml of ion exchange resin Amberlite IRC-50 sodium type (Rohm and Haas Co., USA.). The column was washed with water, eluted with 0.5N HCl at a flow rate 1.3 ml/min. The eluates were fractionated each 10 ml and tuberactinomycin-N activity was found at fractions No. 45-63 observed by ultraviolet absorption method and bioassay.

The thus yielded active fraction, about 200 ml, was neutralized with sodium hydroxide, concentrated to about 15 ml in vacuo, separating the precipitated inorganic salts therefrom. After decolorization with active carbon, 150 ml of methanol was added, the mixture was allowed to stand overnight at 5°C and the precipitate was collected by filtration. The precipitate was washed with

methanol and dried in vacuo to yield crude tuberactinomycin-N hydrochloride (yield, 3.07 g; purity, 7 1.5%; recovery, 62%).

References

Merck Index 3551
Kleeman & Engel p. 347
DOT 13 (1) 21 (1977)
I.N. p.988
Abe, J., Watanabe, T., Nagata, A., Ando, T., Take, T., Izumi, R., Noda, T. and Matsuura, K.; US Patent 3,892,732; July 1,1975; assigned to Toyo Jozo K.K. (Japan)

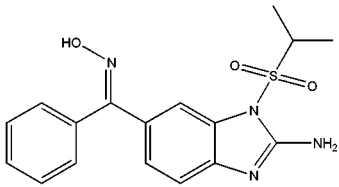
ENVIROXIME

Therapeutic Function: Antiviral

Chemical Name: 1H-Benzimidazol-2-amine, 6-((E)-(hydroxyimino) phenylmethyl)-1-((1-methylethyl)sulfonyl)-

Common Name: Enviroxime; Viroxime Component B

Structural Formula:



Chemical Abstracts Registry No.: 72301-79-2

Trade Name	Manufacturer	Country	Year Introduced
Enviroxime	Eli Lilly	-	-

Raw Materials

4-Aminobenzophenone
Urea
Hydrogen
Cyanogen bromide
Dimethylsulfamoyl chloride
Acetic anhydride
Nickel Raney
Ammonium hydroxide
Triethylamine
Hydroxylamine hydrochloride

Manufacturing Process

300 g (1.52 mole) of 4-aminobenzophenone were added in portions to a stirred solution of 250 ml of acetic anhydride in 250 ml of benzene. The

temperature of the mixture rose to about 70°C. The reaction mixture was stirred overnight. The product was filtered, washed with benzene and dried. The yield of 4-acetamidobenzophenone was 333.8 g (91.5 % yield), melting point 150-152°C (Lit. melting point 155°C).

23 g (0.1 mole) of 4-acetamidobenzophenone, 50 ml of acetic anhydride and 20 ml of acetic acid were stirred together. A solution of 90 % (15 ml), 10 ml of acetic acid and 0.2 g of urea was added dropwise to the mixture. The reaction mixture was maintained at a temperature of about 50°C. The mixture was stirred at ambient temperature whereupon the mixture became very thick. The thick slurry was poured over ice and the insoluble product was filtered to yield 17.7 g (62.5 % yield) of 4-acetamido-3-nitrobenzophenone.

10 g of 4-acetamido-3-nitrobenzophenone were added portion-wise to 40 ml of sulfuric acid. The reaction temperature was moderated with a water bath. After stirring about 45 min the reaction mixture was carefully poured over ice. The precipitated product was filtered to yield 4-amino-3-nitrobenzophenone.

50 g of 4-amino-3-nitrobenzophenone were hydrogenated at room temperature in 945 ml of tetrahydrofuran with 15 g of Raney nickel. After 4 hours 3 equivalents of hydrogen were absorbed. The catalyst was filtered and the filtrate was evaporated in vacuo to a solid residue. The residue was chromatographed over silica gel using ethyl acetate as eluent. Fractions 5-9 were combined to yield 43.6 g (100 % yield) of 3,4-diaminobenzopheone.

42.4 g (o.2 mole) of 3,4-diaminobenzophenone were dissolved in 100 ml of methanol and mixed into one liter of water. 21.8 g (0.2 mole) of cyanogen bromide were added in portions to the reaction mixture with stirring The reaction was continued overnight. The reaction mixture was filtered and the filtrate was neutralized (pH 7.0) with concentrated ammonium hydroxide. The precipitated product was collected, washed with water, and dried in a vacuum to yield 31 g (68.5%) of 2-amino-5(6)-benzoylbenzimidazole.

4.5 g (20 mmole) of 2-amino-5(6)-benzoylbenzimidazole were dissolved in 30 ml of acetone and 4.0 g of triethylamine. A solution of 2.9 g (20 mmole) of dimethylsulfamoyl chloride in 10 ml of acetone was added dropwise to the reaction mixture. The mixture was heated at reflux overnight. The reaction mixture was poured into 400 ml of water. The product was extracted with chloroform. The extract was washed with water, dried (Na_2SO_4) and evaporated in vacuo. The residue was crystallized from ethyl acetate to yield 1.06 g of 1-dimethylaminosulfonyl-2-amino-6-benzoylbenzimidazole, melting point 206-208°C.

172 mg of 1-dimethylaminosulfonyl-2-amino-5(6)-benzoylbenzimidazole, 100 mg of hydroxylamine hydrochloride and 20 ml of methanol were refluxed for 16 hours. The reaction mixture was concentrated to one-half the original volume by heating on the steam bath. 10 ml of buffer (pH=7.0) were added to the mixture. The product precipitated and was filtered to yield 116 mg of 1-dimethylaminosulfonyl-2-amino-5(6)-(α-hydroxyiminobenzyl)benzimidazole, melting point 180-183°C.

References

Paget Charles J., Chamberlin James W., Wikel James H.; US Patent No. 4,118,742; October 3, 1978; Assigned to Eli Lilly and Company (Indianapolis, IN)

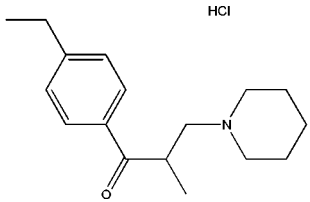
EPERISONE HYDROCHLORIDE

Therapeutic Function: Muscle relaxant

Chemical Name: 1-(4-Ethylphenyl)-2-methyl-3-(1-piperidinyl)-1-propanone hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 64840-90-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Myonal	Eisai	Japan	1983

Raw Materials

4-Ethyl-propiophenone
Piperidine hydrochloride
Paraformaldehyde
Hydrogen chloride

Manufacturing Process

To 60 ml of isopropanol, there are introduced 120 g of 4-ethyl-propiophenone, 28.8g of p-formaldehyde and 107 g of piperidine hydrochloride, and the resulting mixture is heated to reflux on an oil bath with stirring. The heating is continued, and when the reaction mixture solidifies, the state being a sign of completion of the reaction, there are added 500 ml of acetone thereinto. The solidified mass is pulverized by crush, recovered by filtration and washed with acetone. 144 g of the crude dry crystalline substance is thus obtained, which is the hydrochloride of the purposed product. The hydrochloride is recrystallized from isopropanol, and there are obtained the crystalline needles having the melting point of 170°C to 172°C.

References

Merck Index 3555
DFU 7 (12) 907 (1982)
DOT 19 (10) 583 (1983)
Morita, E. and Kanai, T.; US Patent 3,995,047; November 30,1976; assigned to Eisai Co., Ltd. (Japan)

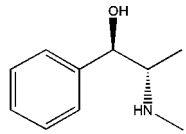
EPHEDRINE

Therapeutic Function: Sympathomimetic; Bronchodilator

Chemical Name: Benzenemethanol, α-(1-(methylamino)ethyl)-, (R-(R*,S*))-

Common Name: Efedrin; Ephedrine

Structural Formula:



Chemical Abstracts Registry No.: 299-42-3

Trade Name	Manufacturer	Country	Year Introduced
CAM	Rybar-UK	-	-
Caniphedrin	G. Streuli and Co. AG	-	-
Ephedrine	AroKor Holdings Inc.	-	-
Efedra	Sanli	-	-
Ephedra	Orion	-	-

Raw Materials

Fermentation product containing phenylpropanolone
Methylamine
Aluminum
L-1-phenylpropanol-1-one-2
Platinum, colloidal solution

Manufacturing Process

120 grams of the fermentation product containing phenylpropanolone obtained by extraction with ether (Biochemische Zeit-schrift Vol. 115, 1921, page 282 et seq.) are allowed to run, without further purification, in for about two hours into a solution of 10 g of methylamine in 500 ml of ether in presence of 20 g of activated aluminum, for example of the type described in British Patent No.

336,412, whilst stirring. Simultaneously 20-30 g of water are added, dropwise. At once the vigorous reaction begins. It is moderated by periodical cooling. Activated aluminum is aluminum, which has been amalgamated with mercury. When it contacts with water, it liberates hydrogen and an insoluble aluminum hydroxide is formed. Activated aluminum thus serves as the source of hydrogen for the reaction. When the reaction is complete the ethereal solution is filtered and the optically active base, which formed is extracted from the filtrate by means of dilute acid. There is obtained the hydrochloride of L-1-phenyl-2-methylamino-propanol-1 having a melting point of 214°C, and having the optical rotation given in the literature. The yield amounts to 25-45 g of the hydrochloride depending upon the nature of the parent material.

360 g of ether extract phenylpropanolone used above as parent material are distilled under reduced pressure. 300 grams of the fraction, which distils at 100-150°C/14 mm Hg are subjected to catalytic hydrogenation in presence of colloidal platinum (70 ml of a 1% solution) and 85 grams of a 33% solution of methylamine. It is advantageous to add some ether to the reaction mixture. When absorption of hydrogen is complete, the ethereal solution is shaken with hydrochloric acid and the L-phenyl-2-methylamino-propanol-1 is isolated from the hydrochloric acid extract. The yield of the hydrochloride amounts to 110 grams. MP: 214°C.

100 g of L-1-phenylpropanol-1-one-2 isolated by the method of Neuberg (Biochemische Zeitschrift Vol. 128, 1922, page 611) are dissolved in 200 ml of ether, 75 g of a solution of methylamine (33%) are added and the whole is shaken for about half an hour; condensation occurs with evolution of heat. The reaction mixture is then treated with hydrogen in presence of 70 ml of a 1% colloidal solution of platinum. The reduction product was isolated as hydrochloride. The hydrochloride of L-phenyl-2-methyl-amino-propanol-1 crystallizes from alcohol in the form of coarse prisms. MP: 214°-216°C. The free base melts at 40°C.

References

Hildebrandt G. et al.; US Patent No. 1,956,950; May 1, 1934; Assigned to Bilhuber, Incorporated, Jersey City, N.J., a corporation of New Jersey

EPICILLIN

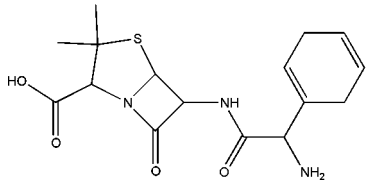
Therapeutic Function: Antibacterial

Chemical Name: 6-[D-2-Amino-2-(1,4-cyclohexadien-1-yl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid

Common Name: D-α-Amino-(1,4-cyclohexadien-1-yl)methylpenicillin

Chemical Abstracts Registry No.: 26774-90-3

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Dexacilline	Squibb	France	1974
Spectacillin	Sandoz	W. Germany	1975
Dexacillin	Squibb	Italy	1977
Florispec	Squibb	-	-
Omnisan	Squibb	-	-
Spectacillin	Biochemie	Austria	-

Raw Materials

D-Phenylglycine
Lithium
Ammonia
Methyl acetoacetate
6-Aminopenicillanic acid

Manufacturing Process

See Cephradine for preparation of D-2-amino-2-(1,4-cyclohexadienyl)acetic acid and then its methyl acetoacetic ester enamine as the starting material.

358 mg of 6-aminopenicillanic acid (APA) (1.66 mmol) are stirred well in 2.5 ml of water while 0.23 ml triethylamine is gradually added with the pH kept under 8.0. Final pH is 7.4; 0.85 ml acetone is added and the solution kept at -10°C.

469 mg methyl acetoacetate enamine of D-2-amino-2-(1,4-cyclohexadienyl)acetic acid sodium salt (1.715 mmol) are stirred in 4.25 ml acetone at -20°C. A microdrop of N-methylmorpholine is added followed by the slow addition of 198 mg of ice cold ethyl chloroformate. Water, 0.43 ml, is added at this point and a turbid solution results. The reaction mixture is stirred for 10 minutes at -20°C.

The turbid solution of mixed anhydride is then added to the 6-APA solution. A complete solution is observed. The solution is stirred for 30 minutes at -10°C, then raised to room temperature, acidified to pH 2.0 with diluted HCl and, with good stirring, the pH is kept at that level for 10 minutes.

The solution is then extracted with 5 ml xylene. The aqueous layer is layered with 5 ml methyl isobutyl ketone and the pH adjusted to 5.0 with 1 N NaOH and chilled overnight. The resulting crystals are filtered off, washed with water and air dried. Yield, 272 mg (44%), decomposes at 202°C.

References

Merck Index 3563
Kleeman & Engel p. 348
DOT 9 (3) 101 (1973)
I.N. p. 381
REM p. 1201
Weisenhorn, F.L., Dolfini, J.E., Bach, G.G. and Bernstein, J.; US Patent 3,485,819; Dec. 23, 1969; assigned to E.R. Squibb & Sons, Inc.

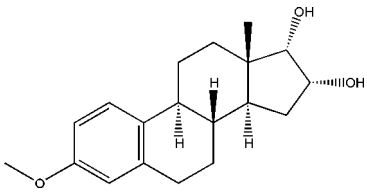
EPIMESTROL

Therapeutic Function: Anterior pituitary activator

Chemical Name: 3-Methoxyestra-1,3,5(10)-triene-16,17-diol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 7004-98-0

Trade Name	Manufacturer	Country	Year Introduced
Stimovul	Organon	W. Germany	1976
Stimovul	Ravasini	Italy	1980
Alene	Organon	-	-

Raw Materials

16-Keto-17(α)-hydroxyestratrienol-3-methyl
Sodium amalgam

Manufacturing Process

Reduction of 16-keto-17(α)-hydroxyestratrienol-3-methyl to 16,17-dihydroxyestratrienol-3-methyl ether: A solution of 800 mg of the alpha ketol methyl ether in 100 cc of ethanol and 10 cc of acetic acid was carefully maintained at 40°C (water bath), and 200 g of freshly prepared sodium amalgam (2%) were added in small pieces with efficient swirling. Before all of

the amalgam had been added, a precipitation of sodium acetate occurred, and at this point an additional 100 cc of 50% acetic acid were added. After all the reducing agent had been added, the mixture was transferred to a separatory funnel with ether and water. The mercury plus aqueous phase was separated, after partitioning, from the ether; the latter may be further washed with water, with 0.5N sodium hydroxide, and again with water to purify the alpha glycol. Evaporation of the ethereal phase yielded a crystalline residue of the isomeric transoid (16(β),17(α)-dihydroxy-steroid-3-methyl ether and cisoid 16(α),17(α)dihydroxy-steroid-3-methyl ether.

References

Merck Index 3566
Kleeman & Engel p. 348
OCDS Vol. 2 p. 13 (1980)
DOT 13 (5) 191 (1977)
I.N. p. 381
Huffman, M.N.; US Patent 2,584,271; February 5, 1952; assigned to G.D. Searle & Co.

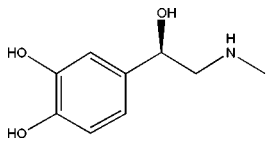
EPINEPHRINE

Therapeutic Function: Vasoconstrictor

Chemical Name: 1,2-Benzenediol, 4-(1-hydroxy-2-(methylamino)ethyl)-, (1R)-

Common Name: Adrenaline; Bi-Epinephrin; Epinefrine; Epinephrine; Epirenemine; Levo-Epinephrine; Racepinefrine; Racepinephrine

Structural Formula:



Chemical Abstracts Registry No.: 51-43-4

Trade Name	Manufacturer	Country	Year Introduced
Adrenalin	Sopharma	Bulgaria	-
Ana-Guard	Bayer Pharmaceutical Corporation	-	-
Brontin Mist	Whitehall Robins Consumer Products	-	-
Epifrin	Allergan	USA	-
Epinephrine	Agri Laboratories Ltd.	USA	-

Trade Name	Manufacturer	Country	Year Introduced
EpiPen	Allerex	Canada	-
Glaucon	Alcon	USA	-
Sus-Phrine	Steris Laboratories, Inc.	USA	-
Vaponefrin	Medeva Pharmaceutical, Inc.	-	-

Raw Materials

ω-Chloro-3,4-dihydroxyacteophenone
Methylamine

Manufacturing Process

1 part by weight of ω-chloro-3,4-dihydroxyacteophenone in 1 part by weight of ethanol was heated with 60% aqueous solution of methylamine. The crystal of 3,4-dihydroxy-ω-methylaminoacteophenone obtained was transformed in hydrochloride by action of diluted hydrochloric acid. The base of (-)-3,4-dihydroxy-ω-methylaminoacteophenone was prepared by addition of ammonium hydroxide solution.

References

DRP 152814, 1903; Hoechst

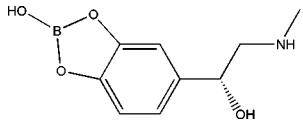
EPINEPHRYL BORATE

Therapeutic Function: Antiglaucoma

Chemical Name: 4-[1-Hydroxy-2-(methylamino)ethyl]-1,2-benzenediol borate

Common Name: Methylaminoethanolcatechol borate; Adrenalin borate

Structural Formula:



Chemical Abstracts Registry No.: 5579-16-8

Trade Name	Manufacturer	Country	Year Introduced
Eppy	Barnes Hind	US	1961
Epinal	Alcol	US	-

Raw Materials

Epinephrine
Boric acid

Manufacturing Process

Epinephrine may be made by isolation from animal adrenal glands or may be synthesized as described by Payne in Ind. Chemist, 37, 523 (1961).

It has been found that epinephrine solutions having a physiological pH and which are stable for months in storage can be prepared by combining with the epinephrine a small amount of sodium bisulfite, boric acid, and oxine (8-hydroxy-quinoline) hereinafter called 8-quinolinol and adjusting the pH with an alkali, such as sodium hydroxide, to the desired pH.

It has been found that from 0.001 to 0.1% of 8-quinolinol can be used. From 0.2 to 5% boric acid may be used. The amount of sodium bisulfite can be varied from 0.1 to 1%. The solutions can contain from 0.1 to 4% epinephrine. The pHs of the solutions can be adjusted to any value within the physiological range, i.e., from 6.5 to 8.5 using any convenient alkali such as sodium hydroxide.

References

Merck Index 3567
Kleeman & Engel p. 349
I.N. p. 382
REM p. 884
Riegelman, S.; US Patent 3,149,035; September 15,1964; assigned to The Regents of the University of California

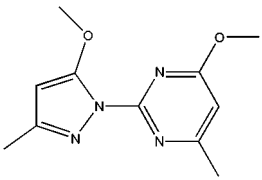
EPIRIZOLE

Therapeutic Function: Antiinflammatory, Analgesic, Antipyretic

Chemical Name: 4-Methoxy-2-(5-methoxy-3-methylpyrazol-1-yl)-6-methylpyrimidine

Common Name: Mepirizole

Structural Formula:



Chemical Abstracts Registry No.: 18694-40-1

Trade Name	Manufacturer	Country	Year Introduced
Mebron	Daiichi Seiyaku	Japan	1970
Mebron	Daiichi Seiyaku	Italy	1979
Daicon	I.B.I.	Italy	1979
Analock	Taito Pfizer	Japan	-
Mepiral	Rober	Spain	-

Raw Materials

4-Methyl-6-methoxy-2-pyrimidinyl-hydrazine
Ethyl acetoacetate
Diazomethane

Manufacturing Process

A mixture of 16.3 g of 4-methyl-6-methoxy-2-pyrimidinyl-hydrazine,13.7 g of ethyl acetoacetate and 16.3 ml of methanol was refluxed 2 hours on a water bath. After a mixture of 4.7 g of sodium hydroxide, 4.7 ml of water and 27 ml of methanol was added dropwise thereto at about 50°C, the reaction mixture was refluxed for 2 hours more, then methanol was distilled off and the residue was dissolved in 130 ml of water. The solution was adjusted to pH 6 with acetic acid. The precipitate was filtered, washed with water and dried to give 24 g (yield: 95.3%) of crystals, MP 97° to 98°C. Recrystallization from ligroin gave 1-(4'-methyl-6'-methoxy-2'-pyrimidinyl)-3-methyl-3-pyrazoline-5-one, MP 102° to 103°C.

To a solution of 4.76 g of 1-(4'-methyl-6'-methoxy-2'-pyrimidinyl)-3-methyl-3-pyrazoline 5-one in 200 ml of ether was added an ether solution containing 6 molar equivalents of diazomethane and the reaction mixture was allowed to stand at room temperature for 20 hours. After distilling off the solvent, the residue was dissolved in 160 ml of water, made alkaline (pH 10) with sodium hydroxide solution and extracted three times with 140 ml of benzene. The extract was washed with a small amount of water, dried over sodium sulfate and evaporated to give a crystalline mass. Recrystallization from isopropylether gave 1-(4'-methyl-6'-methoxy-2'-pyrimidinyl)-3-methyl-5-methoxypyrazole (3.96 g, 84%) as color less prisms, MP 90° to 92°C.

References

Merck Index 3571
Kleeman & Engel p. 349
OCDS Vol. 3 p. 152 (1984)
I.N. p. 382
Naito, T., Oshima, Y., Yoshikawa, T., Kasahara, A., Dohmori, R., Nakai, Y. and Tsukada, W.; South African Patent Application 67/4936; January 19, 1968; assigned to Daiichi Seiyaku Company Limited, Japan

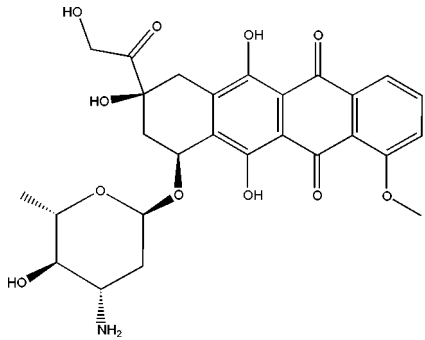
EPIRUBICIN

Therapeutic Function: Antineoplastic

Chemical Name: 5,12-Naphthacenedione, 10-((3-amino-2,3,6-trideoxy-α-L-arabino-hexopyranosyl)oxy)-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S-cis)-

Common Name: 4'-Epiadriamycin; 4'-Epidoxorubicin; Epirubicin; Pidorubicin

Structural Formula:



Chemical Abstracts Registry No.: 56420-45-2

Trade Name	Manufacturer	Country	Year Introduced
Ellence	Pharmacia and Upjohn Co.	-	-
Farmorubicin	Pharmacia and Upjohn Co.	-	-

Raw Materials

Daunorubicin hydrochloride
Bromine
Pyridinium chlorochromate
Trifluoroacetic anhydride
4-Toluenesulfonic acid
Acetyl chloride
Acetic acid potassium
Borane-tetrahydrofuran complex
2,2-Dimethoxypropane
Sodium hydroxide

Manufacturing Process

Conversion of daunorobicin hydrochloride to 4'-epi-doxorubicin hydrochloride employing the trifluoroacetyl moiety for the 3'-amino group protection:

To a solution of 8 g (14 mmol) of daunorubicin hydrochloride in 500 ml of dry MeOH, 5.9 ml (79 mmol, 5.6 eq.) of acetylchloride was added. After refluxing for 1 h the solvents were evaporated in vacuo. Addition of $CHCl_3$ to the residue caused precipitation of daunosamine. After the aminosugar had been filtered off, the filtrate was evaporated in vacuo. Diisopropylether was added to the remaining solid and the mixture was sonicated for 15 min to yield

daunomycinone. In total, 2.55 g (91%) of daunosamine (4-amino-6-methoxy-2-methyltetrahydropyran-3-ol hydrochloride) and 5.5 g (99%) of daunomycinone were obtained, m.p. 209-233°C (dec.).

Under an argon atmosphere, a solution of 1.24 ml (2.5 eq.) of Br_2 in 72.8 ml $CHCl_3$ was added to a solution of 3.90 g (9.8 mmol) of daunomycinone in 390 ml of $CHCl_3$. After stirring the reaction mixture over night at room temperature, the pure bromide 4 precipitated and was filtered out. Yield 4.1 g (88%).The bromide was dissolved in 1.17 L of acetone, 16.7 g of AcOK was added to the mixture which was then refluxed for 5 min. Thereafter the solvents were evaporated in vacuo. The residue was dissolved in $CHCl_3$ and washed with water and brine. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Diisopropylether was added and the mixture was sonicated and filtrated to give doxorubicinone acetate, 3.8 g (97%), m.p. 226-229°C (dec.).

Daunosamine modification:

To a solution of 2.55 g (12.9 mmol) of daunosamine in 64 ml of dry diethylether under an argon atmosphere 5 ml (4.8 eq.) of pyridine was added. The reaction mixture was cooled to -20°C and 3.63 ml of trifluoroacetic acid anhydride was added. After stirring overnight at room temperature, the mixture was filtered and the filtrate was washed with diethylether. The filtrate was subsequently washed with 10% citric acid solution, saturated $NaHCO_3$ and brine. The combined extracts were dried over $MgSO_4$, filtrated and evaporated in vacuo. The residue was purified by flash column chromatography (5% MeOH in $CHCl_3$) to give 2.69 g (81%) of (3-hydroxy-6-methoxy-2-methyltetrahydropyran-4-yl)carbamic acid trifluoromethyl ester, m.p. 137-152°C.

To a solution of 2.5 g (9.7 mmol) of (3-hydroxy-6-methoxy-2-methyltetrahydropyran-4-yl)carbamic acid trifluoromethyl ester in 100 ml of CH_2Cl_2 2.45 g (11.4 mmol) of pyridinium chlorochromate (PCC) was added. After 2 and after 4 hours of refluxing 1.08 g (5.0 mmol) of PCC was added. Again after refluxing the reaction mixture for 8 hours 1.5 g (7.0 mmol) of PCC was added and the mixture was stirred over night. The mixture was poured into 436 ml of diethylether, filtered and evaporated in vacuo. The residue was purified by flash column chromatography (2% acetone in CH_2Cl_2) to give 2.10 g (85%) of (6-methoxy-2-methyl-3-oxotetrahydropyran-4-yl)-carbamic acid trifluoromethyl ester, m.p. 74-98°C.

10 ml of 1 M BH_3·THF was added dropwise to a solution of 2.6 g (10 mmol) of (6-methoxy-2-methyl-3-oxotetrahydropyran-4-yl)carbamic acid trifluoromethyl ester dissolved in a mixture of 200 ml of dry THF and 125 ml of dry MeOH under an argon atmosphere at 0°C. After stirring for 10 min, 1 ml of H_2O was added and the solvents were evaporated in vacuo. The remaining oil was purified by flash column chromatography (3% MeOH in CH_2Cl_2) to give 2.08 g (80%) of 4'-epidaunosamine derivative as a white solid, m.p. 165-167°C. A solution of 2.08 g (8.1 mmol) of 4'-epidaunosamine derivative in 20% of AcOH was refluxed for 3 hours at 90°C. The solution was freeze-dried and purified by flash column chromatography (10% MeOH in CH_2Cl_2) to give 1.38 g (70%) of hemiacetal, m.p. 180-185°C.

3.3 ml (23.5 mmol) of trifluoroacetic anhydride was added to a stirred suspension of 272 mg (1.12 mmol) of hemiacetal in 10 ml of dry diethylether under an argon atmosphere at 0°C. After the suspension had become clear, stirring was continued for 1 hour at room temperature, after that the solvent was cautiously removed in vacuo. To this residue 50 ml of dry CH_2Cl_2 and 10 g of 4 ANG molsieves and 0.27 ml (1.39 mmol) of trimethylsilyl trifluoromethanesulfonate were added under an argon atmosphere at 0°C. The reaction mixture was stirred at 0°C for 1 h and a solution of 0.50 g (1.11 mmol) of doxorubicinone acetate in 100 ml of dry CH_2Cl_2 was added. After stirring for 2 hours at room temperature, the red suspension was poured into a vigoriously stirred solution of saturated $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried over Na_2SO_4, filtered and the solvents were evaporated in vacuo. The remaining red solid was stirred overnight in a mixture of 20 ml of CH_2Cl_2 and 175 ml of MeOH under an argon atmosphere and the solvents were evaporated in vacuo. The remaining red solid was purified by flash column chromatography (4% MeOH in CH_2Cl_2) to give 345 mg (47%) of 4'-epidoxorubicin derivative, [122 mg (24%) of unreacted doxorubicinone acetate was also obtained; m.p. 114-126°C].

225 ml of saturated $NaHCO_3$ was added to a solution of 784 mg (1.15 mmol) of 4'-epidoxorubicin in a mixture of 150 ml of acetone and 75 ml of methanol under an argon atmosphere. After stirring for 3 hours at room temperature, the purple suspension was poured into 600 ml of H_2O and was extracted 3 times with $CHCl_2$. The combined organic extracts were washed with brine, dried over Na_2SO_2, filtered and taken to dryness in vacuo to give 526 mg (72%) of deacetylated compound, m.p. 147-162°C (dec.).

5.1 ml (42 mmol) of 2,2-dimethoxypropane and 1 mg p-toluene sulfonic acid were added to a solution of 107 mg (0.17 mmol) of deacetylated compound in a mixture of 1 ml of dioxane and 20 ml of $CHCl_3$ under an argon atmosphere. After stirring for 24 hours at room temperature, 10 mg of $NaHCO_2$ was added and the solution was stirred for 5 min. The red reaction mixture was washed with water until neutral pH. The organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated in vacuo. The remaining red solid was purified by flash column chromatography (5% MeOH in CH_2Cl_2) to give 86 mg (72%) of compound with protected carbonyl group (a mixture of diastereomers), m.p.146-164°C.

A solution of 325 mg (0.46 mmol) of above compound in a mixture of 50 ml of 0.1 M NaOH and 10 ml of acetone was stirred for 30 min at room temperature under an argon atmosphere. The pH of the reaction mixture was adjusted to 8.4 with a 0.1 M HCl solution and extracted with $CHCl_3$ until the organic layer was colourless. The combined organic extracts were dried over Na_2SO_4, filtered and the solvent was evaporated in vacuo. The residue was dissolved in 20 ml of 0.1 M HCl and stirred for 39 hours at room temperature, the solution was then washed with $CHCl_3$ (to extract the aglycone). The pH of the combined aqueous layer was adjusted to 8.5 with 0.1 M NaOH and extracted with $CHCl_2$ until the organic extract was colourless. The combined organic extracts were dried over Na_2SO_4, filtered and the solution was concentrated. Diethylether and 0.76 ml of 0.6 M HCl in MeOH were added, 4'-

epidoxorubicin hydrochloride precipitated and was filtrated to obtain 118 mg (45%), m.p. 176-185°C (dec.).

References

Rijst M. et al.; US Patent No. 5,874,550; Assigned to Pharmachemie B.V., Ga Haarlem, Netherlands

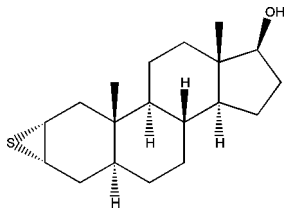
EPITIOSTANOL

Therapeutic Function: Antineoplastic

Chemical Name: 2,3-Epithioandrostan-17-ol

Common Name: Epithioandrostanol

Structural Formula:



Chemical Abstracts Registry No.: 2363-58-8

Trade Name	Manufacturer	Country	Year Introduced
Thiodrol	Shionogi	Japan	1977

Raw Materials

2β-Thiocyanato-3α-methanesulfonyloxy-5α-androstan-17β-ol-17-acetate
Potassium hydroxide

Manufacturing Process

A solution of 2β-thiocyanato-3α-methanesulfonyloxy-5α-androstan-17β-ol 17-acetate (0.82 part by weight) and potassium hydroxide (0.9 part by weight) in diglyme (20 parts by volume) is refluxed on a water bath for 24 hours while stirring. To the reaction mixture, there is added water, and the separated substance is collected by filtration and crystallized from hexane to give 2β,3β-epithio-5α-androstan-17β-ol (0.60 part by weight) as crystals melting at 132.5°C to 134°C.

References

Merck Index 3573
Kleeman & Engel p. 350
DOT 14 (7) 274 (1978)
I.N. p. 383
Komeno, T.; US Patent 3,230,215; January 18, 1966; assigned to Shionogi & Co., Ltd.

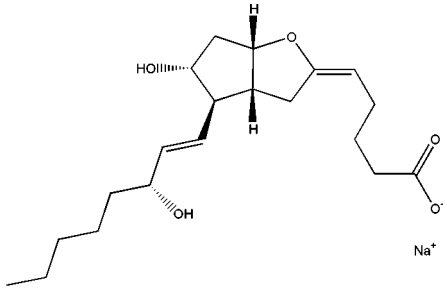
EPOPROSTENOL SODIUM

Therapeutic Function: Platelet aggregation inhibitor, Antimetastatic

Chemical Name: Prosta-5,13-dien-1-oic acid, 6,9-epoxy-11,15-dihydroxy-, (5Z,9α,11α,13E,15S)-, sodium salt

Common Name: Epoprostenol sodium; Prostaglandin I_2; Prostaglandin X

Structural Formula:



Chemical Abstracts Registry No.: 35121-78-9 (Base); 61849-14-7

Trade Name	Manufacturer	Country	Year Introduced
Prostacyclin	ZYF Pharm Chemical	-	-
Flolan	GlaxoSmithKline Pharma	-	-

Raw Materials

Pig aortas
Liquid nitrogen in 0.05 M Tris buffer

Manufacturing Process

Preparation of prostacyclin:

Pig aortas were stripped of adventitia, snap frozen in liquid nitrogen, crushed into a fine powder, resuspended in 0.05 M Tris buffer (pH 7.5) (1:4, w:v) and

homogenised at high speed in a Polytron (KIMENATIC, LUCERNE, SWITZERLAND) homogenizer. The homogenate was centrifuged for 15 min and the resulting supernatant centrifuged again for 5 min. The pellet was discarded, while the pellet obtained after centrifugation of the supernatant was resuspended in deionized water and lyophilized. An average yield of 150 mg of aortic microsomal powder (51% protein) per 100 g of aortic tissue was obtained.

References

Moncada S.; US Patent No. 4,539,333; Sept. 3, 1985; Assigned to Burroughs Wellcome Co. (Research Triangle Park, NC).

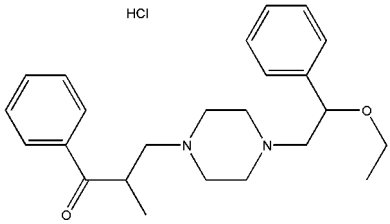
EPRAZINONE HYDROCHLORIDE

Therapeutic Function: Antitussive

Chemical Name: 3-[4-(2-Ethoxy-2-phenylethyl)-1-piperazinyl]-2-methyl-1-phenyl-1-propanone hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 10402-53-6; 10402-90-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Mucitux	Riom	France	1969
Resplen	Chugai	Japan	1974
Eftapan	Merckle	W. Germany	1977
Mucitux	Recordati	Italy	1981
Mukolen	Krka	Yugoslavia	-
Vopop	Lando	Argentina	-

Raw Materials

Propiophenone	1-(2-Phenyl-2-ethoxy)piperazine dihydrochloride
Trioxymethylene	Hydrogen chloride

Manufacturing Process

61.4 g of 0.2M of 1-(2-phenyl-2-ethoxy)piperazine dihydrochloride, 33.5 g (0.25M) propiophenone, 75 g (0.25M) trioxymethylene, 120 ml of ethanol and 0.4 ml of concentrated HCl are heated under reflux for 4 to 5 hours. The product is allowed to crystallize, then filtered and washed with alcohol. It is dried and recrystallized from methanol containing 10% H_2O.

There is thus obtained 60 g of a white crystalline powder soluble in water. Yield: 66%. Melting point: 160°C.

References

Merck Index 3575
Kleeman & Engel p. 350
OCDS Vol. 1 p.64 (1977)
I.N. p. 384
Mauvernay, R.Y.; US Patent 3,448,192; June 3, 1969

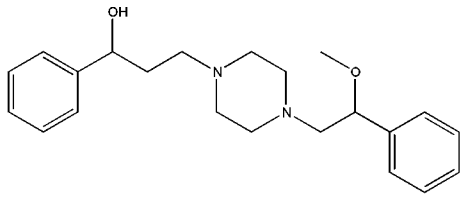
EPROZINOL

Therapeutic Function: Bronchodilator

Chemical Name: 4-(β-Methoxyphenethyl)-α-phenyl-1-piperazinepropanol

Common Name:

Structural Formula:



Chemical Abstracts Registry No.: 32665-36-4

Trade Name	Manufacturer	Country	Year Introduced
Eupneron	Lyocentre	France	1973
Brovel	Lepetit	Italy	1978

Raw Materials

Styrene
t-Butyl hypobromite
Methanol

Piperazine
Acetophenone
Trioxymethylene
Sodium borohydride

Manufacturing Process

Stage 1: Preparation of 2-Phenyl-2-Methoxy-Ethyl Bromide - 1.3 mols of tert-butyl hypobromite is added slowly and with agitation to a mixture of 107 grams (1 mol) of vinyl benzene (styrene) and 250 ml of methanol (99%), kept at -10°C. When the addition of the reactant is finished, the mixture is allowed to return to ambient temperature, it is washed in water and dried on anhydrous Na_2SO_4. Rectification is effected in vacuo in order to obtain a colorless liquid BP_{12}= 113°C, BP_{2-5}=84°C, $n_D^{20.6}$ = 1.5429, yield = 76%.

Stage 2: Preparation of 1-[2-Phenyl-2-Methoxy]-Ethyl-Piperazine - 210 grams of 2-phenyl-2-methoxy-ethyl bromide and 260 grams of anhydrous piperazine are heated for 5 to 6 hours to reflux in 600 ml of ethanol, 500 ml of ethanol is then distilled off and finally the solvent is removed in vacuo. The residue is taken up in 250 ml of benzene and the piperazine hydrobromide is filtered off. The benzene is removed in vacuo. The oily residue is taken up by 450 ml of water and acidification is effected up to pH = 1 by concentrated HCl. The aqueous solution is filtered; the latter is then made alkaline by 50% aqueous NaOH. The liberated base is decanted, the alkaline aqueous solution is washed twice by 150 ml ether. After distillation of the ether, the previously decanted oil is added to the residue and distillation is effected in vacuo. Thus,135 grams of a colorless viscous oil, becoming carbonated in air, is obtained. BP_{14}= 166°C, n_D^{20} =1.5321, yield = 61%.

Stage 3: Preparation of 1-[2-Phenyl-2-Methoxy]-Ethyl-4-[2-Benzoyl-Ethyl]-Piperazine Dihydrochloride -There are heated to reflux and with agitation for 6 hours, 166 grams 1-[2-phenyl-2-methoxy]-ethyl-piperazine, 400 ml ethanol (96°), 260 ml absolute ethanol with 23% HCl gas, 112 grams acetophenone, 32 grams trioxymethylene and 0.8 ml concentrated aqueous HCl. After cooling, the product crystallizes. Recrystallization is effected in ethanol (96°) (1.400 liters for the quantity indicated). 246 grams of a white crystalline powder is thus obtained, slightly soluble in water and alcohol. MP (instant) = 168°C with decomposition, yield 77%.

Stage 4: Preparation of 1-[2-Phenyl-2-Methoxy]-Ethyl-4-[3-Phenyl-3-Hydroxypropyl]-Piperazine Dihydrochloride -In a double-neck flask equipped with a thermometer and a mechanical stirrer, there is placed in suspension in 800 ml of methanol, 233 grams of 1-[2-phenyl-2-methoxy]-ethyl-4-[2-benzoyl-ethyl]-piperazine dihydrochloride (0.55 mol). It is cooled to approximately 5°C, and 46 grams of NaOH pellets dissolved in 80 ml of H_2O are added. When the temperature is about 5°C, one addition of 29.2 grams of sodium borohydride in 40 ml H_2O is made. The ice-bath is then removed and stirring continued at ambient temperature for 6 hours.

Cooling is effected in the ice-bath while slowly adding concentrated HCl up to a pH of 2, while maintaining the temperature around 5°C. It is filtered and an equal volume of H_2O is added. If the solution is cloudy it is washed in ether. It is alkalized by aqueous NaOH (40%), and the oil formed is extracted with

ether. The ether phase is washed with water saturated with NaCl, then it is dried over anhydrous Na_2SO_4.

After evaporation of the solvent, a very thick, colorless oil is obtained. This base is dissolved by 200 ml of absolute ethanol and the quantity of HCl to obtain the dihydrochloride is added. It is left for a few hours over ice, dried, washed with approximately 100 ml of anhydrous ether in order to obtain 190 to 195 grams of 1-[2-phenyl-2-methoxy]-ethyl-4-[3-phenyl-3-hydroxy]-propyl-piperazine dihydrochloride after drying at 60°C in vacuo. The yield is 80%. It is recrystallized from absolute ethanol. The product is in the form of white crystalline powder, soluble in water, slightly soluble in alcohol, insoluble in ethyl acetate.

References

Merck Index 3576
Kleeman & Engel p. 351
OCDS Vol. 2 p. 44 (1980)
DOT 9 (5) 177 (1973)
I.N. p.384
Saunders, H.E. and Mauvernay, R.-Y.; British Patent 1,188,505; April 15, 1970

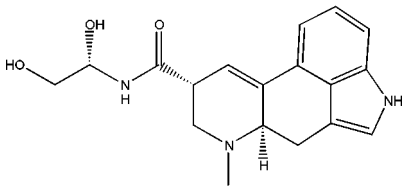
ERGOMETRINE

Therapeutic Function: Oxytocic

Chemical Name: Ergoline-8-β-carboxamide, 9,10-didehydro-N-((S)-2-hydroxy-1-methylethyl)-6-methyl-

Common Name: Ergobasine; Ergometrine; Ergonovine; Ergotocine

Structural Formula:



Chemical Abstracts Registry No.: 60-79-7

Trade Name	Manufacturer	Country	Year Introduced
Ergotrate	Lilly	-	-

Raw Materials

d-Lysergic acid	Trifluoroacetic anhydride
Triethylamine	L-(+)-2-Aminopropan-1-ol

Manufacturing Process

A solution of the mixed anhydride of lysergic acid and trifluoroacetic acid is prepared from 530 mg of d-lysergic acid and 930 mg of trifluoroacetic anhydride in 30 ml of acetonitrile at -20°C. The mixture is allowed to stand at -20°C for about 1.5 hours during which time the suspended material dissolves, and the d-lyserginic acid is converted to the mixed anhydride of liserginic and trifluoroacetic acids. The mixed anhydride can be separated as an oil by evaporating the solvent in vacuo at a temperature about 0°C. The solution containing the mixed anhydride is added to a solution of 300 mg of L-(+)-2-aminopropan-1-ol, and 640 mg of triethylamine in 15 ml of acetonitrile, the triethylamine being employed to displace any L-(+)-2-aminopropan-1-ol from adducts with acid components of the reaction mixture. After 15 minutes of standing at room temperature, the reaction mixture is filtered, and the crystalline material thus obtained is washed with acetonitrile and dried in air. This material is substantially pure d-lysergic acid. The filtrate which contains the desired reaction product is evaporated to dryness in vacuo. The residue is treated with chloroform and water. The chloroform layer is separated, and the aqueous layer is extracted with 4x50 ml portions of chloroform. The combined chloroform extracts washed 4x50 ml portions of cold water in order to remove the residual amounts of amine salts, dried over sodium sulfate and the chloroform is evaporated yielding a crystalline material, which separates when the volume of residual solution is decreased to about 2 ml. The solution is chilled, thereby, causing further crystalline material to separate from solution. The crystalline material is substantially pure ergonovine. The crystalline ergonovine is removed from the solution by filtration, is washed with cold chloroform and dried. MP: 155°-156°C. Paper chromatography shows that this compound is identical with authentic ergonovine produced from crude ergot.

The mother liquors and chloroform washes from the above crystallization of ergonovine are combined, and the solvents are evaporated in vacuo. The residue containing ergonovinine (the "iso" form of ergonovine) is dissolved in 2 ml of ethyl acetate. From this solution crystalline ergonovinine precipitates almost immediately. The crystals are separated by filtration and dried. A sample melts at about 188-190°C. The ergonovinine can be isomerized to ergonovine with alkali for example by employing the method of Stoll and Hofmann, Helvetica Chimica Acta 26, 944 (1943).

The ethyl acetate mother liquor from the preceding isolation of ergonovinine is evaporated to dryness in vacuo and the residue (the mixture of 1-aminopropan-2-ol esters of d-lysergic acid and of d-iso-lysergic acid) is dissolved in 2 ml of ethanol. 0.4 ml of 4 N potassium hydroxide solution in 50% aqueous ethanol are then added, and the resulting mixture is allowed to stand at room temperature in the dark for about two hours. This treatment of the aminopropanol esters of d-lysergic acid and d-isolysergic acid with base rearranges them to the propanol amides of d-lysergic acid and d-iso-lysergic acid, which are ergonovine and ergonovinine, respectively. Solid carbon dioxide is added to the reaction mixture in order to neutralize the potassium hydroxide. The solvents are then removed in vacuo and the residue of

ergonovine and ergonovinine is separated into its components by a chromatography on the basic alumina. Two blue fluorescing zone appear on the alumina column and could light isolate. The mixture (3:1) of benzene and chloroform is used as eluent.

References

Pioch R., US Patent No. 2,736,738; Feb. 28, 1956; Assigned to E. Lilly and Company Indianapolis, Ind. A Corporation of Indiana

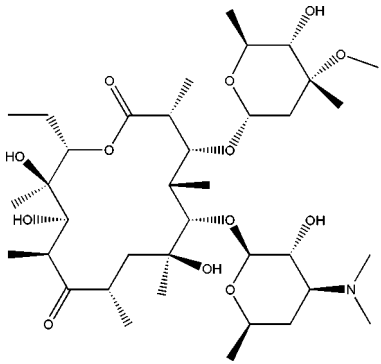
ERYTHROMYCIN

Therapeutic Function: Antibacterial

Chemical Name: Erythromycin A

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 114-07-8

Trade Name	Manufacturer	Country	Year Introduced
Ilotycin	Dista	US	1952
Erythrocin	Abbott	US	1952
E-Mycin	Upjohn	US	1953
Robimycin	Robins	US	1972
Kesso-Mycin	McKesson	US	1973
Staticin	Westwood	US	1980
Eryc	Faulding	US	1980
I/T/S Ilotycin	Lilly	US	1980
Ery Derm	Abbott	US	1980
A/T/S	Hoechst	US	1981

Trade Name	Manufacturer	Country	Year Introduced
Ery-Tab	Abbott	US	1981
T.Stat	Westwood	US	1983
Erymax	Allergan	US	1983
Abomacetin	Mochida	Japan	-
Adamycin	Lederle	-	-
Aknemycin	Hermal	W. Germany	-
Benzamycin	Dermik	US	-
Bisolvanat	Thomae	W. Germany	-
Clafanone	Roche	-	-
Dowmycin	Merrell Dow	-	-
Endoeritrin	Lopez-Brea	Spain	-
Eritrobios	Nuovo. Const. Sanit. Naz.	Italy	-
Eritonormo	Normon	Spain	-
Erycinum	Schering	W. Germany	-
Ery-Max	Astra	Sweden	-
Erythro ST	Nippon Kayaku, Co.	Japan	-
Estromycin	Orion	Finland	-
Ilosone	Lilly	Italy	-
Marocid	Lifepharma	Italy	-
Mistral	Dessy	Italy	-
Orizina	Perga	Spain	-
Pediamycin	Ross	US	-
Polarmicina	Medipolar	Sweden	-
Reciomycin	Recip	Sweden	-
Retcin	D.D.S.A.	UK	-
Rivotrocin	Rivopharm	Switz.	-
RP-Mycin	Reid-Provident	US	-
Taimoxin-F	Taiyo	Japan	-
Ytrocin	Lederle	-	-

Raw Materials

Bacterium Streptomyces erythreus
Starch
Soybean meal

Manufacturing Process

An inoculum broth is prepared having the following composition: 32 pounds starch; 32 pounds soybean meal; 10 pounds corn steep solids; 10 pounds sodium chloride; 6 pounds calcium carbonate; and 250 gallons water.

The broth is placed in an iron tank of 350 gallon capacity and is sterilized by heating it under pressure at a temperature of about 120°C for 30 minutes. The sterilized broth is cooled and inoculated aseptically with spores of Streptomyces erythreus, NRRL 2338. The organism is grown in the broth at about 26°C for a period of 45 hours. During the growth period the broth is

stirred and aerated with sterile air in the amount of about 0.5 volume of air per volume of culture broth per minute.

In a 1,600-gallon iron tank is placed a fermentation broth having the following composition: 153 pounds starch; 153 pounds soybean meal; 51 pounds corn steep solids; 33 pounds calcium carbonate; 51 pounds sodium chloride; and 1,200 gallons water.

The culture broth is sterilized by heating it under pressure at about 120°C for about 30 minutes. The broth is cooled and the above inoculant culture is added aseptically. The organism is grown in the broth for 4 days at a temperature of 26°C. During the growth period the broth is stirred and sterile air is blown through the broth at a rate of about 0.5 volume of air per volume of broth per minute. At the end of the growth period the broth shows an antibiotic activity equivalent to about 150 mcg of erythromycin per ml of broth.

The culture broth (about 1,100 gallons in volume) is adjusted to pH 9.5 with 40% sodium hydroxide solution and is filtered to remove the mycelium, the filtration being assisted by use of 3% of Hyflo Super-Cel, a filter aid, (sold by Johns-Manville Company). The clear filtrate is extracted with amyl acetate in a Podbielniak extractor using a ratio of 1 volume of amyl acetate to 6 volumes of clarified broth. The amyl acetate extract is in turn extracted batchwise with water brought to about pH 5 by the addition of sulfuric acid. Two extractions are carried out, the first with ½ volume and the second with ¼ volume of water adjusted to pH 5 with sulfuric acid. The aqueous extracts are combined and adjusted to pH 8.0 with sodium hydroxide solution.

The alkaline solution is concentrated in vacuo to a volume of about 30 gallons and the solution is then adjusted to pH 9.5 by the addition of aqueous sodium hydroxide and is allowed to stand. Erythromycin separates as a crystalline material. The crystals are filtered off, the mother liquor is adjusted to about pH 8 by the addition of dilute sulfuric acid and is concentrated in vacuo to a volume of about 30 gallons. The solution is adjusted to about pH 9.5 and allowed to stand, whereupon an additional amount of erythromycin separates in crystalline form. The total amount of erythromycin obtained is about 256 grams. The erythromycin is purified by several recrystallizations from aqueous acetone (2:1 mixture), according to US Patent 2,653,899.

References

Merck Index 3624
Kleeman & Engel p. 353
PDR pp. 516, 831, 840, 888, 930, 935, 1307, 1345, 1429, 1557, 1606, 1895
I.N. p. 387
REM p. 1189
Clark, R.J. Jr.; US Patent 2,823,203; February 11, 1958; assigned to Abbott Laboratories
Friedland, W.C., Denison, F.W. Jr. and Peterson, M.H.; US Patent 2,833,696; May 6, 1958; assigned to Abbott Laboratories
Bunch, R.L. and McGuire, J.M.; US Patent 2,653,899; September 29, 1953; assigned to Eli Lilly and Company

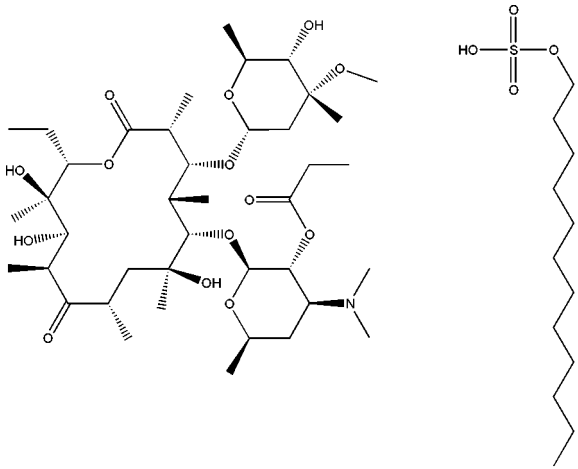
ERYTHROMYCIN ESTOLATE

Therapeutic Function: Antibacterial

Chemical Name: Erythromycin propionate lauryl sulfate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 3521-62-8

Trade Name	Manufacturer	Country	Year Introduced
Ilosone	Dista	US	1958
Biomicron	Isa	Brazil	-
Chemthromycin	Chemo-Drug	Canada	-
Cimetrin	Cimex	Switz.	-
Dreimicina	Dreikehl	Spain	-
Endoeritrin	Lopez-Brea	Spain	-
Erimec	Isola-Ibi	Italy	-
Eriscel	Rachelle	US	-
Eritrazon	Cipan	Portugal	-
Eritrobiotic	Panther-Osfa	Italy	-
Eritrocin	Maipe	Spain	-
Eritrodes	Dessy	Italy	-
Eritroveinte	Madariaga	Spain	-
Erito-Wolf	Incasa-Wolff	Spain	-
Ermysin	Farmos	Finland	-
Ery-Toxinal	Pharma-Selz	W. Germany	-
Erytrarco	Arco	Switz.	-
Erythromyctine	Barlow Cote	Canada	-

Trade Name	Manufacturer	Country	Year Introduced
Erytro-Prot	Proto	Switz.	-
Laurilin	Deva	Turkey	-
Lauromicina	Dukron	Italy	-
Lubomycine	Polfa	Poland	-
Manilina	Lepetit	Italy	-
Neo-Erycinum	Schering	W. Germany	-
Neo-Ilotylin	Lilly	-	-
Novorythro	Novopharm	Canada	-
Propiocine	Roussel	France	-
Proterytrin	Proter	Italy	-
Ritromin	Cophar	Switz.	-
Stellamicina	Pierrel	Italy	-
Togiren	Schwarzhaupt	W. Germany	-

Raw Materials

Monopropionylerythromycin
Sodium lauryl sulfate

Manufacturing Process

16.7 grams of monopropionylerythromycin are dissolved in 50 ml of warm acetone. To the solution are added 6.4 grams of sodium lauryl sulfate dissolved in 50 ml of distilled water containing 2 ml of glacial acetic acid. The white crystalline precipitate of rnonopropionylerythromycin lauryl sulfate which separates is filtered off and dried. It melts at about 135° to 137°C.

References

Merck Index 3625
Kleeman & Engel p. 354
PDR pp. 830, 838, 993, 1606
I.N. p. 388
REM p. 1191
Bray, M.D. and Stephens, V.C.; US Patent 3,000,874; September 19, 1961; assigned to Eli Lilly and Company

ERYTHROMYCIN GLUCEPTATE

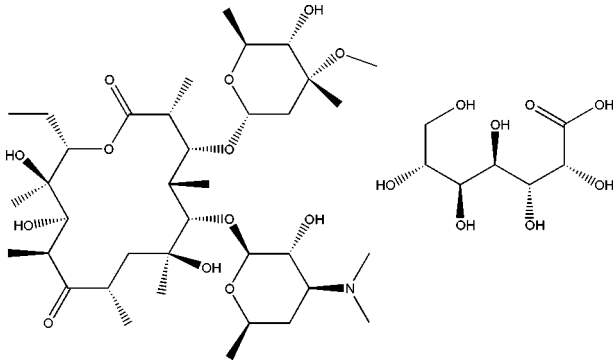
Therapeutic Function: Antibacterial

Chemical Name: Erythromycin glucoheptonic acid salt

Common Name: -

Chemical Abstracts Registry No.: 23067-13-2

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Ilotycin Gluceptate	Dista	US	1954
Erycinum	Schering	-	-
Ilotycin Otic	Lilly	-	-

Raw Materials

Erythromycin
d-Glucoheptonic acid lactone

Manufacturing Process

A solution of 10 grams of d-glucoheptonic acid lactone in 50 ml of distilled water is warmed on a steam bath for about 2 hours to hydrolyze the lactone to the acid. The mixture is cooled and 100 ml of 95% ethanol are added. To the solution of glucoheptonic acid are added about 37 grams of erythromycin and the volume of the reaction mixture is brought to 200 ml by the addition of 95% ethanol. The reaction mixture is stirred for about 2 hours and is filtered through a porcelain filter candle of porosity 02. To provide a sterile product, aseptic technique is used throughout the remainder of the procedure. To the filtered solution are added slowly and with stirring about 1,200 ml of anhydrous ether, to cause precipitation of erythromycin d-glucoheptonate and to keep in solution any excess of unreacted erythromycin. The precipitated erythromycin salt is removed by filtration through a sintered glass funnel, is washed with anhydrous ether and is dried in vacuo. Erythromycin d-glucoheptonate melts over a range of about 95° to 140°C.

References

Merck Index 3626
Kleeman & Engel p. 355
PDR p. 841
I.N. p. 388
REM p. 1190
Shepler, J.T.; US Patent 2,852,429; September 16, 1958; assigned to Eli Lilly and Co.

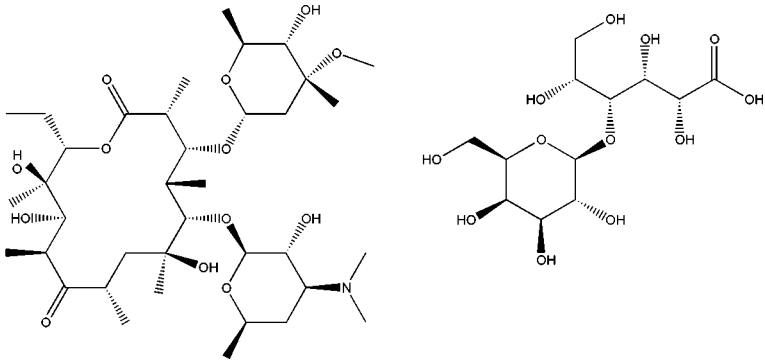
ERYTHROMYCIN LACTOBIONATE

Therapeutic Function: Antibacterial

Chemical Name: Erythromycin lactobionate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 3847-29-8

Trade Name	Manufacturer	Country	Year Introduced
Erythrocin Lactobionate	Abbott	US	1954
Laurylin	Pierrel	Italy	-
Laurylin	Douglas	New Zealand	-
Lubomycine L	Polfa	Poland	-
Proterytrin IV	Proter	Italy	-

Raw Materials

Erythromycin
Lactobiono-delta-lactone

Manufacturing Process

A solution of erythromycin free base is prepared by dissolving 8.0 grams of erythromycin in 25 cc of acetone. 4.0 grams of lactobiono-delta-lactone is dissolved in 25 cc of water. The free lactobionic acid is formed in this solution and it has the molecular formula $C_{12}H_{22}O_{12}$. The two solutions are mixed and evaporated to a gummy residue. This residue is dissolved in 60 cc of water and the solution is frozen and dried in vacuum by lyophilization. The dried residue of erythromycin lactobionate is a white amorphous powder and weighs 11.7 grams. The reaction product has an activity against B. subtilis of 420

units per milligram. Its solubility in water is about 200 mg/cc and the melting point of the white powdery reaction product is 145° to 150°C.

References

Merck Index 3627
Kleeman & Engel p. 356
PDR pp. 519, 872
I.N. p. 388
REM p. 1190
Hoffhine, C.E. Jr.; US Patent 2,761,859; September 4, 1956; assigned to Abbott Laboratories

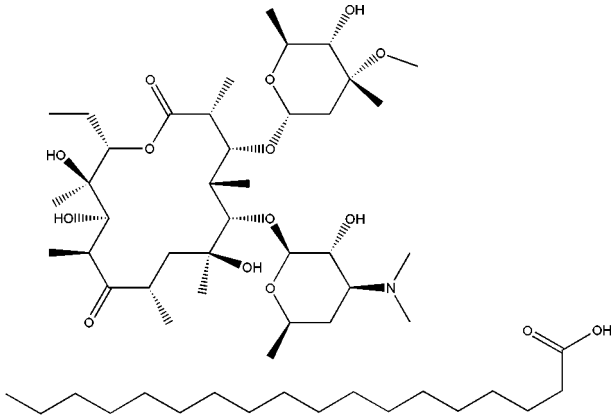
ERYTHROMYCIN STEARATE

Therapeutic Function: Antibacterial

Chemical Name: Erythromycin stearate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 643-22-1

Trade Name	Manufacturer	Country	Year Introduced
Erythrocin Stearate	Abbott	US	1952
Bristamycin	Bristol	US	1971
Ethril	Squibb	US	1972
Erypar	Parke Davis	US	1972
SK-Erythromycin	SKF	US	1972
Qidmycin	Mallinckrodt Inc.	US	1973

Trade Name	Manufacturer	Country	Year Introduced
Pfizer-E	Pfizer	US	1973
Dowmycin-E	Merrell Dow	US	1974
Erythromycin Stearate	Lederle	US	1975
Wyamycin-S	Wyeth	US	1978
Abboticine	Abbott	France	-
Cimetrin	Cimex	Switz.	-
Dura Erythromycin	Durachemie	W. Germany	-
Emisin	Saba	Turkey	-
E-Mycin	Protea	Australia	-
Eratrex	Bristol	-	-
Erisul	Liba	Turkey	-
Eritral	Helvepharm	Switz.	-
Eritro	Iltas	Turkey	-
Eritrolag	Lagap	Switz.	-
Ermysin S	Farmos	Finland	-
Erostin	Knoll	Australia	-
Erymycin	Squibb	-	-
Eryprim	Scarium	Switz.	-
Erythran	Spirig	Switz.	-
Erythrocin	Dainippon	Japan	-
Erythro-S	Sanko	Japan	-
Erythro-Teva	Teva	Israel	-
Ethryn	Faulding	Australia	-
Helvemycin	Helvepharm	Switz.	-
Resibion	Leiras	Finland	-
Rossomicina	Pulitzer	Italy	-
Servitrocin	Servipharm	Switz.	-
Torlamicina	Torlan	Spain	-
Wemid	Bernabo	Argentina	-

Raw Materials

Erythromycin
Stearoyl chloride
1-Ethylpiperidine

Manufacturing Process

To a well-stirred solution of 3.18 grams (10.5 mmol) of stearoyl chloride and 1.24 grams (11.0 mmol) of 1-ethylpiperidine in 50 ml of methylene chloride is added 7.20 grams (10.0 mmol) of erythromycin. After a short time complete solution is obtained and stirring is then discontinued. The solution is allowed to stand overnight. The solution is diluted to 250 ml by the addition of methylene chloride and washed three times with 100 ml portions of water followed by two washes with 5% sodium bicarbonate solution. The organic layer is dried over anhydrous sodium sulfate and filtered, the solvent being removed under diminished pressure. The product is dried to constant weight

at room temperature in a vacuum desiccator.

References

Merck Index 3629
Kleeman & Engel p. 356
PDR pp.521, 993, 1346, 1723, 1999
I.N. p. 388
REM p. 1191
Booth, R.E., Dale, J.K. and Murray, M.F.; US Patent 2,862,921; December 2, 1958; assigned to The Upjohn Company

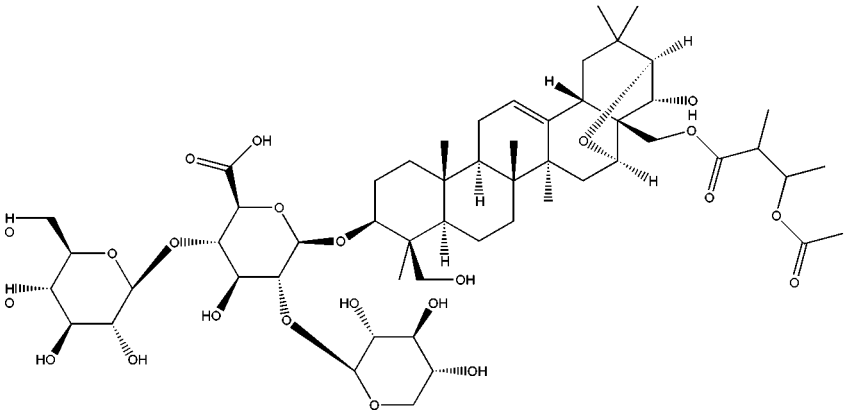
ESCIN

Therapeutic Function: Antiedemic, Capillary protective

Chemical Name: Escin

Common Name: Escin(a)

Structural Formula:



Chemical Abstracts Registry No.: 6805-41-0

Trade Name	Manufacturer	Country	Year Introduced
Aescin	Sinochem	-	-
Yellon	Slovakofarma	-	-
Reparil	MADAUS AG	-	-

Raw Materials

Pulverized horse chestnut seeds
Methanol

Cholesterol

Manufacturing Process

The 1st method of preparation of escin (US Patent No. 3,238,190):

500 g of pulverized horse chestnut seeds were extracted two times for 1 hour with 2.5 L each of aqueous 50% methanol with stirring. The solution was filtered, additional methanol was added thereto to increase the methanol concentration to 65%, and then it was filtered again. The obtained solution containing the extracted saponin had a pH of 5 and was passed through a column of 500 ml (wet volume) of cation exchange resin (Lewatit S-100 of Farben-fabriken Bayer A.G.) which had been treated with 65% methanolic 1% sulfuric acid and then had been washed neutral with 65% methanol. The solution leaving the resin had a pH in the range of about 3 to 4 and was concentrated by distillation to about 4/5 of its original volume. On cooling, crystallization of the escin started and the solution was allowed to stand until the crystallization had been completed. Escin having a melting point of 224-226°C was obtained in a yield of 2%, calculated on the starting material.

The 2st method of preparations of escin (US Patent No. 3,163,636):

An ethereal solution of 1 kg of cholesterol is added to 100 kg of a 10% aqueous-alcoholic horse extract. The resulting emulsion is stirred at 90°C for 1 hour, while the ether is distilled off. The water insoluble saponin-cholesterol precipitate is centrifuged and washed with cold water until the wash water is colorless. The precipitate is air-dried at room temperature. The resulting dust-fine powder is extracted with ether in a Soxhlet apparatus for 10 days. The residue is treated with 20 kg of methanol and the undissolved material is filtered off. The yellowish methanol solution is treated with activated charcoal until it is colorless. The methanol is distilled off in a vacuum, and the residue is dried over phosphorus pentoxide in a vacuum not exceeding 1 mm Hg. The yield of pure sodium escinate obtained thereby is about 0.8 kg (8%).

References

Erbring H., Winkler W.; US Patent No. 3,238,190; Mar. 1, 1966; Assigned to Firma Dr. Adaus and Co. K.G., Cologne-Merheim, Germany

Wagner J., Bosse J.; US Patent No. 3,163,636, Dec. 29, 1964; Assigned to Chemisch-Pharmaceutische Fabrik Adolf Klinge and Co., Munich, Germany

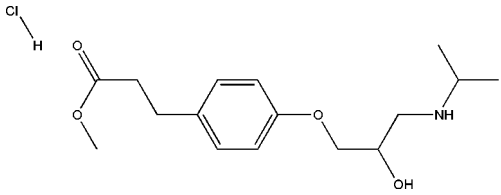
ESMOLOL HYDROCHLORIDE

Therapeutic Function: Beta-adrenergic blocker

Chemical Name: Benzenepropanoic acid, 4-(2-hydroxy-3-((1-methylethyl) amino)propoxy)-, methyl ester hydrochloride

Common Name: Esmolol hydrochloride; Brevibloc

Structural Formula:



Chemical Abstracts Registry No.: 81147-92-4 (Base); 81161-17-3

Trade Name	Manufacturer	Country	Year Introduced
Esmolol hydrochloride	AroKor Holdings Inc.	-	-
Brevibloc	Dupont Co.	-	-
Breviblock	Laboratorios Vargas, S.A.	-	-

Raw Materials

3-(4-Hydroxyphenyl)propionic acid
Potassium carbonate
Isopropylamine
Sulfuric acid
Epichlorohydrin
Hydrogen chloride

Manufacturing Process

A solution of 17 g (0.1 mole) of 3-(4-hydroxyphenyl)propionic acid in 500 mL methanol and 2 mL concentrated sulfuric acid were placed in a Soxhlet extractor charged with 3A molecular sieves. The solution was refluxed for 72 hours and the sieve were exchanged at 24 hour intervals. The reaction medium was then evaporated to an oil which was dissolved in 100 mL toluene and extracted with 100 mL water (3 times). The toluene phase was dried over magnesium sulfate, treated with activated charcoal and evaporated to provide 15 g (80%) of a clear oil. The NMR spectrum was consistent with the methyl 3-(4-hydroxyphenyl)propionate.

The oil described above was utilized directly in the condensation reaction with the epichlorohydrin. A mixture of 0.1 mole of methyl 3-(4-hydroxyphenyl)propionate, 0.2 mole potassium carbonate and 0.4 mole epichlorohydrin in 250 mL acetone was heated to reflux for 24 hours. The reaction medium was then filtered and evaporated. The residue was taken up in 100 mL toluene and washed with 100 mL 1.0 N NaOH and 100 mL water (2 times). The toluene phase was then dried over magnesium sulfate and evaporated to provide the crude product as an oil. Purification was effected by vacuum distillation (156°C/0.4 mm) and provided methyl 3-[4-(2,3-epoxypropoxy)phenyl]propionate. The NMR and IR spectra and elemental analysis data were consistent with the assigned structure.

A mixture of 50 g (0.21 mole) of methyl 3-[4-(2,3-epoxypropoxy)phenyl]propionate and 100 mL of isopropylamine in 100 mL

methanol was heated to reflux for 4 hours. The reaction medium was then evaporated and the resulting oil taken up in methanol and treated with ethereal HCl and provided crystals which were recrystallized in similar fashion to provide 28 g (47%) of white crystals: melting point 85-86°C. The NMR and IR spectra and the elemental analysis data were consistent with the structure of methyl 4-(2-hydroxy-3-((1-methylethyl)amino)propoxy)benzenepropanoate.

In practice it is usually used as hydrochloride.

References

Erhardt P.W., Borgan R.J., O'Donnell J.P.; US Patent No. 4,593,119; June 3, 1986; Assigned to American Hospital Supply Corporation (Evanston, IL)

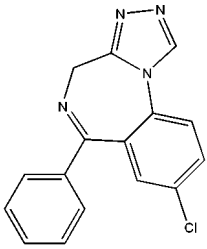
ESTAZOLAM

Therapeutic Function: Hypnotic, Sedative

Chemical Name: 8-Chloro-6-phenyl-4H-[1,2,4]-triazolo[4,3-a][1,4]benzodiazepine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 29975-16-4

Trade Name	Manufacturer	Country	Year Introduced
Eurodin	Takeda	Japan	1975
Nuctalon	Cassenne	France	1978
Esilgan	Cyanamid	Italy	1983
Domnamid	Lundbeck	-	-

Raw Materials

7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-thione
Formic acid hydrazide

Manufacturing Process

A mixture of 5.74 grams (0.020 mol) of 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-thione, 3.6 grams (0.060 mol) of formic acid hydrazide and 200 ml of 1-butanol was refluxed for 3.75 hours with a slow stream of nitrogen bubbling through the mixture. The mixture was concentrated, the residue was suspended in water and the suspension was filtered. The filter cake consisted principally of unchanged starting material. The filtrate was concentrated, ethyl acetate and Skellysolve B hexanes being added during the concentration, giving crude product (2.54 grams), MP 220.5° to 225°C. Recrystallization of this material from ethyl acetate-Skellysolve B hexanes gave 8-chloro-6-phenyl-4H-s-triazolo[4,3-a] [1,4]benzodiazepine, MP 228° to 229°C.

References

Merck Index 3645
Kleeman & Engel p. 357
DOT 11 (5) 185, 211 (1975) & 12 (9) 353 (1976)
I.N. p. 390
Hester, J.B. Jr.; US Patent 3,701,782; October 31, 1972; assigned to The Upjohn Co.

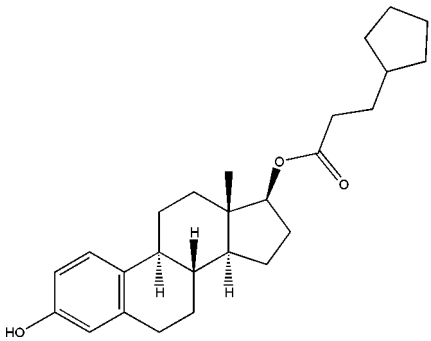
ESTRADIOL CYPIONATE

Therapeutic Function: Estrogen

Chemical Name: Estradiol 17β-cyclopentanepropionate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 313-06-4

Trade Name	Manufacturer	Country	Year Introduced
Depo-Estradiol	Upjohn	US	1952
Depa-Estradiol	Upjohn	US	1952
Cicloestradiolo	Farmigea	Italy	-
Depoestra	Tennessee Pharm.	US	-
Depogen	Hyrex	US	-
E-Cypionate	Legere	US	-
E-Ionate	Reid-Provident	US	-
Estro-Cyp	Keene	US	-
Estrofem	Pasadena	US	-
Estromed-PA	Medics	US	-
Femovirin	Hoechst	-	-
Neoginon Depositum	Lusofarmaco	Italy	-
Oestradiol-Retard	Hepatrol	France	-
Pertradiol	Dexter	Spain	-
Spendepiol	Spencer-Mead	US	-
T-E Cypionate	Legere	US	-

Raw Materials

Estradiol-17β
Cyclopentanepropionyl chloride
Potassium carbonate

Manufacturing Process

A solution of 80.0 grams (0.294 mol) of estradiol-17β in 860 ml of pyridine was cooled in an ice-bath and 130.0 grams (0.81 mol) of cyclopentanepropionyl chloride was added dropwise with stirring during a period of about 20 minutes. The ice-bath was removed, stirring was continued for 1 hour and the reaction mixture was allowed to stand at room temperature overnight. The mixture was warmed on a steam bath and stirred for about 45 minutes, cooled and poured slowly onto about 1,000 grams of ice to which had been added 330 ml of concentrated sulfuric acid. The precipitated product was extracted with 400 to 500 mi of ether, and the extract was washed successively with two 100-ml portions of cold 1 N sulfuric acid, two 100-ml portions of saturated sodium carbonate solution and water until the pH was 7 and dried over anhydrous sodium sulfate. After removal of the drying agent, the solution was concentrated to a volume of about 250 ml and an equal volume of methanol was added.

After chilling overnight a total of 120.0 grams (78.5%) of estradiol 3,17β-dicyclopentanepropionate was obtained which melted at 87° to 90°C. A sample recrystallized from ether methanol for analysis melted at 90.5° to 91.5°C.

To a solution of 2.5 grams (18.1 mmol) of potassium carbonate in 25 ml of water was added 225 ml of methanol followed by 5.0 grams (9.6 mmol) of estradiol 3,17β-dicyclopentanepropionate. The mixture was stirred for 2½ hours at 202°C during which time some precipitation occurred. The mixture

was poured into 700 ml of water with efficient stirring and the precipitated solid was removed by filtration, washed with water and dried.

Recrystallization of the crude product from 80% methanol gave 3.16 grams (83%) of estradiol 17β-cyclopentanepropionate melting at 148° to 151°C. Recrystallization from benzenepetroleum ether raised the MP to 151° to 152°C.

References

Merck Index 3651
Kleeman & Engel p. 360
PDR p. 1033
OCDS Vol. 1 p. 162 (1977)
I.N. p. 391
REM p. 986
Ott, A.C.; US Patent 2.611,773; September 23, 1952; assigned to The Upjohn Company

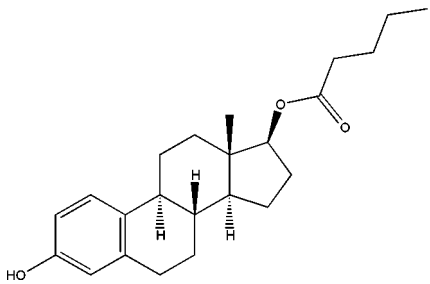
ESTRADIOL VALERATE

Therapeutic Function: Estrogen

Chemical Name: Estradiol valerate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 979-32-8

Trade Name	Manufacturer	Country	Year Introduced
Delestrogen	Squibb	US	1954
Lastrogen	Key	US	1961
Reposo-E	Canfield	US	1961
Estraval PA	Tutag	US	1970
Androtardyl-Oestradiol	S.E.P.P.S.	France	-

Trade Name	Manufacturer	Country	Year Introduced
Ardefem	Burgin-Arden	US	-
Atladiol	I.C.I.	US	-
Depogen	Sig	US	-
Diol-20	Blaine	US	-
Dioval	Keene	US	-
Ditate	Savage	US	-
Dura-Estate	Ries	US	-
Dura-Estradiol	Myers-Carter	US	-
Duratrad	Ascher	US	-
Estate	Savage	US	-
Estral-L	Pasadena	US	-
Femogen	Fellows-Testagar	US	-
Femogex	Stickley	Canada	-
Menaval	Legere	US	-
Oestrogynal	Ascher	W. Germany	-
Ostrin Depo	I.E. Kimya Evi	Turkey	-
Pelanin	Mochida	Japan	-
Primogyn-Depot	Schering	W. Germany	-
Progynon Depot	Schering	W. Germany	-
Progynova	Schering	W. Germany	-
Repestrogen	Spencer-Mead	US	-
Repo-Estra	Central	US	-
Retestrin	Rocky Mtn.	US	-
Span-Est	Scrip	US	-
Testaval	Legere	US	-
Valergen	Hyrex	US	-

Raw Materials

Estradiol
n-Valeric anhydride
Potassium carbonate

Manufacturing Process

2.3 parts of estradiol are mixed with 12 parts of pyridine and 10 parts of n-valeric anhydride and the mixture is heated for some time at 115°C in the oil bath. The cooled solution is mixed with 250 parts of water, whereupon an oil separates; this is extracted with ether. The separated ethereal solution is washed successively with N sulfuric acid, water, N sodium carbonate solution and water and then dried. The ether is then removed and the residue purified by distillation in a high vacuum. The estradiol di-n-valerate forms a yellowish oil according to US Patent 2,205,627.

1 part of estradiol-3,17-n-divalerianate (boiling point at 0.01 mm = 220° to 230°C bath temperature; made, e.g., by the action of n-valeric anhydride on a solution of estradiol in pyridine) is mixed with 50 parts of a solution of 0.5% strength of potassium carbonate in methyl alcohol of 95% strength, and the whole is stirred for some time at 20°C. The oily n-di-valerianate passes

gradually into solution. The solution is neutralized and the precipitate is produced by the addition of about 200 parts of water. This finely crystalline product is filtered and washed successively with water, dilute sodium carbonate solution and again with water. It may be further purified by crystallization from a mixture of methyl alcohol and water. The estradiol-17-mono-n-valerianate melts at 144° to 145°C according to US Patent 2,233,025.

References

Kleeman & Engel p. 655
PDR pp. 1033, 1604
OCDS Vol. 1 p. 162 (1977)
I.N. p. 391
REM p. 986
Miescher, K. and Scholz, C.; US Patent 2,205,627; June 25, 1940; assigned to the Society of Chemical Industry in Basle, Switzerland
Miescher, K. and Scholz, C.; US Patent 2,233,025; February 25, 1941; assigned to Ciba Pharmaceutical Products, Incorporated

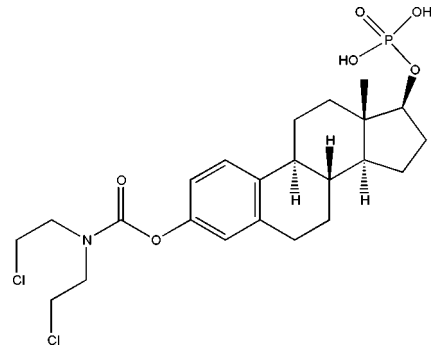
ESTRAMUSTINE PHOSPHATE

Therapeutic Function: Cancer chemotherapy

Chemical Name: Estradiol-3-N-bis(β-chloroethyl)carbamate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 4891-15-0

Trade Name	Manufacturer	Country	Year Introduced
Estracyt	Bastian Werk	W. Germany	1973
Estracyt	Lundbeck	UK	1977
Estracyt	Roche	France	1981

Trade Name	Manufacturer	Country	Year Introduced
Estracyt	Roche	Italy	1981
Emcyt	Roche	US	1982
Estracyt	Abello	Spain	-
Estracyt	Leo	Sweden	-

Raw Materials

Bis(β-chloroethyl)amine
Phosphorus oxychloride
Phosgene
Estradiol

Manufacturing Process

A solution in dry benzene of 82 grams of bis(β-chloroethyl)amine freshly liberated from its hydrochloride is added gradually to a solution of 36 grams of carbonyl chloride (phosgene) in benzene at a temperature below 10°C. The mixture is mechanically stirred for 3 hours, the precipitate of bis(β-chloroethyl)amine hydrochloride is removed by filtration and the benzene is distilled off on a water bath. The residue is distilled in vacuo and the N-chloroformyl-bis(β-chloroethyl)amine is obtained as a pale yellow oil with a BP of 114° to 116°C at 1 mm Hg.

To a solution of 16.35 grams of estradiol in 75 ml of dry pyridine, 21.00 grams of the abovementioned chloroformyl-bis(β-chloroethyl)amine are added while stirring and cooling with ice-water.

The reaction mixture is allowed to stand at room temperature for 60 to 70 hours under the exclusion of air humidity. Then the excess of the chloroformyl compound is hydrolyzed with crushed ice. Ethyl acetate is added and after shaking, the ethyl acetate solution is separated and washed with water, dried over sodium sulfate and evaporated in vacuo to dryness.

The residue is the 3-N-bis(beta-chloroethyl)carbamate of estradiol. The compound melts at 101° to 103°C after recrystallization from isopropyl ether plus hexane (1:1).

To a solution of 2.3 ml of phosphorus oxychloride in 50 ml of dry pyridine is added a solution of 2.2 grams of 3-N-bis(β-chloroethyl)carbamate of estradiol while stirring and at a temperature of about -10°C. The reaction mixture is allowed to stand at about 0°C for 1½ hours, whereupon it is hydrolyzed by pouring it into ice-water. The main part of the pyridine is evaporated in vacuo, whereupon the residue is poured into 100 ml of cold 3.5 N hydrochloric acid with stirring. The precipitate thus obtained is isolated and washed with 0.1 N hydrochloric acid and water.

The compound, which consists of the 17-phosphate of estradiol-3-N-bis(β-chloroethyl)carbamate, melts under decomposition at about 155°C. It is soluble in an aqueous solution of alkali.

References

Merck Index 3653

Kleeman & Engel p. 361
PDR p, 1483
OCDS Vol. 3 p. 83 (1984)
DOT 8 (11) 415 (1972)
I.N. p. 392
REM p. 1155
Fex, H.J., Hogberg, K.B., Konyves, I. and Kneip, P.H.0.J; US Patent 3,299,104; Jan. 17, 1967; assigned to Leo AB, Sweden

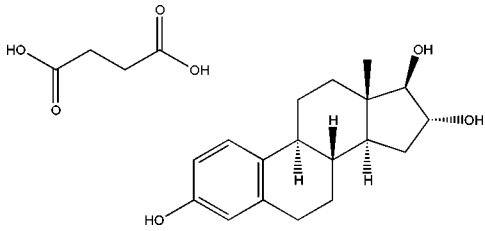
ESTRIOL SUCCINATE

Therapeutic Function: Estrogen

Chemical Name: Estra-1,3,5(10)-triene-3,16α,17β-triol succinate

Common Name: 16α-Hydroxyestradiol

Structural Formula:



Chemical Abstracts Registry No.: 514-68-1

Trade Name	Manufacturer	Country	Year Introduced
Hemostyptanon	Endopancrine	France	1966
Orgastyptin	Organon	W. Germany	-
Ovestin	Ravasini	Italy	-
Synapause	Noury Pharma	W. Germany	-
Synapause	Organon	France	-
Synapasa	Erco	Denmark	-

Raw Materials

Estriol
Succinic anhydride

Manufacturing Process

A mixture consisting of 8 grams of estriol, 20 grams of succinic acid anhydride

and 60 ml of pyridine is heated at 90°C for 4 hours, after which the reaction mixture is poured into water. The aqueous solution is extracted with ether, the ether layer is separated, washed with diluted sulfuric acid and after that with water until neutral, then evaporated to dryness to obtain 14 grams of an amorphous substance. Melting point 82° to 86°C. This drying residue proves to consist of a mixture of estriol disuccinate and estriol monosuccinate, which are separated by repeated crystallization from a mixture of methanol and water.

References

Merck Index 3654
Kleeman & Engel p. 362
I.N. p. 392
Organon Laboratories Limited, England; British Patent 879,014; October 4, 1961

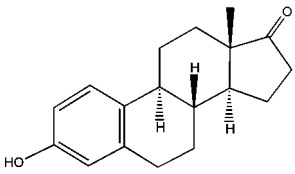
ESTRONE

Therapeutic Function: Estrogen

Chemical Name: Estra-1,3,5(10)-trien-17-one, 3-hydroxy-

Common Name: Estrone; Foliculina; Follicular hormone; Folliculine; α-Follikelhormon; Follikulin; Ketohydroxyestrin; Ketooxyoestrin; Oestrone

Structural Formula:



Chemical Abstracts Registry No.: 53-16-7

Trade Name	Manufacturer	Country	Year Introduced
Estrone	Abbott	-	-
Estrone	Lilly	-	-
Estrone	Wyeth	-	-
Kolpon	Organon	-	-
Ovex	Leo Danmark	-	-
Theelin	Parke Davis	-	-
Menformon	Organon	-	-
Estrusol	Cooper	-	-
Estrusol	Shanghai Lansheng Corporation	-	-

Raw Materials

1-Vinyl-1,2,3,4-tetrahydronaphthalene-1,6-diol
2-Methylcyclopentane-1,3-dione
Triton B
Hydrochloric acid
Hydrogen
Palladium on calcium carbonate

Manufacturing Process

1-Vinyl-1,2,3,4-tetrahydronaphthalene-1,6-diol reacts with 2-methylcyclopentane-1,3-dione in the presence of Triton B in tert-butanol gives a good yield of $\delta^{1,3,5(10),9(11)}$-8,14-secoestratetraen-3-ol-14,17-dione, melting point 124°-126°C (from methanol).

$\delta^{1,3,5(10),9(11)}$-8,14-Secoestratetraen-3-ol-14,17-dione under influence of hydrochloric acid in tetrahydrofurane cyclises into $\delta^{1,3,5(10),8,14}$-estrapentaen-3-ol-17-one, melting point 216°-218°C.

$\delta^{1,3,5(10),8,14}$-Estrapentaen-3-ol-17-one is converted to d,l-8-dehydroestrone by selective hydrogenation with hydrogen, melting point 251°-254°C (from methanol). Exhaustive hydrogenation of $\delta^{1,3,5(10),8,14}$-estrapentaen-3-ol-17-one give d,l-8-isoestrone.

d,l-8-Isoestrone in the presence of hydrochloric acid in tetrahydrofurane isomerizes into d,l-9(11)-dehydroestrone, melting point 262°-265°C (from alcohol).

Hydrogenation of d,l-9(11)-dehydroestrone in tetrahydrofuran in the presence of $Pd/CaCO_3$ yields the estrone, melting point 251°-252°C (from acetone).

References

Zakharichev A.V. et al.; Tetrahedron Letters N 3, pp.171-174
Ananchenko S.N., Torgov I.V.; Tetrahedron Letters N 23, pp.1553-1558

ESTROPIPATE

Therapeutic Function: Estrogen

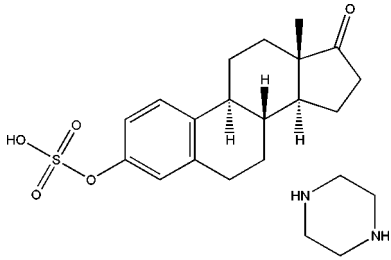
Chemical Name: Estra-1,3,5(10)-trien-17-one, 3-(sulfooxy)-, compd. with piperazine (1:1)

Common Name: Estropipate; Piperazine estrone sulfate; Pipestrone

Chemical Abstracts Registry No.: 7280-37-7

1484 Estropipate

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Estropipate	ZYF Pharm Chemical	-	-
Harmogen	Pharmacia	-	-
Sulestrex Piperazine	Abbott	-	-

Raw Materials

Urine
Extragents: n-butyl alcohol, benzol, chloroform, ether, ethyl acetate
Sodium hydroxide

Manufacturing Process

Step 1). A 100 L quantity of urine is adjusted by the addition of acid (hydrochloric acid is preferred but not essential) to a pH of 4 and extracted with a suitable solvent such as n-butyl alcohol, benzol, chloroform or ether in a continuous extraction apparatus. By using the countercurrent principle we find that this volume of urine may readily be extracted during one day's time and the active fraction transferred completely to a 4 L volume of butyl alcohol. This alcoholic solution is chilled and filtered from salts and other insoluble matter.

Step 2). The butyl alcohol extract is distilled to dryness in vacuum and the brown tarry residue (300 to 600 g). Residue is extracted with benzol using successive volumes of 1.5, 1.0, and 0.75 L of hot benzol, which treatment dissolves the active principle.

Step 3). The benzol solution is then chilled, poured from the insoluble matter and distilled using a vacuum to complete removal of benzol. The residue from the distillation is treated with e 200 mL of butyl alcohol to which solution or suspension 4 L of petroleum ether (boiling point 60-80°C) are added. The resultant solution and suspension then extracted five to eight times with 800 mL of water to each portion of which sufficient 10% NaOH is added to maintain a reaction alkaline to phenolphthalein. In this manner the hormone is transferred to the alkaline aqueous solution. This solution is chilled to 2°C for a day and poured from tarry material which separates. Subsequent purification of the hormone is based upon the fact that it possesses a sufficient acidic property so that it can be removed from certain organic solvents by means of alkali, and that it can be removed in turn from alkaline

solutions by successive extractions with organic solvents.

Step 4). The slightly alkaline aqueous solution is extracted five times with successive (800-1200 mL) portions of ether (peroxide-free). This combined ether extract is then distilled and the active residue treated first with 80 mL butyl alcohol and then with 1500 mL of petroleum ether as in Step 3.

Step 5). The petroleum ether solution is then extracted 4 to 6 times with 300 mL portions of dilute NaOH solution and filtered. The alkaline filtrate is then extracted six times with 400 mL portions of sulfuric ether, thus again transferring the hormone to ether solution. Up to this stage usually 60-75% of the total activity is accounted for. For example in a typical experiment the original crude material contained 300.000 units and the assay of the ether solution obtained at the end of Step 5, assayed fully 200.000 units. In the subsequent steps, however, a considerable amount of scattering of the active material occurs and hence all by-products are worked back into the process.

Step 6). The ether solution is distilled to dryness and yields a yellowish oil. The oil is leached with 200-240 mL of cold 0.2 N NaOH solution, repeating the extraction 4 or 5 times, and combining and filtering the alkaline extract. This aqueous alkaline solution is then extracted with six successive portions of sulfuric ether using about 300 mL of peroxide-free ether extract.

Step 7). The ether solution resulting from Step 6 is distilled and the residue crystallized from 25% aqueous ethyl alcohol or from 25% aqueous acetone.

As an alternative method of procedure, the following may be substituted for Steps 4 to 7 inclusive of the above process. After distilling the benzol, the tarry mass may be stirred directly with 2000 mL of hot 0.3 N NaOH with a mechanical stirrer. The suspension is chilled and the supernatant Liquid poured or siphoned off. Repetition of the extraction two or three times is advisable. The alkaline aqueous solution is then extracted five or six times with 400 mL portions of sulfuric ether, thus transferring the hormone to ether solution. After distillation of the ether the residue is steam distilled as long as a distillate other than water is obtained. The condensed water is removed by vacuum distillation and the small amount of dark tarry residue leached 5 times with 50 mL of hot 0.3 N NaOH. This solution is filtered and the filtrate extracted with sulfuric ether (100 mL, 6 times). The ether solution is distilled and the residue leached with cold 0.3 N NaOH using 20 mL five times. This alkaline solution is filtered and extracted with 50 mL of sulfuric ether five times. Upon distillation of the ether and solution of the residue in a small quantity of hot ethyl alcohol, the hormone separates in semi-crystalline balls which may be filtered off. A further quantity is obtained by adding 3 volumes of water to the alcoholic solution. It may be recrystallized from 25% aqueous ethyl alcohol or from 25% aqueous acetone or from any of the following: chloroform, benzol, ethyl acetate, ethyl ether or petroleum ether. The final product consists of colorless crystals which, when crystallized from dilute alcohol, possess a distinct rhomboid outline. The crystals melt at 242-243°C (248-249°C corrected) with some decomposition.

Hormone was used with piperazine (1:1).

References

Doisy E. A., Groves W., Thayer S. A., Veler C. D.; US Patent No. 1,967,350; October 6, 1930; Assigned to President and Board of Trustees of St. Louis University, St. Louis, Mo.

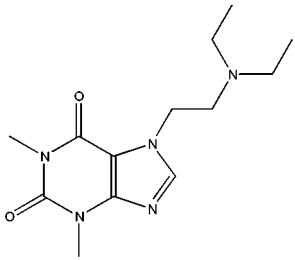
ETAMIPHYLLINE

Therapeutic Function: Diuretic, Cardiotonic, Smooth muscle relaxant, Respiratory stimulant

Chemical Name: 1H-Purine-2,6-dione, 7-(2-(diethylamino)ethyl)-3,7-dihydro-1,3-dimethyl-

Common Name: Etamiphylline; Parephyllin

Structural Formula:



Chemical Abstracts Registry No.: 314-35-2

Trade Name	Manufacturer	Country	Year Introduced
Dalophylline	Arnolds Veterinary Products	-	-
Solufillina	BOI	-	-

Raw Materials

Theophylline
β-Diethylaminoethyl chloride

Manufacturing Process

One mol of theophylline was dissolved in a 1% aqueous solution of 1 mol of caustic soda. One mol of β-diethylaminoethyl chloride was added, and the mixture was boiled for 6 hours with reflux, while stirring.

The product was evaporated to dryness in vacuum, and the dry, pasty residue was taken up in acetone, to separate the desired compound from sodium

chloride associated therewith. The acetone solution was distilled to remove solvent and 1,3-dimethyl-7-(β-diethylamino)ethylxanthine-7-(β-(diethylamino)ethyl)theophylline was obtained as a white mass. MP: 74°C. The product is very soluble in water, alcohol and acetone.

References

Moussalli M.J. et al.; GB Patent No. 669,070; June 14, 1949

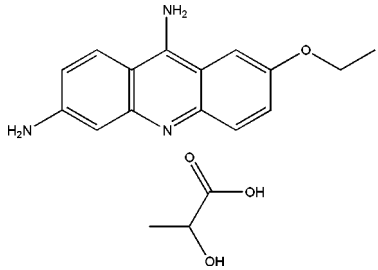
ETHACRIDINE LACTATE

Therapeutic Function: Antiseptic, Antibacterial

Chemical Name: Acridine, 6,9-diamino-2-ethoxy-, lactate

Common Name: Acrinoli lactas; Aethacridinlactat; Etacridin; Etakridin; Ethacridine lactate; Lactacridine

Structural Formula:



Chemical Abstracts Registry No.: 1837-57-6; 442-16-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Rivanol	Sopharma	-	-
Rivanol	Winthrop	-	-
Rivanol	Chinosolfabrik	-	-
Ethodin	Winthrop	-	-
Metifex	Cassella-med	-	-
Amobin	Starke	-	-
Acrinol	Hele Chemical	-	-
Metifex	Artesan	-	-
Metifex	Klosterfrau	-	-
Urocridin	Fresenius	-	-
Urocridin	Schiwa	-	-

Raw Materials

6-Nitro-9-chloro-2-ethoxyacridine
Ethylene glycol
Nitro-4-ethoxy-diphenylamine-6-carboxylic acid
Phosphorous oxychloride
Urea
Iron

Manufacturing Process

A mixture of 250 parts by volume of ethylene glycol, 50 parts by weight of 6-nitro-9-chloro-2-ethoxyacridine (obtained by reaction of 52 parts by weight of 30 nitro-4-ethoxy-diphenylamine-6-carboxylic acid with phosphorous oxychloride), 10 parts by weight of ammonium chloride, and 11 parts by weight of urea were heated to 170°C and stirred for 1 hour at 170°-175°C. Subsequently, the whole was cooled to 100°C, the reaction mixture was introduced into 1000 parts by volume of water, rendered acidic to Congo paper by means of hydrochloric acid and the 6-nitro-9-amino-2-ethoxyacridine precipitated was filtered off. By reduction iron according to Bechamp, 6,9-diamino-2-ethoxy-acridine hydrochloride was obtained with yield of 83% as the yellow needles. The base was prepared by adding an equivalent of NaOH. MP: 124°C.

In practice it is usually used as lactate.

References

D.R. Patent No. 393,411; Oct. 11, 1922; Fabwerke vorm. Meister Lucius and Bruning in Hochst a.M.
Neeb R.; DB Patent No. 1,952,086; Oct. 16, 1969

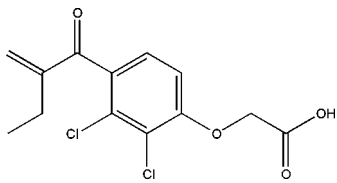
ETHACRYNIC ACID

Therapeutic Function: Diuretic

Chemical Name: [2,3-Dichloro-4-(2-methylene-1-oxobutyl)phenoxy]acetic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 58-54-8

Trade Name	Manufacturer	Country	Year Introduced
Hydromedin	MSD	W. Germany	1966
Edecrin	MSD	UK	1966
Edecrin	MSD	US	1967
Edecrin	MSD	Italy	1967
Edecrine	MSD	France	1968
Crinuryl	Assia	Israel	-
Edecril	Merck-Banyu	Japan	-
Reomax	Bioindustria	Italy	-
Taladren	Malesci	Italy	-

Raw Materials

2,3-Dichlorophenoxyacetic acid
Aluminum chloride
Dimethylamine hydrochloride
n-Butyryl chloride
Paraformaldehyde

Manufacturing Process

Step A: Preparation of 2,3-Dichloro-4-Butyrylphenoxy Acid - The product is prepared using the following ingredients: 22.1 grams (0.1 mol) 2,3-dichlorophenoxyacetic acid; 21.3 grams (0.2 mol) n-butyryl chloride; and 53.3 grams (0.4 mol) powdered aluminum chloride.

The 2,3-dichlorophenoxyacetic acid and n-butyryl chloride are placed in the reaction vessel and stirred while the aluminum chloride is added portionwise over a 45-minute period. The mixture then is heated on the steam bath for 3 hours and allowed to cool to room temperature. The gummy product obtained is added to a mixture of 300 ml of crushed ice and 30 ml concentrated hydrochloric acid. The resulting mixture is extracted with ether and the extract evaporated at reduced pressure. The residue is suspended in boiling water and dissolved by addition of a minimum quantity of 40% sodium hydroxide. After treatment with decolorizing charcoal and filtering, the hot filtrate is made acid to Congo red paper and chilled in ice.

The oil that separates is extracted with ether, the extract dried over anhydrous sodium sulfate and then evaporated at reduced pressure. The residue is dissolved in boiling benzene (75 ml) treated with decolorizing charcoal, filtered, treated with boiling cyclohexane (275 milliliters) and cooled to give 22.3 grams of 2,3-dichloro-4-butyrylphenoxyacetic acid. After several recrystallizations from a mixture of benzene and cyclohexane, then from methyl cyclohexane, next from a mixture of acetic acid and water, and finally from methylcyclohexane, the product melts at 110° to 111°C (corr).

Step B: Preparation of 2,3-Dichloro-4-[2-(Dimethylaminomethyl) Butyryl]Phenoxyacetic Acid Hydrochloride - In a 100 ml round flask equipped with an outlet tube suitable for application of intermittent suction, an intimate mixture of 5.20 grams (0.0179 mol) 2,3-dichloro-4-butyrylphenoxyacetic acid; 0.63 gram (0.0209 mol) paraformaldehyde; 1.59 grams (0.0195 mol) dry dimethylamine hydrochloride; and 4 drops acetic acid is heated on the steam

bath for about 1.5 hours during which period suction is applied for about 1 minute intervals five or six times. Upon cooling, a solid is obtained, The crude reaction product is triturated with ether to give 5.8 grams (85%) of 2.3-dichloro-4-[2-dimethylaminomethyl)butyryl]phenoxyacetic acid hydrochloride in the form of a white solid. After two recrystallizations from a mixture of methanol and ether, the product melts at 165° to 167°C.

Step C: Preparation of 2,3-Dichloro-4-(2-Methylenebutyryl) Phenoxyacetic Acid - The Mannich compound obtained as described above is treated with aqueous sodium bicarbonate to form 2,3-dichloro-4-(2-methylenebutyryl)phenoxyacetic acid, MP 115° to 118°C. Two recrystallizations from a mixture of benzene and cyclohexane give white solid material melting at 118.5° to 120.5°C.

References

Merck Index 3664
Kleeman & Engel p. 364
PDR p. 1173
OCDS Vol. 1 p. 120 (1977) & 2, 103 (1980)
DOT 2 (1) 14 (1966)
I.N. p. 22
REM p. 942
Schultz, E.M. and Sprague, J.M.; US Patent 3,255,241; June 7, 1966; assigned to Merck & Co., Inc.

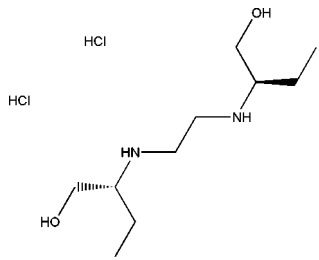
ETHAMBUTOL HYDROCHLORIDE

Therapeutic Function: Antitubercular

Chemical Name: (R)-2,2'-(1,2-Ethanediyldiimino)bis-1-butanol dihydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 74-55-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Myambutol	Lederle	US	1967
Myambutol	Cyanamid	W. Germany	1967
Myambutol	Lederle	UK	1967
Miambutol	Cyanamid	Italy	1967
Myambutol	Lederle	France	1970
Abbutol	Abbott	-	-
Afimocil	Prodes	Spain	-
Anvital	Cheminova Espanola	Spain	-
Cidanbutol	Cidan	Spain	-
Dexambutol	Sobio	France	-
Ebutol	Kaken	Japan	-
EMB-Fatol	Saarstickstoff-Fatol	W. Germany	-
Embutol	Saba	Turkey	-
Esanbutol	Lederle	Japan	-
Etambrin	Lopez-Brea	Spain	-
Etambutol Beta	Beta	Argentina	-
Etambutyl	Stholl	Italy	-
Etapiam	Piam	Italy	-
Etbutol	Leiras	Finland	-
Etibi	Zoja	Italy	-
Etibi	Gerot	Austria	-
Farmabutol	Farmabion	Spain	-
Fimbutol	Sanomed	Spain	-
Inagen	Morgens	Spain	-
Mycobutol	I.C.I.	Italy	-
Olbutam	Carlo Erba	Italy	-
Oributol	Orion	Finland	-
Stambutol	Pharmacal	Finland	-
Sural	Chinoin	Hungary	-
Syntomen	VEB Berlin Chemie	E. Germany	-
Tambutol	Atabay	Turkey	-
Tisiobutol	Capitol	Spain	-
Tuberol	Deva	Turkey	-

Raw Materials

2-Amino-1-butanol
Ethylene dichloride
Hydrogen chloride
Sodium hydroxide

Manufacturing Process

To 27 grams (2.55 mols) of 2-amino-1-butanol was added 100 grams (1.0 mol) of ethylene dichloride. The mixture was heated at reflux and in a few minutes, the exothermic reaction required the removal of exterior heating. After 10 minutes, exterior heating was recommenced for an additional 20 minutes. The hot mixture was then treated with 300 ml of methanol and then cautiously with 84 grams (2.1 mols) of sodium hydroxide in 80 ml of water.

The precipitated sodium chloride was removed by filtration. The excess 2-amino-1-butanol distilled as light yellow oil at 83° to 87°C/13 mm. The viscous residue distilled at 165° to 170°C/0.6 mm as a light yellow oil which tended to solidify in the air condenser; yield, 108 grams.

Recrystallization by dissolving in 80 ml of hot ethanol, adding about 150 ml of petroleum ether (BP 90° to 100°C) and cooling at 5°C overnight, gave 64 grams of white crystals melting at 128° to 132.5°C. This, on recrystallization from 100 ml of 95% ethanol, gave 35 grams of white crystals melting at 134.5° to 136°C and a second crop of 10 grams melting at 132.5° to 134°C which is the meso base. Its dihydrochloride melts at 202° to 203°C.

From the ethanolic filtrates upon addition of 130 ml of about 4 N ethanolic hydrochloric acid and cooling, there was obtained 55 grams of white crystals melting at 176.5° to 178°C and a second crop of 10 grams melting at 171.5° to 174.5°C. This is the dl racemate dihydrochloride.

References

Merck Index 3666
Kleeman & Engel p. 367
PDR p. 1020
OCDS Vol. 1 p. 222 (1977)
DOT 3 (4) 133 (1967)
I.N. p. 395
REM p. 1214
Wilkinson, R.G. and Shepherd, R.G.; US Patent 3,297,707; January 10, 1967; assigned to American Cyanamid Company

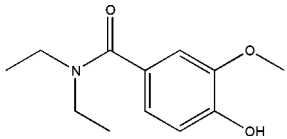
ETHAMIVAN

Therapeutic Function: Central and respiratory stimulant

Chemical Name: N,N-Diethyl-4-hydroxy-3-methoxybenzamide

Common Name: Vanillic acid diethylamide

Structural Formula:



Chemical Abstracts Registry No.: 304-84-7

Trade Name	Manufacturer	Country	Year Introduced
Emivan	U.S.V.	US	1961

Trade Name	Manufacturer	Country	Year Introduced
Corivanil	Sirt-B.B.P.	Italy	-
Romecor	Benvegna	Italy	-
Vandid	Riker	UK	-
Vandid	Lentia	W. Germany	-

Raw Materials

Vanillinic acid
Diethylamine
Phosphorus pentoxide

Manufacturing Process

4 g of vanillinic acid are mixed with 3.6 g of diethylamine, after cooling 2.2 g of phosphorus pentoxide and the same amount of glass powder are added, and then reacted with xylene until a thin paste has been formed. The latter is boiled for some hours in the reflux cooler, moisture being excluded. Decantation follows, and the residue is dissolved by means of a warm solution of potassium carbonate until only glass powder or small amount of impurities remain undissolved, and then the xylene solution is shaken up therewith, The xylene solution is then separated, the aqueous layer is again extracted with ether, and the ether extract is combined with the xylene solution. The mixture is then distilled under the lowest possible pressure, collecting the fraction between 170°C and 250°C (referred to 10 Torr), and purifying it by further fractionation. In this way a slightly yellowish oil is obtained, which crystallizes after some time. By dissolving in ligroin and crystallizing, pure vanillinic acid diethylamide is obtained in the form of white needles; MP 95°C to 95.5°C.

References

Merck Index 3667
Kleeman & Engel p. 365
OCDS Vol. 2 p. 94 (1980)
Kratzl, K. and Kvasnicka, E.; US Patent 2,641,612; June 9, 1953; assigned to Oesterreichishe Stickstoffwerke A.G. (Austria)

ETHAMSYLATE

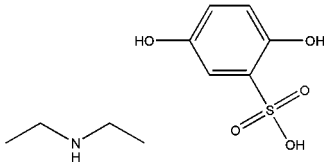
Therapeutic Function: Hemostatic

Chemical Name: 2,5-Dihydroxybenzenesulfonic acid compound with N-ethylethanamine

Common Name: Diethylammonium cyclohexadien-4-ol-1-one-4-sulfonate

Chemical Abstracts Registry No.: 88-46-0

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Dicynone	Delalande	France	1965
Dicynene	Delalande	Italy	1967
Altodor	Delalande	W. Germany	1967
Dicynene	Delalande	UK	1971
Aglumin	Eisai	Japan	-
Dicynone	Torii	Japan	-
Eselin	Ravizza	Italy	-

Raw Materials

Diethylamine bisulfite
1,4-Benzoquinone

Manufacturing Process

163 grams of pure diethylamine bisulfite are added to an ethyl alcohol solution of 108 grams of 1,4-benzoquinone at a temperature not above 5°C and under continuous stirring. After reaction, the alcohol is removed by distilling under vacuum. The product is recrystallized from ethyl alcohol at 80°C. Yield: 198 grams of diethylammonium cyclohexadienol 4-one-1-sulfonate-4. MP 125°C.

References

Merck Index 3669
Kleeman & Engel p. 366
Laboratories OM Societe Anonyme, Switzerland; British Patent 895,709; May 9, 1962

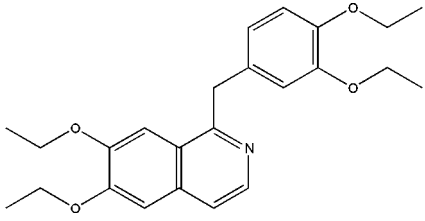
ETHAVERINE

Therapeutic Function: Spasmolytic, Vasodilator, Antiarrhythmic

Chemical Name: Isoquinoline, 1-((3,4-diethoxyphenyl)methyl)-6,7-diethoxy-

Common Name: Aethaverin; Etaverina; Ethaverine; Ethylpapaverine; Tetraethylpapaverine

Structural Formula:



Chemical Abstracts Registry No.: 486-47-5

Trade Name	Manufacturer	Country	Year Introduced
Ethaverine	Shanghai Lansheng Corporation	-	-
Am-Thav	Amid Laboratories Inc.	-	-
Isovex	U.S. Chemical	-	-
Myoquin	Hickam	-	-
Pavaspan	Jamieson-McKames	-	-

Raw Materials

2-Amino-1-(3,4-diethoxy-phenyl)ethanol
(3,4-Diethoxy-phenyl)acetyl chloride
$POCl_3$

Manufacturing Process

(1) 1 part of 2-(3,4-diethoxy-phenyl)-N-[2-(3,4-diethoxy-phenyl)-2-hydroxy-ethyl]acetamide (homoveratroyl hydroxyhomo-veratrylamine), prepared from 2-amino-1-(3,4-diethoxy-phenyl)ethanol and (3,4-diethoxy-phenyl)acetyl chloride, is dissolved in a neutral solvent, such as, for example, chloroform or benzene. Thereupon, 1 to 3 parts of phosphorus oxychloride are added to the resulting solution and the no whole is heated for some hours under a reflux condenser. It should be pointed out here that it is also possible to occur by allowing the amide solution to flow on to the phosphorus oxychloride with the application of heat or in the cold. Instead of this, it is also possible to carry out the reaction in such a way that the reaction mixture is first allowed to stand in the cold. Then it completed by heating. The base produced in both cases is obtained by shaking with chloroform after distilling off the solvent and after alkalization. MP: 145°-147°C.

(2) 1 part of 2-(3,4-dimethoxyphenyl)ethylamine is dissolved in 2 parts of benzene, 1 to 2 parts of phosphorus pentachloride are added thereto and the whole is heated to boiling. After heating for several hours, the base, which is formed can be isolated as above described. MP: 147°C.

(3) 1 part of N-(3,4-diethoxyphenylacetyl)-β-oxy-β-(3,4-diethoxyphenyl)ethylamine is dissolved in benzene or chloroform, mixed with 1 to 3 parts by weight of phosphorus oxychloride and boiled under a reflux condenser for 3 hours whereupon 6,7-diethoxy-1-(3',4'-

diethoxybenzyl)isoquinoline base can be isolated in the usual way. MP: 99°-101°C.

References

Wolf E.; US Patent No. 1,962,224; June 12, 1934

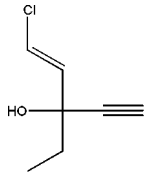
ETHCLORVYNOL

Therapeutic Function: Sedative, Hypnotic

Chemical Name: 1-Chloro-3-ethyl-1-penten-4-yl-3-ol

Common Name: Ethyl β-chlorovinyl ethynyl carbinol

Structural Formula:



Chemical Abstracts Registry No.: 113-18-8

Trade Name	Manufacturer	Country	Year Introduced
Placidyl	Abbott	US	1965
Arvynol	Pfizer	UK	-
Arvynol	Taito Pfizer	Japan	-
Nostel	Dainippon	Japan	-
Roeridorm	Pfizer-Roerig	-	-
Serenesil	Abbott	UK	-

Raw Materials

Acetylene
Lithium
Ethyl β-chlorovinyl ketone

Manufacturing Process

Acetylene was passed into a stirred solution of 3.05 grams (0.44 mol) of lithium in 300 ml of liquid ammonia until the blue color exhibited by the mixture had disappeared. Ethyl β-chlorovinyl ketone (47.4 grams; 0.40 mol) dissolved in 50 ml dry ether was then added to the resulting solution of

lithium acetylide over a period of 20 minutes, during which the color deepened through yellow to reddish-brown. The mixture was stirred under reflux maintained with a Dry Ice condenser for 2 hours. Thereafter, dry ether (200 ml) was added and the ammonia was permitted to evaporate with stirring overnight.

The residue was poured into a slurry of ice and water containing 30 grams (0.50 mol) of acetic acid. After separating the ether layer, the aqueous layer was washed with two 200 milliliter portions of ether. The combined ether extracts were washed with saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate and evaporated in a stream of pure nitrogen. Three successive distillations of the residue gave 46.3 grams (80.2% yield) of a colorless liquid, boiling point 28.5° to 30°C at 0.1 mm Hg.

References

Merck index 3677
Kleeman & Engel p. 369
PDR p. 551
I.N. p. 396
REM p. 1070
Bayley, A. and McLamore, W.M.; US Patent 2,746,900; May 22,1 956; assigned to Chas. Pfizer & Co., Inc.

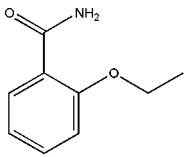
ETHENZAMIDE

Therapeutic Function: Analgesic

Chemical Name: Benzamide, 2-ethoxy-

Common Name: Aethoxybenzamidum; Atenzamide; Aethenzamide

Structural Formula:



Chemical Abstracts Registry No.: 938-73-8

Trade Name	Manufacturer	Country	Year Introduced
Ethenzamide	Tongxiang Hengda Chemical Co., Ltd.	-	-
Aethoxybenzamidum	Saniver	-	-
Etenzamide	Shanghai Lansheng Corporation	-	-

Raw Materials

Salicylic amide
Diethyl sulphate

Manufacturing Process

500 g of salicylic amide are dissolved in 1.5 L of 10% alcohol by means of 146 g of sodium hydroxide. 560 g diethyl sulphate are added, the mixture is frequently shaken during four hours and kept cold. 20 hours later the 2-ethoxy-benzamide is precipitated in a gritty state and is removed by suction and dried at 50°-100°C. The yield is 540 g or about 90%. MP: 130°C.

References

G.B. Patent No. 656,746; Aug. 9, 1948; Assigned: H. Lundberk and Company, Kemisk Pharmaceutisk Laboratorium A/S, a company organized under law of Denmark, of 7, Ottiliavej, Copenhagen, Denmark

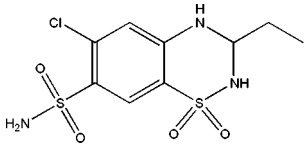
ETHIAZIDE

Therapeutic Function: Diuretic

Chemical Name: 6-Chloro-3-ethyl-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

Common Name: Acthiazidum

Structural Formula:



Chemical Abstracts Registry No.: 1824-58-8

Trade Name	Manufacturer	Country	Year Introduced
Ethiazide	Tokyo Tanabe	Japan	1970
Hypertane	Medo-Chemicals	UK	-

Raw Materials

5-Chloro-2,4-disulfamylaniline
Propionaldehyde

Manufacturing Process

A mixture of 2.9 grams of 5-chloro-2,4-disulfamyl-aniline in 20 ml of anhydrous diethylene glycoldimethylether, 0.44 gram of propionaldehyde and 0.5 ml of a solution of hydrogen chloride in ethyl acetate (109.5 grams hydrogen chloride per 1,000 ml) is heated to 80° to 90°C and maintained at that temperature for 1 hour. The reaction mixture is concentrated under reduced pressure; on addition of water, the product separates and is then recrystallized from ethanol or aqueous ethanol to yield the desired 6-chloro-3-ethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide, MP 269° to 270°C.

References

Merck Index 3681
Kleeman & Engel p. 370
OCDS Vol. 1 p. 358 (1977)
I.N. p. 397
Ciba Limited, Switzerland; British Patent 861,367; February 22, 1961

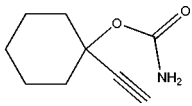
ETHINAMATE

Therapeutic Function: Sedative

Chemical Name: 1-Ethynylcyclohexanol carbamate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 126-52-3

Trade Name	Manufacturer	Country	Year Introduced
Valmid	Dista	US	1955
Valamin	Schering	W. Germany	-

Raw Materials

1-Ethinyl-1-cyclohexanol
Phosgene
Ammonia

Manufacturing Process

A solution of 34 cc (0.5 mol) of liquid phosgene in 150 cc of absolute ether is reacted while cooling with a mixture of sodium chloride and ice, first with 62 grams (0.5 mol) of 1-ethinyl cyclohexanol-1 and then with 64 cc (0.5 mol) of quinoline. The precipitated quinoline chlorohydrate is filtered off and the filtrate is reacted with ammonia in ether. In this manner 45 grams of the carbamic acid ester of 1-ethinyl cyclohexanol are obtained. Yield: 53% of the theoretical yield. The ester boils at 108° to 110°C/3 mm and on recrystallization from cyclohexane, yields colorless needles melting at 94° to 96°C.

References

Merck Index 3682
Kleeman & Engel p. 370
PDR p. 846
I.N. p. 397
REM p. 1070
Junkmann, K. and Pfeiffer, H.; US Patent 2,816,910; December 17, 1957; assigned to Schering AG, Germany

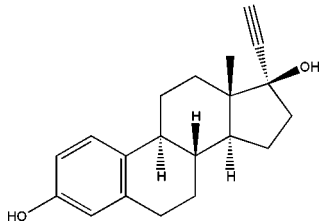
ETHINYLESTRADIOL

Therapeutic Function: Estrogen

Chemical Name: 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol

Common Name: 17-Ethinylestradiol

Structural Formula:



Chemical Abstracts Registry No.: 57-63-6

Trade Name	Manufacturer	Country	Year Introduced
Estinyl	Schering	US	1944
Lynoral	Organon	US	1945
Eticyclol	Ciba	US	1947
Ethinyl Oestradiol	Roussel	France	1950

Trade Name	Manufacturer	Country	Year Introduced
Diogyn-E	Pfizer	US	1953
Provest	Upjohn	US	1964
Norlestrin	Parke Davis	US	1964
Oracon	Mead Johnson	US	1965
Feminone	Upjohn	US	1970
Demulen	Searle	US	-
Duramen	Leo	Sweden	-
Edrol	Virax	Australia	-
Ertonyl	Schering	-	-
Estigyn	Allen and Hanburys	UK	-
Etifollin	Nyegaard	Norway	-
Etivex	Leo	Sweden	-
Farmacyrol	Farmaryn	W. Germany	-
Follikoral	Arcana	Austria	-
Gynetone	Schering	US	-
Gynolett	Labopharma	W. Germany	-
Gynoral	Teva	Israel	-
Kolpi Gynaedron	Artesan	W. Germany	-
Metroval	Kwizda	Austria	-
Oradiol	Van Pelt and Brown	US	-
Orestralyn	McNeil	US	-
Ovahormon	Teikoku Zoki	Japan	-
Ovex	Ratiopharm	W. Germany	-
Progynon	Schering	W. Germany	-
Turisteron	Jenapharm	W. Germany	-
Ylestrol	Ferndale	US	-

Raw Materials

Ammonia
Acetylene
Potassium
Estrone

Manufacturing Process

In about 250 cc of liquid ammonia (cooled with dry ice and acetone) are dissolved about 7.5 g of potassium and into the solution acetylene is passed until the blue color has disappeared (about 3 hours). Then slowly a solution or suspension of 3 g of estrone in 150 cc of benzene and 50 cc of ether is added. The freezing mixture is removed, the whole allowed to stand for about 2 hours and the solution further stirred overnight. Thereupon the reaction solution is treated with ice and water, acidified with sulfuric acid to an acid reaction to Congo red and the solution extracted five times with ether. The combined ether extracts are washed twice with water, once with 5% sodium carbonate solution and again with water until the washing water is neutral. Then the ether is evaporated, the residue dissolved in a little methanol and diluted with water. The separated product is recrystallized from aqueous methanol. The yield amounts to 2.77 g. The 17-ethinyl-estradiol-3,17 thus

obtained melts at 142°C to 144°C.

References

Merck Index 3683
Kleeman & Engel p. 371
PDR pp. 1104, 1297, 1358, 1372, 1616, 1680, 1793, 1952, 1960, 1965, 1983
I.N. p. 397
REM p. 987
Inhoffen, H.H. and Hohlweg, W.; US Patent 2,265,976; December 9, 1941; assigned to Schering Corp.

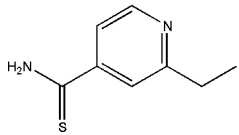
ETHIONAMIDE

Therapeutic Function: Antitubercular

Chemical Name: 2-Ethyl-4-pyridinecarbothioamide

Common Name: Ethyl isonicotinic thioamide

Structural Formula:



Chemical Abstracts Registry No.: 536-33-4

Trade Name	Manufacturer	Country	Year Introduced
Trecator	Theraplix	France	1959
Trecator-SC	Ives	US	1962
Ethimide	Tanabe	Japan	-
Ethinamin	Takeda	Japan	-
Ethiocidan	Cidan	Spain	-
Iridocin	Bayer	-	-
Itiocide	Kyowa	Japan	-
Nicotion	Leiras	Finland	-
Rigenicid	Gedeon Richter	Hungary	-
Sertinon	Daiichi	Japan	-
Teberus	Dainippon	Japan	-
Thiomid	Nikken	Japan	-
Thioniden	Kaken	Japan	-
Trescatyl	May and Baker	UK	-
Tubenamide	Seiko	Japan	-
Tubermin	Meiji	Japan	-

Trade Name	Manufacturer	Country	Year Introduced
Tuberoid	Sankyo	Japan	-
Tuberoson	Shionogi	Japan	-

Raw Materials

Methyl ethyl ketone
Ethyl oxalate
Hydrogen chloride
Phosphorus oxychloride
Phosphorus pentoxide
Ammonia
Cyanacetamide
Ethanol
Hydrogen
Hydrogen sulfide

Manufacturing Process

Ethyl Propionyl-Pyruvate: 36 grams of methyl ethyl ketone and 73 grams of ethyl oxalate are condensed in the presence of sodium ethylate, the reaction mixture being refluxed in an alcoholic medium. 28 grams of the desired product having a boiling point of 100° to 105°C/6 mm are obtained.

3-Cyano-4-Carbethoxy-6-Ethyl-2-Pyridone: 205 cc of 60% alcohol, 22 grams of the product just obtained, 11 grams of cyanacetamide and 4.5 cc of piperidine are refluxed. 19 grams of product having a melting point of 211°C are obtained.

4-Carboxy-6-Ethyl-2-Pyridone: 30 grams of the cyanopyridone just obtained are refluxed with concentrated hydrochloric acid. 13.5 grams of product having a melting point of 308°C are obtained.

2-Chloro-4-Carbethoxy-6-Ethyl-Pyridine: 26 grams of the product just obtained are treated with 81 grams of phosphorus pentachloride in 45 cc of phosphorus oxychloride. The phosphorus oxychloride is distilled off in a vacuum and the residue is treated with absolute alcohol. After distillation there are obtained 24 grams of product having a boiling point of 127° to 131°C/8 mm.

Ethyl-2-Ethyl-Isonicotinate: 10 grams of the ester just obtained dissolved in 80 cc of absolute alcohol containing 5.5 grams of potassium acetate are hydrogenated catalytically on 5% palladium black. 8 grams of product having a boiling point of 120° to 124°C/14 mm are obtained.

2-Ethyl-Isonicotinic-Amide: 20 grams of the ether just obtained are agitated, with 25 cc of concentrated ammonia. 11 grams of product having a melting point of 131°C are obtained.

2-Ethyl-Isonicotinic Nitrile: The 11 grams of the amide just obtained are treated with 15 grams of phosphorus anhydride at 160° to 180°C in a vacuum. 6 grams of a liquid residue are obtained.

Alpha-Ethyl-Isonicotinic Thioamide: The 6 grams of the liquid just obtained, in solution in 15 cc of absolute alcohol containing 2 grams of triethanolamine, are treated with hydrogen sulfide. 6.5 grams of the desired product having a melting point of 166°C are obtained.

References

Merck Index 3686
Kleeman & Engel p. 371
PDR p. 1982
OCDS Vol. 1 p. 255 (1977)
I.N. p. 397
REM p. 1216 Chimie et Atomistique, France: British Patent 800,250: August 20, 1958

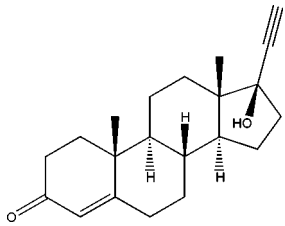
ETHISTERONE

Therapeutic Function: Progestin

Chemical Name: Pregn-4-en-20-yn-3-one, 17-hydroxy-, (17α)-

Common Name: Aethinyltestosteron; Anhydrohydroxyprogesterone; Aethisteron; Ethinyltestosterone; Ethisterone; Etisteron(a); Praegninum; Pregneninolone; Pregnin

Structural Formula:



Chemical Abstracts Registry No.: 434-03-7

Trade Name	Manufacturer	Country	Year Introduced
Lutocyclin	Ciba	-	-
Lutocylol	Ciba	-	-
Ora-Lutin	Parke Davis	-	-
Progestoral	Organon	-	-
Pranone	Schering	-	-
Syngestrotabs	Pfizer	-	-
Trosinone	Abbott	-	-
Ethisterone	Wuhan Sanjing Chemical Co., Ltd.	-	-
Ethisterone	Jiangxi Yuneng Pharmchem Co., Ltd.	-	-

Raw Materials

$\delta(^{5:6})$-17-Ethinyl-androstendiol-(3:17)
Tertiary aluminum butylate

Manufacturing Process

0.5 part of $\delta^{5:6}$-17-ethinyl-androstendiol-(3:17) is dissolved in 10 parts of dry acetone, the solution is mixed with a solution of 1 part of tertiary aluminum butylate in 40 parts of absolute toluene and the whole is heated to boiling in a reflux apparatus for 21 hours. After the reaction mixture has cooled it is diluted with 100 parts of ether, the solution is washed with dilute mineral acid and with water, dried and the solvent is evaporated. In this manner there is obtained $\delta^{5:6}$-17-ethinyl-androstene-3-one-17-ol (ethisterone); MP: 270°-272°C; it may be recrystallized from ethyl acetate.

References

Ruzicka L.; US Patent No. 2,272,131; Feb. 3, 1942; Assigned to Ciba Pharmaceutical Products, Incorporated, Summit, N.J. a corporation of New Jersey

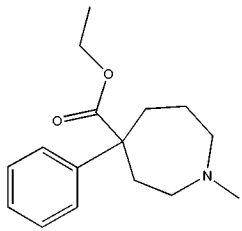
ETHOHEPTAZINE

Therapeutic Function: Analgesic

Chemical Name: Hexahydro-1-methyl-4-phenylazepine-4-carboxylic acid ethyl ester

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 77-15-6

Trade Name	Manufacturer	Country	Year Introduced
Zactane	Wyeth	US	1957
Equagesic	Wyeth	US	-
Mepro	Schein	US	-

Trade Name	Manufacturer	Country	Year Introduced
Panalgin	Padil	Italy	-
Zactipar	Wyeth	UK	-
Zactirin	Banyu	Japan	-

Raw Materials

Phenylacetonitrile	N-(2-Chloroethyl)dimethylamine
Sodium amide	Trimethylene bromide
Sulfuric acid	Ethanol

Manufacturing Process

As a starting material, phenylacetonitrile was reacted with N-(2-chloroethyl)dimethylamine. This then underwent the following reaction sequence.

Preparation of 1-Dimethylamino-3-Cyano-3-Phenyl-6-Bromohexane: 65.8 grams (0.35 mol) of 2-phenyl-4-dimethylaminobutyronitrile in 350 cc of absolute ether was dripped into a stirred suspension of 17.5 grams (0.45 mol) of sodamide in 350 cc of absolute ether during 1 hour, keeping the reaction mixture under a dry nitrogen atmosphere. The mixture was stirred an additional hour at room temperature and then 1 hour at reflux temperature. The mixture was diluted with 250 cc of absolute ether, cooled in an ice bath, then, while stirring, a solution of 74.7 grams (0.37 mol) of trimethylene bromide in 250 cc of absolute ether added at once. The yellow suspension continued to be stirred at ice-bath temperature for 1 hour, then at room temperature for 1 hour, and finally at reflux temperature for 3 hours. The mixture was cooled and the sodium bromide, which had precipitated in quantitative yield, was filtered off and washed with ether. The light yellow ethereal filtrate contained the product. This compound could be stored for some time in a hydrocarbon solvent, e.g., n-heptane, at +5°C.

Preparation of 4-Phenyl-4-Cyano-N-Methyl Azacycloheptane Methobromide: A 0.1 M nitrobenzene solution of 1-dimethylamino-3-cyano-3-phenyl-6-bromohexane was kept at 100°C for 1 hour whereby the quaternary salt precipitated out; MP 246° to 247°C.

Preparation of 4-Phenyl-4-Cyano-N-Methyl Azacycloheptane: 6.2 grams (0.02 mol) of the methobromide quaternary salt was suspended in 150 cc of tetralin. While vigorously stirring, the mixture was heated to its reflux temperature, whereupon the solid began to disintegrate and go into solution. The stirring and refluxing was continued 1 hour, then the mixture cooled, water added, and the layers separated. The tetralin solution was extracted with 3 M aqueous hydrochloric acid, the acid extract washed with ether, then made alkaline with aqueous sodium hydroxide and extracted with ether. The ether extracts were dried, filtered, and the solvent distilled off. Vacuum distillation of the liquid residue gave the tertiary amine, BP 119° to 121°C/0.25 mm.

Preparation of 4-Phenyl-4-Carbethoxy-N-Methyl Azacycloheptane: A solution of 8.4 grams (0.04 mol) of the cyclic aminonitrile in 10.6 grams concentrated sulfuric acid and 2.6 grams water was kept at 110° to 120°C (bath

temperature) for 3 hours. Then, while repeatedly adding absolute ethanol, 95% aqueous ethanol was slowly distilled off during 16 hours. The reaction mixture was concentrated to 50 cc, cooled, poured into 200 cc of a cold saturated aqueous solution of sodium carbonate and extracted with ether. The ether extract after drying and filtering yielded, by distillation, the aminoester, BP 122° to 124°C/0.3 mm.

References

Merck Index 3691
Kleeman & Engel p. 373
PDR p. 1606
OCDS Vol. 1 p. 303 (1977)
I.N. p. 398
REM p. 1116
Diamond, J. and Bruce, W.F.; US Patent 2,666.050; January 12, 1954; assigned to American Home Products Corporation

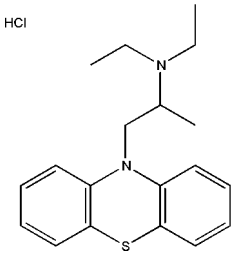
ETHOPROPAZINE HYDROCHLORIDE

Therapeutic Function: Antiparkinsonian

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

Common Name: Profenamin

Structural Formula:



Chemical Abstracts Registry No.: 1094-08-2; 522-00-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Parsidol	Warner Lambert	US	1954
Parkin	Yoshitomi	Japan	1973
Parsidol	Sevenet	France	1981
Dibutil	Bayer	-	-
Lysivane	May and Baker	US	-
Parsitan	Rhone Poulenc	Canada	-

Trade Name	Manufacturer	Country	Year Introduced
Parsotil	Rhodia Iberica	Spain	-
Rodipal	Deutsches Hydrierwerk	E. Germany	-

Raw Materials

Phenthiazine
Methyl iodide
2-Chloro-1-diethylaminopropane
Magnesium
Hydrogen chloride

Manufacturing Process

6.2 grams of phenthiazine in 100 cc of warm dry benzene was added during 1 hour with stirring, and in an atmosphere of hydrogen, to the Grignard reagent prepared from 1 gram of magnesium, 6.2 grams of methyl iodide, and 20 cc of dry ether. After boiling for 30 minutes, a solution of 6.6 grams of 2-chloro-1-diethylamino propane in 10 cc of dry benzene was added during 1 hour to the boiling solution, and heating was maintained for a further 1.5 hours.

The reaction mixture was then cooled and treated with aqueous ammonium chloride and chloroform added to dissolve an oil at the interface of the benzene and aqueous layers. The chloroform-benzene extract was extracted with 2 N hydrochloric acid and the acid extract was basified at 5° to 10°C with 50% aqueous sodium hydroxide.

There was obtained a mixture of N-(2'-diethylamino-2'-methylethyl)phenthiazine and N-(2'-diethylamino-1'-methylethyl)phenthiazine in the form of a viscous yellow oil, BP 202° to 205°C/2 mm. This oil was treated in ethereal solution with ethereal hydrogen chloride and gave a white solid which was fractionally crystallized from ethylene dichloride. The less soluble fraction, N-(2'-diethylamino-2'-methylethyl)phenthiazine hydrochloride formed colorless rhombs, MP 223° to 225°C. The more soluble N-(2'-diethylamino-1'-methylethyl)phenthiazine hydrochloride was obtained as colorless prismatic needles, MP 166° to 168°C.

References

Merck Index 3696
Kleeman and Engel p. 765
PDR p. 1380
OCDS Vol. 1 p. 373 (1977)
I.N. p. 807
REM p. 932
Berg, S.S. and Ashley, J.N.; US Patent 2,607,773; August 19, 1952; assigned to Societe des Usines Chimiques Rhone-Poulenc, France

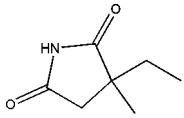
ETHOSUXIMIDE

Therapeutic Function: Anticonvulsant

Chemical Name: 3-Ethyl-3-methyl-2,5-pyrrolidinedione

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 77-67-8

Trade Name	Manufacturer	Country	Year Introduced
Zarontin	Parke Davis	US	1960
Suxinutin	Parke Davis	W. Germany	1960
Zarontin	Parke Davis	UK	1960
Zarontin	Parke Davis	France	1965
Zarontin	Parke Davis	Italy	1966
Asamid	Pliva	Yugoslavia	-
Emeside	Lab. For Appl. Biol.	UK	-
Epileo-Petitmal	Eisai	Japan	-
Ethymal	Hillel	Israel	-
Etomal	Orion	Finland	-
Petinamide	Gerot	Austria	-
Petnidan	Desitin	W. Germany	-
Pyknolepsinum	ICI Pharma	W. Germany	-
Simatin	Geistlich	Switz.	-

Raw Materials

Ethyl cyanoacetate
Hydrogen cyanide
Sulfuric acid
Methyl ethyl ketone
Sodium hydroxide
Ammonia

Manufacturing Process

α-Ethyl-α-methylsuccinimide is known in the prior art as a chemical entity, having been prepared according to the method described by Sircar, J. Chem. Soc., 128:600 (1927), and characterized in J. Chem. Soc., 128:1254 (1927).

In its manufacture, methyl ethyl ketone is condensed with ethylcyanoacetate to give ethyl-2-cyano-3-methyl-2-pentenoate. That, in turn, adds HCN to give ethyl-2,3-dicyano-3-methyl pentanoate. Saponification and decarboxylation gives 2-methyl-2-ethyl succinonitrile. Heating with aqueous NH_3 gives the diamide which loses NH_3 and cyclizes to ethosuximide.

References

Merck Index 3697
Kleeman & Engel p. 373
PDR p. 1396
OCDS Vol. 1 p. 228 (1977)
I.N. p. 398
REM p. 1078
Miller, C.A. and Long, L.M.; US Patent 2,993,835; July 25, 1961; assigned to Parke, Davis and Company

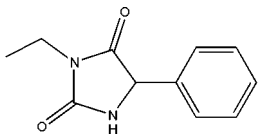
ETHOTOIN

Therapeutic Function: Anticonvulsant

Chemical Name: 3-Ethyl-5-phenyl-2,4-imidazolidinedione

Common Name: 3-Ethyl-5-phenylhydantoin

Structural Formula:



Chemical Abstracts Registry No.: 86-35-1

Trade Name	Manufacturer	Country	Year Introduced
Peganone	Abbott	US	1957
Accenon	Dainippon	Japan	-

Raw Materials

Benzaldehyde cyanohydrin
Urea
Hydrogen chloride
Ethyl iodide

Manufacturing Process

Benzaldehyde cyanohydrin is reacted with urea to displace the hydroxyl group of the cyanohydrin. That intermediate is treated with HCl to convert the urea nitrogen to a nitrile. The resultant imine is hydrolyzed to the phenylhydantoin. Alkylation with ethyl iodide gives ethotoin, as described by A. Pinner in Chem. Ber. 21, 2325 (1888).

References

Merck Index 3698
Kleeman & Engel p. 374
PDR p. 546
OCDS Vol. 1 p. 245 (1977)
I.N. p. 398
REM p. 1083
Close, W.J.; US Patent 2.793.157; May 21, 1957; assigned to Abbott Laboratories

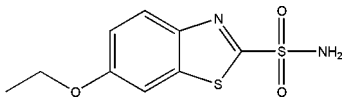
ETHOXZOLAMIDE

Therapeutic Function: Diuretic

Chemical Name: 6-Ethoxy-2-benzothiazolesulfonamide

Common Name:

Structural Formula:



Chemical Abstracts Registry No.: 452-35-7

Trade Name	Manufacturer	Country	Year Introduced
Cardrase	Upjohn	US	1957
Ethamide	Allergan	US	1967
Glaucotensil	Farmila	Italy	-
Redupressin	Thilo	W. Germany	-
Poenglausil	Poen	Argentina	-

Raw Materials

6-Ethoxybenzothiazole-2-thiol
Sodium hypochlorite
Ammonia
Potassium permanganate

Manufacturing Process

Preparation of 6-Ethoxybenzothiazole-2-Sulfenamide: A solution prepared by dissolving 21.0 grams (0.1 mol) of 6-ethoxybenzothiazole-2-thiol, Sebrell and Boord, J. Am. Chem. Soc. 45: 2390 to 2399 (1923), in 75 ml of water containing 5 grams of sodium hydroxide, and 75 ml of 10% sodium hypochlorite solution were added simultaneously to 300 ml of concentrated ammonium hydroxide which was cooled to 0°C, and vigorously stirred. During

the addition the temperature was not allowed to rise above 5°C. The resulting solid was recovered by filtration, washed thoroughly with water, and dried at room temperature under reduced pressure. There was obtained 21 grams of 6-ethoxybenzothiazole-2-sulfenamide melting at 132° to 155°C (decomposition). Recrystallization from ethyl acetate gave a product melting at 140.5° to 143°C (decomposition).

Preparation of 6-Ethoxybenzothiazole-2-Sulfonamide: A solution of 3.39 grams (0.015 mol) of the sulfenamide in 100 ml of acetone was treated dropwise, with stirring, with a solution of 3.5 grams of potassium permanganate in 100 ml of water. The temperature rose to 42°C. After stirring an additional 10 minutes the reaction mixture was filtered to remove manganese dioxide, the latter was washed with 100 ml of warm water, and the combined filtrates were concentrated under reduced pressure to remove acetone. The residual solution was treated with charcoal, filtered and acidified with concentrated hydrochloric acid. After standing in the refrigerator for 4 hours the solid sulfonamide was recovered by filtration, washed with water and dried. There was obtained 2.37 grams of 6-ethoxybenzothiazole-2-sulfonamide melting at 180° to 190°C. Recrystallization from ethyl acetate-Skellysolve B gave 1.25 grams of material melting at 188° to 190.5°C.

References

Merck Index 3704
Kleeman & Engel p. 374
OCDS Vol. 1 p. 327 (1977)
DOT 14 (5) 207 (1978)
I.N. p. 399
Korman, J.; US Patent 2,868,800; January 13, 1959; assigned to The Upjohn Company

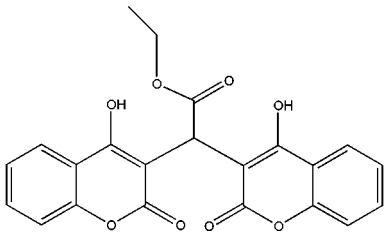
ETHYL BISCOUMACETATE

Therapeutic Function: Anticoagulant

Chemical Name: 4-Hydroxy-α-(4-hydroxy-2-oxo-2H-1-benzopyran-3-yl)-2-oxo-2H-1-benzopyran-3-acetic acid ethyl ester

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 548-00-5

Trade Name	Manufacturer	Country	Year Introduced
Tromexan	Geigy	US	1950
Biscouron	Ayerst	-	-
Stabilene	Auclair	France	-

Raw Materials

Benzotetronic acid
Glyoxylic acid ethyl ester ethyl alcoholate

Manufacturing Process

7 g of benzotetronic acid are dissolved in 750 cc of water at boiling temperature and there after 10.5 g of glyoxylic acid ethyl ester ethyl alcoholate are added. After a short while the liquid becomes turbid and gradually a white deposit is separated. The deposit is filtrated and dried in vacuo. The melting point is 172°C to 174°C; after recrystallization from methyl alcohol 153°C to 154°C.

The crude product is dissolved in sodium lye, filtrated by means of animal charcoal precipitated by means of hydrochloric acid, and recrystallized from methyl alcohol. The melting point is 153°C to 154°C.

References

Merck Index 3719
Kleeman & Engel p. 375
I.N. p. 400
Rosicky, J.; US Patent 2,482,511; September 20, 1949; assigned to Spojene Farmaceuticke Zovody (Czechoslovakia)

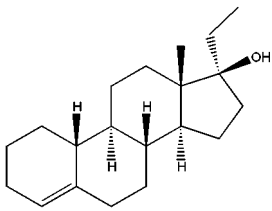
ETHYLESTRENOL

Therapeutic Function: Anabolic

Chemical Name: 19-Nor-17α-pregn-4-en-17-ol

Common Name: 17α-Ethyl-17β-hydroxy-19-norandrostene

Structural Formula:



Chemical Abstracts Registry No.: 965-90-2

Trade Name	Manufacturer	Country	Year Introduced
Maxibolin	Organon	US	1964
Durabolin	Organon	-	-
Orabolin	Organon	UK	-
Orgabolin	Organon-Sankyo	Japan	-
Orgaboline	Organon	France	-

Raw Materials

17α-Ethyloestradiol-3-ethylether
Lithium
Ethylamine

Manufacturing Process

4.5 grams of lithium cut to small pieces are added to 435 ml of dry ethylamine which is cooled in ice. After the solution turns blue 9 grams of 17α-ethyloestradiol-3-ethylether dissolved in 900 ml of dry ether are added.

Subsequently, the reaction mixture is stirred at a temperature of 0° to 5°C for 20 hours, after which 50 ml of absolute ethanol are added. Then the ethylamine is distilled off at low pressure. To the remaining solution 50 ml of ether and 50 ml of water are added. The water layer is separated and extracted a few times with ether. The collected ether extracts are added to the ethereal layer, after which this ethereal solution is washed with a 2 N hydrochloric acid solution, subsequently with a saturated sodium bicarbonate solution, and then with water. The ethereal solution is then dried on sodium sulfate and finally evaporated to dryness.

The crude product is distributed between equal parts of petroleum ether and 70% methanol. From the petroleum ether layer 5.6 grams of Δ^4-17α-ethyl-17β-hydroxy-19-norandrostenewith a melting point of about 50°C are obtained.

References

Merck Index 3750
Kleeman & Engel p. 375
PDR p. 1286
OCDS Vol. 1 p. 170 (1977)
I.N. p. 400
REM p. 1001
Szpilfogel, S.A. and de Winter, M.S.; US Patent 2,878,267; March 17, 1959; assigned to Organon Inc.
Szpilfogel, S.A., Hanegraaf, J.A. and van Dijck, L.A.; US Patent 3,112,328; Nov. 26,1963; assigned to Organon Inc.

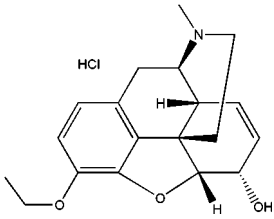
ETHYLMORPHINE HYDROCHLORIDE

Therapeutic Function: Analgesic, Antitussive, Mydriatic

Chemical Name: Morphinan-6-ol, 7,8-didehydro-4,5-epoxy-3-ethoxy-17-methyl-, (5-α,6-α)-, hydrochloride

Common Name: Aethomorphinum; Ethylmorphinhydrochlorid; Codethyline; Codetilina; Ethomorphine; Ethylmorphine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 125-30-4; 76-58-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Ethylmorphine hydrochloride	Yick-Vic Chemicals and Pharmaceuticals (HK) Ltd.	-	-
Cosylan	Pfizer	-	-
Cocillana-Etyfin	Pharmacia Upjohn Co.	-	-

Raw Materials

Morphinane sodium
Benzene sulfonic acid methylethyl ester

Manufacturing Process

To a solution of 199 parts of morphinane sodium in 900 parts of methanol was added a solution of 60 parts of benzene sulfonic acid methylethyl ester. The mixture was stirred at heating to give the ethylmorphine.

In practice it is usually used as hydrochloride.

References

Merck Index, Monograph number: 3876, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
DE Patent No. 131,980; Apr. 19, 1901; Assigned to E. Merck, Darmstadt

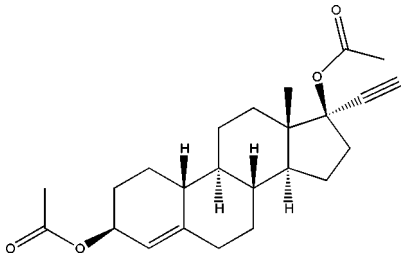
ETHYNODIOL DIACETATE

Therapeutic Function: Progestin; Oral contraceptive ingredient

Chemical Name: 3β,17β-Diacetoxy-17α-ethynyl-4-estrene

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 297-76-7

Trade Name	Manufacturer	Country	Year Introduced
Lutometrodiol	Searle	France	1965
Ovulen	Searle	US	1966
Femulen	Searle	Italy	1971
Femulen	Searle	UK	1973
Alfames E	Dr. Kade	W. Germany	-
Conova	Searle	UK	-
Demulen	Searle	US	-
Luteonorm	Seronol	Italy	-
Metrodiol	Byla	France	-
Metrulen	Searle	US	-
Ovamin	Searle	UK	-

Raw Materials

17α-Ethynyl-19-norandrost-4-ene-3β,17β-diol (ethynodiol)
Acetic anhydride

Manufacturing Process

A mixture of 30 parts of 17α-ethynyl-19-norandrost-4-ene-3β,17β-diol, 360 parts of dry pyridine, and 111 parts of acetic anhydride, under nitrogen, is stirred and heated at the reflux temperature for about 5 hours. This reaction mixture is cooled, then poured into approximately 3,500 parts of cold water and the resulting aqueous mixture is stirred at room temperature for about 0.5 hour. The precipitate which forms is collected by filtration, then is washed on the filter with water and dried in air. This solid material is extracted into ether, and the ether solution is washed successively with 10% aqueous

hydrochloric acid and 5% aqueous sodium bicarbonate.

Drying over anhydrous sodium sulfate containing decolorizing carbon followed by removal of the solvent by distillation at reduced pressure affords an oil which solidifies on standing. Recrystallization of that solid by dropwise dilution with water of a methanol solution affords 17α-ethynyl-19-norandrost-4-ene-3β,17β-diol 3,17-diacetate, melting at about 126° to 127°C.

References

Merck Index 3807
Kleeman & Engel p. 384
PDR p. 1680
OCDS Vol. 1 pp. 165, 186 (1977)
DOT4 (1) 9 (1966)
REM p. 991
Klimstra, P.D.; US Patent 3,176,013; March 30, 1965; assigned to G.D. Searle and Co.

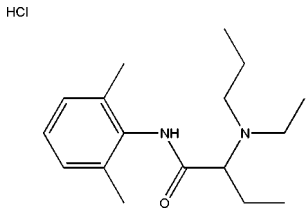
ETIDOCAINE HYDROCHLORIDE

Therapeutic Function: Local anesthetic

Chemical Name: N-(2,6-Dimethylphenyl)-2-(ethylpropylamino)butanamide hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 36637-19-1; 36637-18-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Duranest	Astra	US	1976
Duranest	Astra	W. Germany	1976
Duranest	Bellon	France	1977

Raw Materials

2-Bromobutyric acid

Sulfonyl chloride	2,6-Xylidine
Potassium iodide	n-Propylamine
Diethyl sulfate	Hydrogen chloride

Manufacturing Process

α-(n-Propylamino)-n-butyro-2,6-xylidide(0.243 mol) and freshly distilled diethyl sulfate (1.6 mols were mixed in a flask equipped with reflux condenser, drying tube and stirrer. The mixture was stirred for 5 hours at 90°C. After cooling, water (110 ml) was added with stirring for 15 minutes followed by 4M HCl (110 ml). The solution was washed with ether (3 X 100 ml) and made alkaline with 7M NaOH to pH 10-11. The freed base was taken up in ether (3 X 100 ml); the extracts were dried over sodium sulfate, filtered and evaporated. The residue was dissolved in absolute ether (200 ml) and the hydrochloride prepared by addition of ethereal hydrogen chloride. The precipitate was filtered, washed with ether, and recrystallized twice from absolute ethanol/ether and from isopropanol/isopropylether; MP 203°C to 203.5°C; yield: 0.126 mol (52%).

The starting material is prepared by reacting 2-bromobutyric acid with sulfonyl chloride to give the acid chloride. It is then reacted with 2,6-xylidine, then with potassium iodide followed by n-propylamine.

References

Merck Index 3811
Kleeman & Engel p. 376
PDR p. 591
OCDS Vol. 2 p. 95 (1980)
I.N. p. 403
REM p. 1051
Adams, H.J.F., Kronberg, G.H. and Takman, B.H.; US Patent 3,812,147; May 21, 1974; assigned to Astra Pharmaceutical Products, Inc.

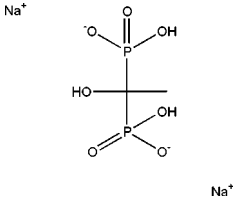
ETIDRONATE DISODIUM

Therapeutic Function: Bone calcium regulator

Chemical Name: (1-Hydroxyethylidene)bisphosphonic acid disodium salt

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 7414-83-7; 2809-21-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Etidron	Gentili	Italy	1977
Didronel	Procter and Gamble	US	1978
Didronel	Gist Brocades	UK	1980
Didronel	Procter and Gamble	Switz.	1980
Didronel	Beytout	France	1982
Diphos	Boehringer Mannheim	W. Germany	1982
Difosfen	Rubio	Spain	-
Diphosphonat	Procter and Gamble	US	-

Raw Materials

Phosporous acid
Acetic anhydride
Sodium hydroxide

Manufacturing Process

Phosphorous acid was premixed with acetic acid to form a 50 wt % solution of phosphorous acid dissolved in acetic acid. The acids were mixed on a molar basis of 1.36:1, acetic acid to phosphorous acid, and this corresponded on a mol percentage basis to 57.6% acetic acid and 42.4% phosphorous acid. Acetic anhydride was continuously metered into a stream of the phosphorous acid-acetic acid mixture to form the reaction solution. The acetic anhydride was metered into the acid mixture at a mol ratio of 1.33 mols of acetic anhydride per mol of phosphorous acid. The metering rates were 18.5 lb/hr of the phosphorous acid/acetic acid premixed solution and 15.1 lb/hr acetic anhydride. The reaction solution was continuously passed through a heat exchanger where it was heated to 190°F then it was continuously fed into a two stage back-mix reaction zone where due to the heat of reaction the temperature rose to 275°F. The average residence in the reaction zone was 27 min. The reaction zone consisted of two back-mix reactors each having a capacity of 7.5 pounds of the reaction solution. A stream of reaction solution was continuously with drawn from the second reactor and continuously mixed with a stream of water which was being metered at a rate of 2 lb/hr. This amount of water corresponded to 18% excess over the theoretical amount necessary to hydrolyze all of the acetyl-containing compounds in the reaction solution to free acids. The hydrolyzed solution was continuously passed through a heat exchanger and cooled to room temperature after which the solution was continuously passed to a crystallizer where, with agitation, the ethane-1-hydroxy-1,1-diphosphonic acid crystallized. The slurry was then filtered and the crystals were recovered and dried. Analysis of the product showed a conversion rate of phosphorous acid to ethane-1-hydroxy-1,1-diphosphonic acid of 86%. Sodium hydroxide may be used to give the disodium salt.

References

Merck Index 3812
Kleeman & Engel p. 377
PDR p. 1275

DOT 4 (3) 104 (1978)
I.N. P.23
REM p. 979
Rogovin, L., Brawn, D.P. and Kalberg, J.N.; US Patent 3,400,147; September 3, 1968; assigned to The Procter and Gamble Co.

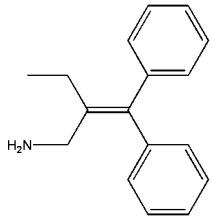
ETIFELMINE

Therapeutic Function: Central stimulant, Antihypotensive

Chemical Name: 2-Diphenylmethylenebutylamine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 341-00-4

Trade Name	Manufacturer	Country	Year Introduced
Etifelmine	Giulini	W. Germany	1963
Tensinase D	Chemiphar	Japan	1975
Gilutensin	Giulini	W. Germany	-

Raw Materials

2-Ethyl-3-hydroxy-3,3-diphenyl propionitrile
Hydrogen
Hydrogen chloride

Manufacturing Process

(a) Preparation of 2-ethyl-3-hydroxy-3,3-diphenyl-propylamine: 10 g of 2-ethyl-3-hydroxy-3,3-diphenyl-propionitrile are dissolved in 200 ml of methanol. 10 ml of acetic acid are added to the mixture, and the mixture is hydrogenated in the presence of platinum as catalyst. After the hydrogen uptake or consumption has ceased, the reaction is interrupted, the catalyst is filtered off and the filtrate is evaporated in vacuo to dryness. The residue is dissolved in water and, after the addition of 1 ml of hydrochloric acid, the solution extracted with ether. The acidified ether-phase is discarded. The aqueous phase is made alkaline with ammonia, whereby the base crystallizes

out. The crystals are recovered and recrystallized from methanol. The melting point of the 2-ethyl-3-hydroxy-3,3-diphenyl-propylamine thereby obtained is 132°C.

(b) Preparation of 2-ethyl-3,3-diphenyl-1-amino-propene-(2)-hydrochloride: 5 g of 2-ethyl-3-hydroxy-3,3-diphenyl-propylamine are dissolved in 50 ml of acetic acid. Gaseous hydrogen chloride is passed through the solution for 10 minutes, and thereafter the solution is boiled for one hour under reflux. The solution is then distilled to dryness. The residue is dissolved in water and the acidified solution extracted with ether. The aqueous phase is separated, made alkaline with ammonia and extracted with ether. The ether phase is dried over sodium sulfate, the ether distilled off and the residue is dissolved in methanolic hydrogen chloride. On the addition of absolute ether, the hydrochloride of 2-ethyl-3,3-diphenyl-1-amino-propene-(2) is crystallized out. The crystalline substance thereby obtained has a melting point of 232°C.

References

Merck Index 3813
Kleeman & Engel p. 377
I.N. p. 403
Gebruder Giulini, G.m.b.H.; British Patent 936,041; September 4, 1963

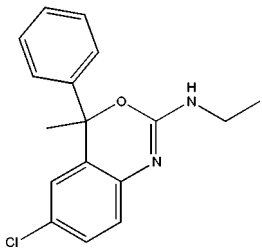
ETIFOXINE

Therapeutic Function: Tranquilizer

Chemical Name: 2-Ethylamino-4-methyl-4-phenyl-8-chloro-4H-3,1-benzoxazine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 21715-46-8

Trade Name	Manufacturer	Country	Year Introduced
Stresam	Beaufour	France	1971

Raw Materials

5-Chloro-2-amino-α-methyl-α-phenylbenzyl alcohol
Ethyl mustard oil (ethyl isothiocyanate)
Mercury oxide

Manufacturing Process

(a) A solution of 50 g of 5-chloro-2-amino-α-methyl-α-phenylbenzyl alcohol in 150 ml of ether is mixed with 35 g of ethyl mustard oil and kept for 48 hours at room temperature. Part of the solvent is then distilled off under reduced pressure and the crystalline residue is filtered to yield 53 g (= 79% of theory) of pure 5-chloro-2-(ω-ethylthioureido)-α-methyl-α-phenylbenzyl alcohol melting at 101°C to 103°C. On crystallization from benzene + petroleum ether a higher-melting modification melting at 112°C to 114°C is sometimes obtained.

(b) 33.5 g of the thiourea derivative obtained under (a) are mixed with 43 g of mercury oxide in 300 ml of ethanol and stirred and refluxed for 30 minutes. The reaction mixture is filtered hot and the solvent is evaporated, to yield 2-ethyl-amino-4-methyl-4-phenyl-6-chloro-4H-3,1-benzoxazine as an almost colorless oil which soon solidifies in crystalline form. Recrystallization from petroleum ether furnishes 26 g (= 87% of theory) of colorless crystals melting at 90° to 92°C.

References

Merck Index 3814
DFU 6 (9) 550 (1981)
DOT 9 (6) 242 (1973)
Kuch, H., Schmitt, K., Seidl, G. and Hoffmann, I.; US Patent 3,725,404; April 3, 1973; assigned to Farbwerke Hoechst AG

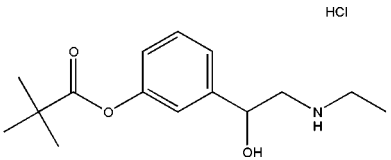
ETILEFRINE PIVALATE HYDROCHLORIDE

Therapeutic Function: Adrenergic

Chemical Name: 1-(3'-Pivaloyloxyphenyl)-2-ethylaminoethanol-1 hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 943-17-9; 709-55-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Circupon	Troponwerke	W. Germany	1972
Amphodyn	Klinge	W. Germany	-
Effortil	Boehringer Ingelheim	W. Germany	-
Ethyfron	Sawai	Japan	-
Eti-Puren	Klinge	W. Germany	-
Hishiherin-S	Hishiyama	Japan	-
Hyurina	Seiko	Japan	-
Presotona	Erco	Denmark	-
Pulsamin	Teikoku	Japan	-
Soledoton M	Soledum	W. Germany	-
Theoral	S.S. Pharm	Japan	-
Tonus-Forte	Sanorania	W. Germany	-
Tri-Effortil	Boehringer Ingelheim	W. Germany	-

Raw Materials

1-(3'-Hydroxyphenyl)-2-(N-benzylaminomethyl)ethan-1-one
Pivalic anhydride
Hydrogen

Manufacturing Process

30 parts of 1-(3'-hydroxyphenyl)-2-(N-benzylaminomethyl)-ethan-1-one are mixed with 100 parts of pyridine and 30 parts of pivalic anhydride and dissolved while warming. After heating for 1 hour under reflux, the acylation is complete. After concentrating the reaction solution, the product is precipitated from acetone/ether. Yield: 96.4% of 1-(3'-pivaloyloxyphenyl)-2-(N-benzylaminomethyl)-ethan-1-one.

3 parts of palladium/charcoal (10% strength) are prehydrogenated in water, thereafter 10 parts of 1-(3'-pivaloyloxyphenyl)-2-(N-benzylaminoethyl)-ethan-1-one, dissolved in a 10-fold amount of water, are added dropwise at room temperature and hydrogenation is carried out until 1 mol of hydrogen has been taken up. After filtering off the catalyst, a further 3 parts of palladium/charcoal are added and hydrogenation is carried out until a further mol of hydrogen has been taken up. The catalyst is separated off and after removal of the solvent the hydrogenation product is reprecipitated from acetone/petroleum ether and from methanol/ether until it is pure according to thin layer chromatography. Yield: 38.8% of 1-(3'-pivaloyloxyphenyl)-2-ethylaminoethanol-1 hydroxide, melting point 208°C to 209°C.

References

Merck Index 3815
DFU 4 (6) 413 (1979)
Kleeman & Engel p. 378
I.N. p.403

Chemisch-Pharmazeutische Fabrik, Adolf Klinge and Co.; British Patent 1,358,973; July 3, 1974

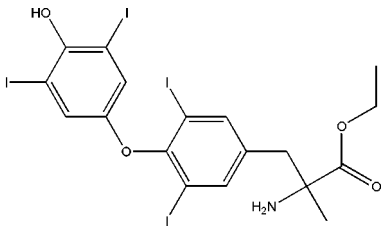
ETIROXATE

Therapeutic Function: Antihyperlipoproteinemic

Chemical Name: O-(4-Hydroxy-3,5-diiodophenyl)-3,5-diiodo-α-methyltyrosine ethyl ester

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 17365-01-4

Trade Name	Manufacturer	Country	Year Introduced
Skleronorm	Gruenenthal	W. Germany	1977

Raw Materials

α-Methylthyroxine
Ethanol

Manufacturing Process

7.91 g of α-methyl thyroxine are suspended in 150 cc of ethanol. While heating, the solution is saturated with dry hydrogen chloride. Thereafter, the solvent is distilled off at reduced pressure. The residue is dissolved in a mixture of ethanol and water (1:1). Adding a 5% solution of sodium hydrogen carbonate in water, the ethyl ester of α-methyl thyroxine precipitates; melting point: 156°C to 157°C after recrystallization from ethanol. The yield is 6.05 g, i.e., 74% of the theoretical yield.

References

Merck Index 3820
Kleeman & Engel p. 378

DOT 13 (5) 197 (1977)
I.N. p. 404
Kummer, H. and Beckmann, R.; US Patent 3,930,017; December 30, 1975

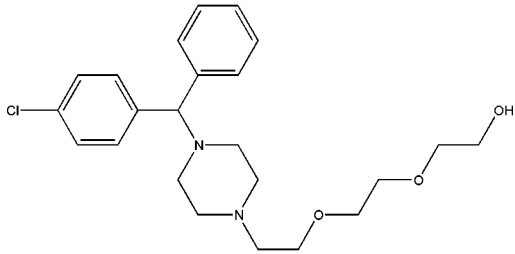
ETODROXIZINE

Therapeutic Function: Hypnotic

Chemical Name: 2-[2-[2-[4-(p-Chloro-α-phenylbenzyl)-1-piperazinyl]ethoxy] ethoxy]ethanol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 17692-34-1

Trade Name	Manufacturer	Country	Year Introduced
Vesparax	UCB Chemie	W. Germany	1973
Drimyl	Cassenne	France	-
Indunox	UCB	-	-

Raw Materials

1-(2-Hydroxyethyl)piperazine
p-Chlorobenzhydryl chloride
Diethylene glycol
Thionyl chloride
Potassium carbonate

Manufacturing Process

A mixture of 1.5 mols of 1-(2'-hydroxyethyl)piperazine and 1 mol of p-chlorobenzhydryl chloride is heated at 150°C for 15 minutes. The substance is dissolved in water, basified by caustic soda and extracted with benzene.

By purifying the benzene extract in vacuo, a 75% yield is obtained of 1-p-chlorobenzhydryl-4-(2'-hydroxyethyl)piperazine which has a boiling point of 205°C/0.02 mm Hg.

0.2 mol of 1-p-chlorobenzhydryl-4-(2'-hydroxyethyl)piperazine is dissolved in 300 cc of dry benzene and a solution of 36 grams of thionyl chloride in 100 cc of dry benzene is added cold with agitation. Reflux heating is then carried out until sulfur dioxide has ceased to be evolved.

The solvent is evaporated in vacuo, the residue is dissolved in anhydrous acetone and the hydrochloride formed is filtered. The corresponding base is liberated by treating the aqueous solution of this hydrochloride with an excess of potassium carbonate. A benzene extraction is effected and the benzene solution of the base is dried over potassium carbonate.

This benzene solution is then added to an equimolecular solution of the monosodium derivative of diethyleneglycol in a considerable excess of diethyleneglycol. The benzene is removed by distillation and the residue is heated in a boiling water-bath with agitation for 3 hours.

The excess diethyleneglycol is removed in vacuo and the residue dissolved in water and then in benzene. The benzene extract is washed several times in water, then purified in vacuo. The 1-p-chlorobenzhydryl-4-(2'-[2"-(2"'-hydroxyethoxy)-ethoxy]-ethyl)piperazine obtained distills at 250°C/0.01 mm Hg.

References

Merck Index 3823
Kleeman & Engel p. 379
I.N. p. 404
Morren, H.; British Patent 817,231; July 29, 1959

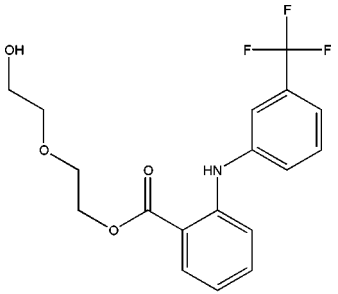
ETOFENAMATE

Therapeutic Function: Antiinflammatory

Chemical Name: 2-[[-3-(Trifluoromethyl)phenyl]amino]benzoic acid-2-(2-hydroxyethoxy) ethyl ester

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 30544-47-9

Trade Name	Manufacturer	Country	Year Introduced
Rheumon	Troponwerke	W. Germany	1977
Rheumon	Bayer	Switz.	1979
Bayrogel	Bayropharm	Italy	1980
Flogoprofen	Wassermann	Spain	-

Raw Materials

N-(3-Trifluoromethylphenyl)anthranilic acid
2-(2-Chloroethoxy)ethanol

Manufacturing Process

16.0 g (0.05 mol) of the potassium salt of N-(3-trifluoromethylphenyl)-anthranilic acid are dissolved in 60 ml of dimethylformamide and heated to 110°C, and 6.2 g (0.05 mol) of 2-(2-chloroethoxy)-ethanol are slowly added. The reaction mixture is then heated to boiling for 2 hours. The precipitated potassium chloride is filtered off and the solvent is removed by evaporation. The residue is separated over a column with 400 g of silica gel (particle size 0.05 to 0.2 mm), using a 1:1 mixture of cyclohexane and glacial acetic acid as eluting agent. 16.0 g of the 2-(2-hydroxyethoxy)-ethyl ester of N-(3-trifluoromethylphenyl)-anthranilic acid are obtained in the form of a pale yellow oil which does not crystallize and cannot be distilled.

References

Merck Index 3824
Kleeman & Engel p. 380
DOT 14 (1) 9 (1978)
I.N. p.404
Boltze, K.H., Brendler, O. and Lorenz, D.; US Patent 3,692,818; September 19, 1972; assigned to Troponwerke Dinklage & Co. (W. Germany)

ETOFIBRATE

Therapeutic Function: Antihyperlipidemic

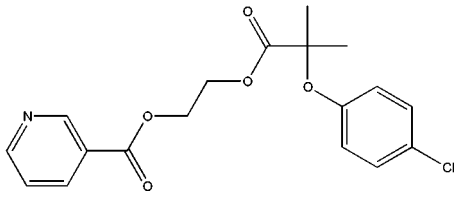
Chemical Name: 2-Hydroxyethylnicotinate-2-(p-chlorophenoxy)-2-methyl propionate

Common Name: -

Chemical Abstracts Registry No.: 31637-97-5

Trade Name	Manufacturer	Country	Year Introduced
Lipo-Merz	Merz	W. Germany	1974
Noflevan	Alter	Spain	-

Structural Formula:



Raw Materials

2-(p-Chlorophenoxy)-2-methylpropionic acid
Ethylene oxide
Nicotinic acid

Manufacturing Process

A stream of ethylene oxide is passed through a solution of 107 g of 2-(p-chlorophenoxy)-2-methylpropionic acid and 2 g of zinc chloride in 200 ml of toluene, previously heated to between 55°C and 60°C, until 24 g of the gas have been dissolved. The reaction is allowed to continue for five hours, with gentle stirring. After this time has elapsed, the solution is cooled and washed successively with water, dilute ammonia and water until its pH becomes neutral. It is dried over anhydrous sodium sulfate, the solvent is separated off under vacuum, and the resulting liquid is the monoglycol ester of 2-(p-chlorophenoxy)-2-methylpropionic acid.

The product thus prepared is sufficiently pure to be used in the subsequent reaction. In this way, 107 g of the ester are prepared, which represents a yield of 83%.

To a solution of 93.8 g of the monoglycol ester in 500 ml of benzene, there are added 55 g of nicotinic acid chloride and 25 g of trimethylamine dissolved in 200 ml of benzene. The solution is stirred gently at a temperature of 60°C for two hours. After this time, the solution is cooled and washed successively with water, dilute hydrochloric acid, dilute ammonia and water until neutrality, it is dried over anhydrous sodium sulfate, and the solvent is evaporated under vacuum: in this way 110 g of glycol 2-(p-chlorophenoxy)-2-methylpropionate nicotinate is prepared, which represents a yield of 84%. The product is a slighly yellow oil having a refraction index of n_D^{20} =1.5422 and which is distilled with decomposition at 214°C at a pressure of 0.3 mm.

References

Kleeman & Engel p, 380
DOT 11 (2) 459 (1975)
I.N. p. 405
Letelier, C.S. and Grafulla, F.C.; US Patent 4,028,369; June 7, 1977; assigned to Alter S.A. (Spain)

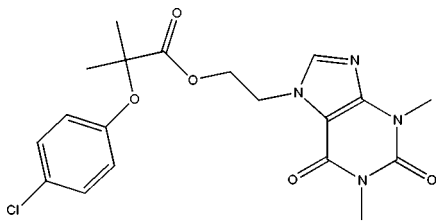
ETOFYLLINE CLOFIBRATE

Therapeutic Function: Antihyperlipidemic

Chemical Name: 1-(Theophyllin-7-yl)ethyl 2-(p-chlorophenoxy)isobutyrate

Common Name: Theofibrate

Structural Formula:



Chemical Abstracts Registry No.: 519-37-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Duolip	Merckle	W. Germany	1981
Duolip	Mepha	Switz.	1981

Raw Materials

2-(p-Chlorophenoxy)isobutyric acid
7-Hydroxyethyltheophylline

Manufacturing Process

107.3 g (0.5 mol) 2-(p-chlorophenoxy)isobutyric acid and 56.0 g (0.25 mol) 7-hydroxyethyltheophylline were suspended together in 250 ml xylene. They were heated together for 15 hours in a water separator following the addition of 1.5 g p-toluenesulfonic acid. The solution was next agitated with dilute sodium bicarbonate solution (0.5 mol $NaHCO_3$), water washed and evaporated in a rotary evaporator.

The residue was then crystallized from isopropanol, yielding 58.0 g (55% yield) of 1-(7-theophyllinyl)-2-ethyl[2-(p-chlorophenoxy)-isobutyrate] . The compound had a melting point of 131°C to 132°C.

References

Merck Index 9113
DFU 2 (12) 800 (1977)
Kleeman & Engel p. 381
DOT 17 (9) 370 (1981)
I.N. p. 405

Metz, G. and Specker, M.; US Patent 3,984,413; October 5, 1976; assigned to L. Merckle K.G. (W. Germany)

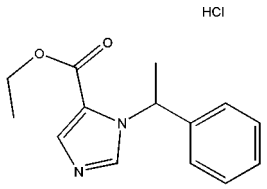
ETOMIDATE HYDROCHLORIDE

Therapeutic Function: Hypnotic

Chemical Name: 1-(1-Phenylethyl)-5-(ethoxy-carbonyl)imidazole hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 33125-97-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Hypnomidate	Janssen	W. Germany	1977
Hypnomidate	Janssen	UK	1979
Amidate	Abbott	US	1983
Radenarcon	Arzneimittelwerk Dresden	E. Germany	-

Raw Materials

dl-1-Phenylethylamine
Formic acid
Potassium thiocyanate
Sodium carbonate
Ethyl chloroacetate
Sodium
Nitric acid

Manufacturing Process

To a mixture of 1,115 parts dl-1-phenylethylamine and 950 parts dimethylformamide are added successively 655 parts triethylamine and 1,130 parts ethyl chloroacetate. After the addition is complete, the whole is stirred overnight. Then there are added 5,600 parts anhydrous ether and the whole is filtered.

The filtrate is washed four times with water, dried and evaporated, yielding dl-N-[(ethoxycarbonyl)methyl] -1-phenylethylamine. This residue is dissolved in

4,800 parts xylene while refluxing and to this solution are added 450 parts formic acid. After boiling for a few hours, the mixture is cooled and washed successively three times with a 20% solution of formic acid, water, sodium hydrogen carbonate solution.

The organic layer is then dried, filtered and evaporated. The oily residue is distilled in vacuo, yielding 1,600 parts dl-N-formyl-N-[(ethoxycarbonyl)methyl]-1-phenylethylamine (boiling point 160°C to 170°C at 0.8 mm pressure). 30 parts of a sodium dispersion, 50% in paraffin oil are added to 450 parts tetrahydrofuran and the whole is slowly heated to a temperature of 40°C, while stirring. While maintaining this temperature (cooling on a water bath is necessary) there are added portionwise 30 parts ethanol.

After the addition is complete, the whole is cooled on an ice bath and there is added dropwise a solution of 144 parts dl-N-formyl-N-[(ethoxycarbonyl)methyl]-1-phenylethylamine in 133 parts ethyl formate. After the addition is complete, the mixture is stirred overnight at room temperature.

Then there are added 160 parts ether. After stirring for 5 minutes the mixture is poured into 1,500 parts water. The aqueous layer is separated, washed twice with 80 parts diisopropyl ether and then there are added successively 114 parts concentrated hydrochloric acid and 90 parts potassium thiocyanate in 200 parts water. The mixture is stirred for 24 hours, where upon an oil is separated.

After the addition of 750 parts water, a crystalline product is precipitated. The mixture is further stirred overnight. The solid is then filtered off and recrystallized from a mixture of ethanol and water (1:1 by volume) to yield dl-1-(phenylethyl)-2-mercapto-5-(ethoxycarbonyl)imidazole; its melting point is 129.8°C to 130.8°C.

To a stirred mixture of 140 parts nitric acid (d = 1.37), 1 part sodium nitrate and 240 parts water are added portionwise 89 parts dl-1-(1-phenylethyl)-2-mercapto-5-(ethoxycarbonyl)imidazole. After the addition is complete, the whole is stirred for 2 hours at room temperature. The free base is liberated by addition of solid sodium carbonate and the whole is extracted with 120 parts anhydrous ether while heating. The aqueous layer is separated and extracted twice with 80 parts anhydrous ether.

The combined extracts are dried over magnesium sulfate, filtered and to the filtrate is added 2-propanol previously saturated with gaseous hydrogen chloride. The precipitated salt is filtered off, dried for 2 days at 60°C, to yield dl-1-(1-phenylethyl)-5-(ethoxycarbonyl)imidazole hydrochloride. It has a melting point 142°C to 142.8°C.

References

Merck Index 3828
DFU 1 (10) 461 (1976)
Kleeman & Engel p. 381
OCDS Vol. 3 p. 135 (1984)
DOT15 (11) 475 (1979)

I.N. p. 405
REM p. 1044
Godefroi, E.F. and Van Der Eijcken, C.A.M.; US Patent 3,354,173; November 21, 1967; assigned to Janssen Pharmaceutica NV (Belgium)

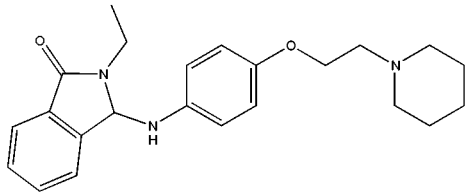
ETOMIDOLINE

Therapeutic Function: Muscle relaxant

Chemical Name: 2-Ethyl-2,3-dihydro-3-[[4-[2-(1-piperidinyl)ethoxy]phenyl]-amino]-1H-isoindol-1-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 21590-92-1

Trade Name	Manufacturer	Country	Year Introduced
Smedolin	Yamanouchi	Japan	1976
Amidoline	Erba	Italy	-

Raw Materials

1-Oxo-3-(aminophenyl-p-ethoxypiperidino)isoindoline
Sodium hydride
Ethyl iodide

Manufacturing Process

31.3 g of 1-oxo-3-(aminophenyl-p-ethoxypiperidino)-isoindoline (0.0892 mol) are dissolved in 500 ml of anhydrous N,N-dimethylformamide. To this solution 5.75 g of NaH (0.105 mol) and 7.24 ml of CH_2CH_2I (0.0945 mol) are added and the resulted mixture is heated at 70°C for 1 hour, and then poured into an excess of water. 1-oxo-2-ethyl-3-(aminophenyl-p-ethoxypiperidino)-isoindoline (MP 106°C to 107°C) is obtained by crystallization with ligroin.

1-oxo-2-ethyl-3-(iminophenyl-p-ethoxypiperidino)-isoindoline (MP 103°C to 104°C) is obtained as a byproduct with the above compound. This latter compound was reduced to produce 1-oxo-2-ethyl-3-(aminophenyl-p-

ethoxypiperidino)-isoindoline.

References

Merck Index 3829
I.N. p. 406
Giraldi, P.N. and Mariotti, V.; US Patent 3,624,206; November 30, 1971; assigned to Carlo Erba S.p.A. (Italy)

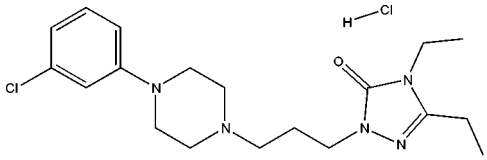
ETOPERIDONE HYDROCHLORIDE

Therapeutic Function: Antidepressant, Anxiolytic

Chemical Name: 1,2,4-Triazol-3-one, 2-(3-(4-(3-chlorophenyl)-1-piperazinyl)propyl)-4,5-diethyl-2,4-dihydro-, monohydrochloride

Common Name: Etoperidone hydrochloride; Tropene

Structural Formula:



Chemical Abstracts Registry No.: 52942-31-1 (Base); 57775-22-1

Trade Name	Manufacturer	Country	Year Introduced
Etoperidone hydrochloride	ZYF Pharm Chemical	-	-
Depraser	Lepori Ltd.	-	-
Depraser	Farma Lepori	-	-
Staff	Sigma Tau	-	-

Raw Materials

3,4-Diethyl-δ(2)-1,2,4-triazolin-5-one
Sodium hydride
N-Metachlorophenyl-N'-(3-chloro-n-propyl)piperazine
Hydrochloric acid
Sodium
3-Bromo-1-chloropropane
N-MetachlorophenyIpiperazine

Manufacturing Process

(a). 3,4-Diethyl-δ^2-1,2,4-triazolin-5-one (62 g) is dissolved in anhydrous dioxane (about 500 ml) and NaH (21 g) in a 50 percent oily suspension is added. The solution is heated for 30 min under reflux and N-metachlorophenyl-N'-(3-chloro-n-propyl)piperazine (119 g) is added under stirring. The solution is heated for 20 hours under reflux. The solvent is then eliminated under reduced pressure and the residue is treated with 2 N HCl. The solution is washed with ether so as to eliminate the oil present in the hydride solution, and made alkaline with 50% K_2CO_3. It is extracted with ether and dried, the solvent is eliminated and the residue is distilled under reduced pressure. 115 g of 2-(3-(4-(3-chlorophenyl)-1-piperazinyl)propyl)-4,5-diethyl-2,4-dihydro-1,2,4-triazol-3-one are obtained. B.P. 230°C/0.5 mm.

2-(3-(4-(3-Chlorophenyl)-1-piperazinyl)propyl)-4,5-diethyl-2,4-dihydro-1,2,4-triazol-3-one hydrochloride was prepared by standard procedures, melting point 197-198°C (recrystallization from isopropanol).

(b). 3,4-Diethyl-δ^2-1,2,4-triazolin-5-one (1 g) and 3-bromo-1-chloropropane (6.6 g) are added to a solution of Na (0.98 g) in methanol (20 ml). The solution is refluxed until the pH becomes neutral, poured into water, extracted with ether. The solvent is eliminated and the residual oil is distilled. 1-(3-Chloropropyl)-3,4-diethyl-δ^2-1,2,4-triazolin-5-one boils at 121°C/0.05 mm.

1-(3-Chloropropyl)-3,4-diethyl-δ^2-1,2,4-triazolin-5-one (1.0 g), N-metachlorophenylpiperazine (0.9 g) and triethylamine (0.46 g) in toluene (25 ml) are refluxed for 12 hours. The solution is treated with 5 N NaOH, extracted with ether and steam-distilled. The residue is extracted with ether and the ethereal solution is treated with ethereal HCl. 2-(3-(4-(3-Chlorophenyl)-1-piperazinyl)propyl)-4,5-diethyl-2,4-dihydro-1,2,4-triazol-3-one hydrochloride has melting point 197-198°C (recrystallization from isopropanol).

References

Palazzo G.; US Patent No. 3,857,845; Dec. 31, 1974; Aziende Chimische Ruinite Angeline Francesco A.C.R., A.F.S.p.A., Rome, Italy

ETOPOSIDE

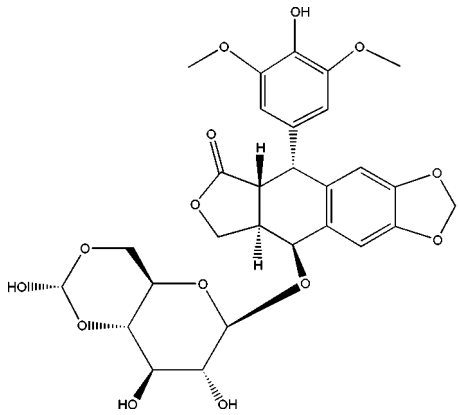
Therapeutic Function: Antitumor, Antineoplastic

Chemical Name: Furo(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6(5aH)-one, 9-((4,6-O-(1R)-ethylidene-β-D-glucopyranosyl)oxy)-5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-, (5R,5aR,8aR,9S)-

Common Name: Etoposide

Chemical Abstracts Registry No.: 33419-42-0

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Etopos	Lemery	Mexico	-
Etosid	Cipla Limited	India	-
Etoposide	Pierre Fabre Medicament	France	-
Etoposide	Pharmacia and Upjhon	Austria	-
Etoposid-Ebewe	Ebewe	Austria	-
Eposin	Medac	-	-
Lastet	Nippon Kayaku, Co.	Japan	-
Vepesid	Bristol-Myers Squibb	Italy	-
Vepesid	Bristol-Myers Pharm Ltd.	-	-

Raw Materials

2,3-Di-O-dichloroacetyl-1-O-benzyloxycarbonyl-(4,6-O-ethylidene)-β-D-glucopyranose
Palladium on carbon
4'-Demethyl-epi-podophyllotoxin
Zinc acetate dihydrate
Boron trifluoride etherate
Trimethylsilyl trifluoromethane sulfonate
Celite/basic alumina column

Manufacturing Process

Preparation of 2,3-Di-O-dichloroacetyl-(4,6-O-ethylidene)-β-D-glucopyranose (hydrogenolysis)

An over-dried 100 mL three-necked round bottom flask fitted with a stir bar, low temperature thermometer, and H_2 inlet was charged with 2,3-di-O-

dichloroacetyl-1-O-benzyloxycarbonyl-(4,6-O-ethylidene)-β-D-glucopyranose (1.8 mmol), in acetone (15-30% concentration) and 10% palladium on activated carbon powder (0.2 mmol). The solution was stirred until uniform and then cooled to -10°C to 0°C. After the reaction was over the catalyst was filtered over sintered glass containing a plug of celite under reduced pressure. The sintered glass is washed trice with one times the total reaction volume of anhydrous acetone and the filtrates are pooled and then concentrated to dryness under reduced pressure at a temperature close to 30°C. The crude residue was dried under vacuum at ambient temperature and above compound was thus obtained as white foam in 98% yield with a melting point of 130°-132°C (from acetone).

Preparation of 4'-Demethyl-epi-podophyllotoxin-4-(2,3-di-O-dichloroacetyl-4,6-O-ethylidene)-β-D-glucopyranoside

An oven-dried, three-neck 250 mL round bottom flask was fitted with a stir bar, low temperature thermometer, septa and argon inlet, was introduced with 4'-demethyl-epi-podophyllotoxin (1 mmol), dry molecular sieve (1/16 δ pellets) and anhydrous dichloromethane (20-50% concentration). 2-3-Di-O-dichloroacetyl-(4,6-O-ethylidene)-β-D-glucopyranose (1.7 mmol) in dichloromethane (10-20% concentration) was added via double-ended needle. The suspension was stirred until homogenous and then cooled to -40°C to -60°C in an atmosphere of argon and in the absence of moisture. To the stirred suspension was added via a syringe, trimethylsilyl trifluoromethane sulfonate (2 mmol) over 30 minutes. The reaction was held at between -50°C and -40°C for 30 minutes. The course of the coupling reaction was monitored by thin layer chromatography. The suspension was allowed to warm to about -30°C and filtered through a short celite/basic alumina column, eluting twice with one times the total reaction volume of dichloromethane. The pooled filtrate was evaporated under reduced pressure to yield the crude intermediate product 4'-demethyl-epi-podophyllotoxin-4-(2,3-di-O-dichloroacetyl-4,6-O-ethylidene)-β-D-glucopyranose (yield 80%). This crude product is used directly in the next step without any purification. A sample was purified by the chromatraton for spectroscopic identification. The results are as follows: m.p.: 242°-243°C (from methanol).

Preparation of 4-Demethyl-epi-podophyllotoxin-4-(4,6-O-ethylidene)-β-D-glucopyranose (etoposide)

To 0.8 mmol of 4'-demethyl-epi-podophyllotoxin-4-(2,3-di-O-dichloroacetyl-4,6-O-ethylidene)-β-D-glucopyranose in 10-25% concentration in methanol is added 1.5 mmol of zinc acetate dihydrate. The reaction mixture is refluxed with stirring under heating for 90 minutes. After completion of the reaction, the mixture is cooled and the volume reduced to one third by rotary evaporation under reduced pressure. Working up is effected by diluting the reaction solution with 100 mL dichloromethane and 100 mL of water. The aqueous phase was washed with 50 mL of dichloromethane. The combined dichloromethane phases was washed twice with 50 mL water, 15 mL of methanol was added to the first wash to prevent precipitation of etoposide. The organic phase was dried over anhydrous sodium sulphate, filtered and concentrated by evaporation under vacuum to an amorphous solid. This solid was re-crystallized from methanol/n-pentane at -4°C to 0°C, thus obtaining colorless amorphous powder of Etoposide (yield 68%), if the mother liquors are treated the yield will be higher). Melting point: 256°-258°C.

Preparation of Etoposide employing 2,3-di-O-dichloroacetyl-(4,6-O-ethylidene)-β-D-glucopyranose and boron trifluoride etherate as catalyst

4'-Demethyl-epi-podophyllotoxin (1 mmol) and 2,3-di-O-dichloroacetyl-(4,6-O-ethylidene)-β-D-glucopyranose (2 mmol) were introduced into dry dichloromethane under anhydrous condition. When the temperature was stabilized to -20°C to -30°C, boron trifluoride etherate (1.5 mmol) was added slowly with stirring. Reaction was continued at this temperature and monitored by thin layer chromatography. After the completion of the reaction as evidenced by TLC, the solution was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude intermediate product 4'-demethyl-epi-podophyllotoxin-4-(2,3-di-O-dichloroacetyl-4,6-O-ethylidene)-β-D-glucopyranose. This crude product was then converted to etoposide by following the procedure as above described. The yield of final product etoposide was about 60%.

References

Naidu R.; US Patent No. 6,384,201 B1; May 7, 2002; Assigned to Phytogen Life Sciences Inc., Delta (CA)

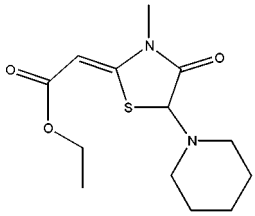
ETOZOLIN

Therapeutic Function: Diuretic

Chemical Name: 2-Carbethoxymethylene-3-methyl-5-piperidino-thiazolidin-4-one ester

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 73-09-6

Trade Name	Manufacturer	Country	Year Introduced
Elkapin	Goedecke	W. Germany	1977
Elkapin	Goedecke	Italy	1983
Etopinil	Wassermann	Spain	-

Raw Materials

2-Carbethoxymethylene-3-methyl-4-thiazolidinone
Bromine
Piperidine

Manufacturing Process

To a stirred solution of 20 g (0.1 mol) 2-carbethoxymethylene-3-methyl-4-thiazolidinone in 120 ml chloroform is added, dropwise, a solution of 5 ml (0.1 mol) bromine in 20 ml chloroform. The solvent is removed by distillation and the residue crystallized from methanol to yield 18 g (65%) of 2-carbethoxymethylen-3-methyl-5-bromo-4-thiazolidinone, MP 76°C.

To a solution of 28 g (0.1 mol) 2-carbethoxymethylene-3-methyl-5-bromo-4-thiazolidinone prepared as described in 200 ml benzene is added (0.2 mol) piperidine and the mixture is allowed to stand for 3 hours at 25°C. The resulting suspension is filtered to remove the precipitated piperidine hydrobromide and the filtrate is evaporated to dryness. The residue is taken up in ether, filtered and the filtrate saturated with dry hydrogen chloride to yield the hydrochloride salt of 2-carbethoxymethylene-3-methyl-5-piperidino-4-thiazolidinone, MP 158°C to 159°C.

References

Merck Index 3835
DFU 3 (4) 282 (1978)
Kleeman & Engel p. 383
DOT 14 (6) 239 (1978)
I.N. p. 407
Satzinger, G.; US Patent 3,072,653; January 8, 1963; assigned to Warner-Lambert Pharmaceutical Co.

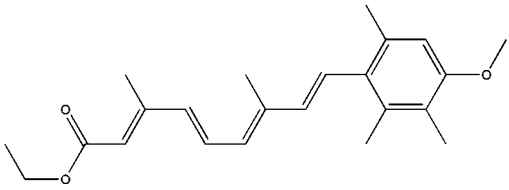
ETRETINATE

Therapeutic Function: Antipsoriatic, Antitumor

Chemical Name: Ethyl all-trans-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 54350-48-0

Trade Name	Manufacturer	Country	Year Introduced
Tigason	Roche	UK	1981
Tigason	Roche	Switz.	1982
Tigason	Roche	France	1983
Tigason	Roche	W. Germany	1983
Tigason	Roche	Sweden	1983
Tigason	Sauter	Switz.	-

Raw Materials

5-(4-Methoxy-2,3,6-trimethylphenyl)-3-methylpenta-2,4-diene-1-triphenylphosphonium bromide
Sodium hydride
3-Formylcrotonic acid butyl ester
Potassium hydroxide
Ethyl iodide
Potassium carbonate

Manufacturing Process

228 g of 5-(4-methoxy-2,3,6-trimethylphenyl)-3-methyl-penta-2,4-diene-1-triphenylphosphonium bromide are introduced under nitrogen gassing into 910 ml of dimethylformamide and treated with cooling at 5°C to 10°C within 20 minutes with 17.5 g of a suspension of sodium hydride (about 50% by weight) in mineral oil. The mixture is stirred for 1 hour at about 10°C, then treated at 5°C to 8°C dropwise with 61.8 g of 3-formylcrotonic acid butyl ester, heating for 2 hours at 65°C, subsequently introduced into 8 liters of ice water, and, after the addition of 300 g of sodium chloride, thoroughly extracted with a total of 18 liters of hexane. The extract is washed 5 times with 1 liter of methanol/water (6:4 parts by volume) each time and 2 times with 1.5 liter of water each time, dried over sodium sulfate and evaporated under reduced pressure to leave 9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester, MP 80°C to 81°C as the residue.

125.8 g of 9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester are introduced into 2,000 ml of abs. ethanol and treated with a solution of 125.8 g of potassium hydroxide in 195 ml of water. The mixture is heated to boiling under nitrogen gassing for 30 minutes, then cooled, introduced into 10 liters of ice water and, after the addition of about 240 ml of concentrated hydrochloric acid (PH 2-4), thoroughly extracted with a total of 9 liters of methylene chloride. The extract is washed with about 6 liters of water to neutrality, dried over calcium chloride and evaporated under reduced pressure. The residue is taken up in 700 ml of hexane. The precipitated 9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid melts at 228°C to 230°C.

60 g of 9-(4-methoxy -2,3,6-trimethylphenyl)-3,7-dimethyl-nona-2,4,6 8-tetraen-1-oic acid are dissolved in 1,000 ml of acetone. After the addition of 128 g of ethyl iodide and 128 g of potassium carbonate, the solution is stirred under nitrogen gassing for 16 hours at 55°C to 60°C and subsequently

evaporated under reduced pressure. The residue is dissolved in 1,300 ml of petroleum ether (BP 80°C to 105°C). The 9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester crystallizing out at -20°C, melts at 104°C to 105°C.

References

Merck Index 3836
DFU 2 (3) 199 (1977) (As Ro 10/9359) & 4 (12) 911 (1979) (As Etretinate)
DOT 18 (3) 120 (1982)
I.N. p. 407
Bollag, W., Ruegg, R. and Ryser, G.; US Patent 4,105,68l; August 8, 1978; assigned to Hoffmann-La Roche, Inc.
Bollag, W., Ruegg, R. and Ryser, G.; US Patent 4,215,215; July 29, 1980; assigned to Hoffmann-La Roche, Inc.

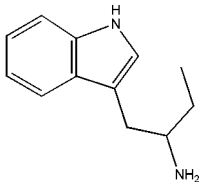
ETRYPTAMINE

Therapeutic Function: Central stimulant

Chemical Name: α-Ethyl-1H-indole-3-ethanamine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 2235-90-7

Trade Name	Manufacturer	Country	Year Introduced
Monase	Upjohn	US	1961

Raw Materials

3-(2'-Ethyl-2'-nitrovinyl)indole
Hydrogen

Manufacturing Process

A mixture of 5 parts of 3-(2'-ethyl-2'-nitrovinyl)indole in 80 parts of ethanol saturated with ammonia gas is shaken in an atmosphere of hydrogen at 100 atmospheres pressure and at 20°C in the presence of 1 part of a 5%

palladium on carbon catalyst until the theoretical amount of hydrogen is absorbed. The catalyst is removed by filtration. The ethanol and ammonia are then removed from the filtrate by distillation under reduced pressure. The residual oil is dissolved in 170 parts of dry ether, 50 parts of potassium hydroxide pellets are added and the solution is kept at 18°C to 22°C for 2 hours. The mixture is filtered and hydrogen chloride is passed into the filtrate to precipitate crude (α-ethyltryptamine hydrochloride. This is purified by crystallization from methanol/ethyl acetate and it then has a MP of 221°C.

References

Merck Index 3837
I.N. p. 407
Young, E.H.P.; British Patent 933, 786; August 14, 1963; assigned to Imperial Chemical Industries Ltd.

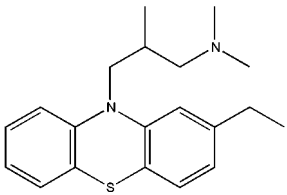
ETYMEMAZINE

Therapeutic Function: Neuroleptic, Antihistaminic, Hypnotic

Chemical Name: 10-[3-(Dimethylamino)-2-methylpropyl]-2-ethylphenothiazine

Common Name: Aethylisobutrazin; Ethotrimeprazine; Ethylisobutrazine; Ethyltrimeprazine; Etymemazine

Structural Formula:



Chemical Abstracts Registry No.: 523-54-6

Trade Name	Manufacturer	Country	Year Introduced
Nuital	Vaillant-Defresne	-	-
Sergetyl	Vaillant-Defresne	-	-
Etylmemazine	Shanghai Lansheng Corporation	-	-

Raw Materials

Sodium amide

2-Ethyl-10H-phenothiazine
1-Dimethylamino-2-methyl-3-chloropropane
Methanesulfonic acid

Manufacturing Process

2.33 g 95% sodium amide were added to a boiling solution of 11.35 g 2-ethyl-10H-phenothiazine (BP: 135°-136°C) in 150 ml dry xylene by stirring at reflux for 1.5 hours. The solution of 7.72 g of 1-dimethylamino-2-methyl-3-chloropropane in 90 ml of dry xylene was poured in the above solution at the same temperature for 45 minutes. The mixture was heated at reflux else 18 hours. On cooling it was stirred with the mixture of 70 ml 1 N methanesulfonic acid and 40 ml water whereupon a xylene layer was removed. The water layer was extracted with 200 ml ether and basified with 10 ml NaOH (d=1.33), again extracted with ether and dried over potassium carbonate. The ether was distilled off, a residue was distilled to give 10-(3-dimethylamino-2-methylpropyl)-2-ethylphenothiazine; BP: 162°-182°C/0.45 mm.

The prepared base was in 60 ml acetone dissolved and 24.5 ml 1.7 N HCl was added and a precipitate of ethyl-2-(dimethylamino-3-methyl-2-propyl)-10-phenothiazine chlorohydrate dropped out. It was filtered off, washed with acetone and ether and dried. MP: 160°-163°C.

References

Jacob R.M. et al.; D.B. Patent No. 1,034,638; Nov. 3, 1955

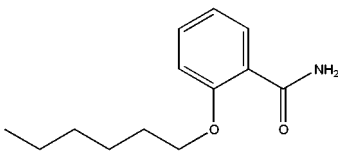
EXALAMIDE

Therapeutic Function: Antifungal

Chemical Name: 2-(Hexyloxy)benzamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 53370-90-4

Trade Name	Manufacturer	Country	Year Introduced
Hyperan	S.S. Pharm	Japan	1980

Raw Materials

Salicylamide	Sodium
Ethanol	n-Hexyl bromide

Manufacturing Process

4.6 g sodium were dissolved in 150 ml ethanol and 27.4 g (0.2 mol) salicylamide added. The solution was refluxed gently and 24.6 g (0.2mol) n-hexyl-bromide added gradually. The mixture was refluxed for six hours, the precipitated sodium bromide filtered off, and most of the alcohol removed by distillation. Water was then added to the residue, and the 2-n-hexyloxybenzamide filtered off. It crystallized from 50% aqueous ethanol in colorless crystals, MP 71°C.

References

Merck Index 3858
DOT 16 (8) 246 (1980)
I.N. p. 410
MacRae, F.J. and Seymour, D.E.; British Patent 726,786; June 5, 1952; assigned to Herts Pharmaceuticals Ltd.

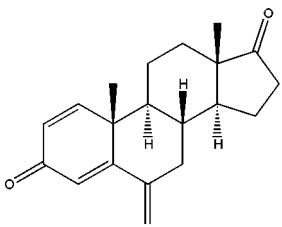
EXEMESTANE

Therapeutic Function: Antineoplastic

Chemical Name: Androsta-1,4-diene-3,17-dione, 6-methylene-

Common Name: Exemastine; Exemestane

Structural Formula:



Chemical Abstracts Registry No.: 107868-30-4

Trade Name	Manufacturer	Country	Year Introduced
Exemestane	Pharmacia and Upjohn	-	-
Exemestane	Hangzhou Verychem Science and Technology Co., Ltd.	-	-

Trade Name	Manufacturer	Country	Year Introduced
Exemestane	ZYF Pharm Chemical	-	-
Aromasin	Pharmacia	-	-
Nikidess	Pharmacia and Upjohn	-	-

Raw Materials

6-Methylenandrost-4-ene-3,17-dione
Dichlorodicyanobenzoquinone

Manufacturing Process

0.50 g of 6-methylenandrost-4-ene-3,17-dione and 0.57 g of dichlorodicyanobenzoquinone were refluxed in 20 ml of anhydrous dioxane for about 15 hours. To remove the DDQ the suspension was filtered through alumina. After evaporation of the solvent the residue was dissolved in ethyl acetate, the organic layer washed with water, dried over sodium sulfate and the solvent removed under vacuum. The crude product was chromatographed on silica gel using hexane/ethyl acetate to yield 0.25 g of pure 6-methylenandrosta-1,4-diene-3,17-dione, m.p. 188-191°C, λ_{max} 247 nm (ε 13.750).

References

Buzzetti F., Barbugian N., Lombardi P., di Salle E.; US Patent No. 4,808,616; Feb. 28, 1989; Assigned to Farmitalia Carlo Erba S.r.l. (Milan, IT)
Buzzetti F., Barbugian N., Lombardi P., di Salle E.; DE Patent No. 3,622,841; 1987-01-15; Assigned to ERBA FARMITALIA (IT)

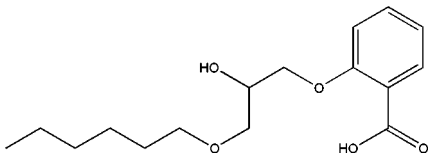
EXIPROBEN

Therapeutic Function: Choleretic

Chemical Name: 2-[3-(Hexyloxy)-2-hydroxypropoxy]benzoic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 26281-69-6

Trade Name	Manufacturer	Country	Year Introduced
Droctil	Ciba Geigy	Italy	1971
Etopalin	Ciba Geigy	-	-

Raw Materials

p-Hydroxybenzoic acid methyl ester
3-Hexoxy-2-hydroxy-1-chloropropane
Sodium hydroxide
Hydrogen chloride

Manufacturing Process

p-Hydroxy-benzoic acid methyl ester was subjected to a condensation reaction with 3-hexoxy-2-hydroxy-1-chloropropane in the presence of sodium ethylate and ethanol as a solvent, yielding p-(3-hexoxy-2-hydroxy)-propoxy-benzoic acid methyl ester.

62 g of this intermediate product were admixed with 250 cc of 2N sodium hydroxide and the resulting mixture was refluxed for three hours. The reaction mixture was allowed to cool and was made acid with concentrated hydrochloric acid while cooling it on ice. An oil separated out which was extracted with ether. The ether extract solution was dried over sodium sulfate and then the ether was distilled off, leaving a crystalline mass as a residue. The crystalline product was recrystallized from a mixture of benzene and petroleum ether, yielding a compound having a MP of 68°C.

References

Merck Index 3860
I.N. p. 410
Ohnacker, G.; US Patent 3,198,827; August 3, 1965; assigned to Boehringer Ingelheim G.m.b.H. (Germany)