E

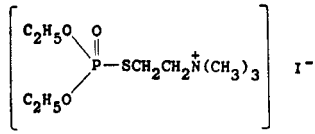
ECHOTHIOPATE IODIDE

Therapeutic Function: Cholinergic (ophthalmic)

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

Common Name: O,O-diethyl-S-β-dimethylaminoethyl thiophosphate methyl iodide

Structural Formula:



Chemical Abstracts Registry No.: 513-10-0

Trade Name	Manufacturer	Country	Year Introduced
Phospholine Iodide	Ayerst	U.S.	1959
Phospholine Iodide	Promedica	France	1966
Echiodide	Alcon	U.S.	1977
Phospholine Iodide	Santen	Japan	–
Phospholine Iodide	Ayerst	U.K.	–
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 diethylchloro-phosphate (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.; U.S. Patent 2,911,430; November 3, 1959; assigned to Campbell Pharmaceuticals, Inc.

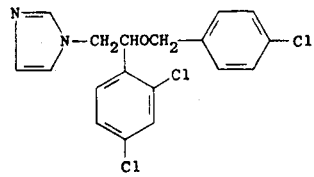
ECONAZOLE NITRATE

Therapeutic Function: Antifungal

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

Common Name: –

Structural Formula:



(base)

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	U.K.	1978
Pevaryl	Cilag Chemie	W. Germany	1978
Skilar	Italchemie	Italy	1979
Paravale	Otsuka	Japan	1981
Spectazole	Ortho	U.S.	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

p-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.; U.S. Patent 3,717,655; February 20, 1973; assigned to Janssen Pharmaceutica NV, Belgium

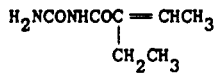
ECTYLUREA

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	U.S.	1956
Levanil	Upjohn	U.S.	1959
Cronil	Farmigea	Italy	–
Distasol	Locatelli	Italy	–
Ektyl	A.C.O.	Sweden	–
Neuroprocin	Minerva-Chemie	Neth.	–

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.; U.S. Patents 2,854,379; September 30, 1958; and 2,931,832; April 5, 1960; both assigned to Miles Laboratories, Inc.

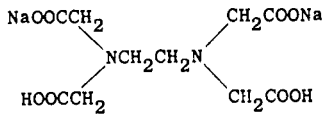
EDETATE DISODIUM

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	U.S.	1959
Cheladrate	Pharmex	U.S.	—
Diso-Tate	O'Neal, Jones	U.S.	—
Idranal	Riedel de Hahn	W. Germany	—
Komplexon III	Chemische Fabrik	Switz.	—
Uni Wash	United	U.S.	—

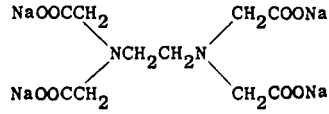
Raw Materials

Ethylene diamine
Formaldehyde
Sodium cyanide
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.; U.S. Patent 2,407,645; September 17, 1946; assigned to The Martin Dennis Co.

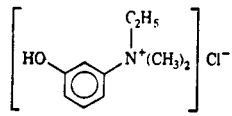
EDROPHONIUM CHLORIDE

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	U.S.	1951
Tensilon	Roche	U.K.	–
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 dryness 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.; U.S. Patents 3,469,011; September 23, 1969 and 3,527,813; September 8, 1970; both assigned to Air Reduction Company, Incorporated

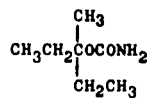
EMYLCAMATE

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	U.S.	1960

Raw Materials

3-Methyl-3-pentanol
Trichloroacetic acid
Potassium cyanate
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.; U.S. Patent 2,972,564; February 21, 1961; assigned to A/B Kabi (Sweden)

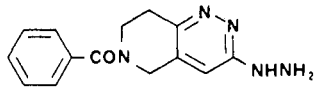
ENDRALAZINE

Therapeutic Function: Hypotensive

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

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[4,3-c] 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-tetrahydropyrido[4,3-c] pyridazine: Produced from 30.3 g of 5,6,7,8-tetrahydro-3(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.; U.S. Patent 3,838,125; September 24, 1974; assigned to Sandoz Ltd.
Schenker, E.; U.S. 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: CHF_2OCF_2CHFCl

Chemical Abstracts Registry No.: 13838-16-9

Trade Name	Manufacturer	Country	Year Introduced
Ethrane	Ohio Medical	U.S.	1972
Ethrane	Abbott	Italy	1974
Ethrane	Deutsche Abbott	W. Germany	1975
Ethrane	Abbott	U.K.	1977
Ethrane	Abbott	France	1978
Ethrane	Dainippon	Japan	1981
Aerrane	Ohio Medical	U.K.	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.; U.S. Patents 3,469,011; September 23, 1969 and 3,527,813; September 8, 1970; both assigned to Air Reduction Company, Incorporated

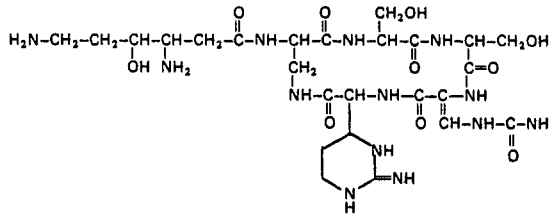
ENVIOMYCIN

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., U.S.A.). The column was washed with water, eluted with 0.5 N 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, 71.5%; 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.; U.S. Patent 3,892,732; July 1, 1975; assigned to Toyo Jozo K.K. (Japan)

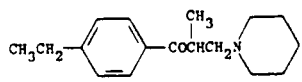
EPERISONE HCl

Therapeutic Function: Muscle relaxant

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

Common Name: –

Structural Formula:



(base)

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, 28.8 g 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.; U.S. Patent 3,995,047; November 30, 1976; assigned to Eisai Co., Ltd. (Japan)

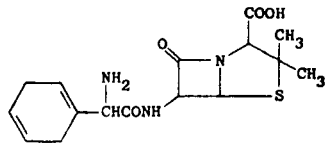
EPICILLIN

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

Structural Formula:



Chemical Abstracts Registry No.: 26774-90-3

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
Ammonia
6-Amino penicillanic acid
Lithium
Methyl acetoacetate

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-methyl-morpholine is added followed by the slow addition of 198 mg of ice cold ethyl chloro-formate. 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.; U.S. Patent 3,485,819; Dec. 23, 1969; assigned to E.R. Squibb & Sons, Inc.

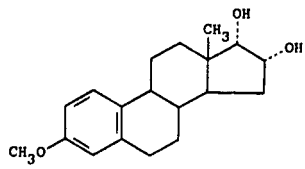
EPIMESTROL

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 0.5 N 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.; U.S. Patent 2,584,271; February 5, 1952; assigned to G.D. Searle & Co.

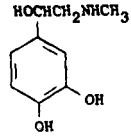
EPINEPHRYL BORATE

Therapeutic Function: Antiglaucoma drug

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

Common Name: Methylaminoethanolcatechol borate; adrenalin borate

Structural Formula:



(base)

Chemical Abstracts Registry No.: –

Trade Name	Manufacturer	Country	Year Introduced
Eppy	Barnes-Hind	U.S.	1961
Epinal	Alcon	U.S.	–

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.; U.S. Patent 3,149,035; September 15, 1964; assigned to The Regents of the University of California

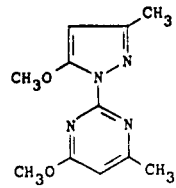
EPIRIZOLE

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 colorless 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

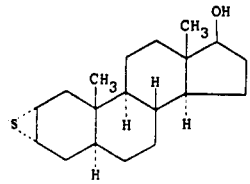
EPITIOSTANOL

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.; U.S. Patent 3,230,215; January 18, 1966; assigned to Shionogi & Co., Ltd.

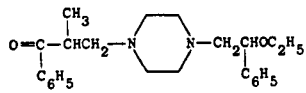
EPRAZINONE HCl

Therapeutic Function: Antitussive

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

Common Name: —

Structural Formula:



(base)

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

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

Manufacturing Process

61.4 g of 0.2 M of 1-(2-phenyl-2-ethoxy)piperazine dihydrochloride, 33.5 g (0.25 M) propiophenone, 75 g (0.25 M) 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.; U.S. Patent 3,448,192; June 3, 1969

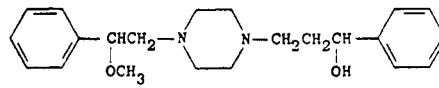
EPROZINOL

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
Acetophenone
Sodium borohydride
Piperazine
Trioxymethylene

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 vinylbenzene (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

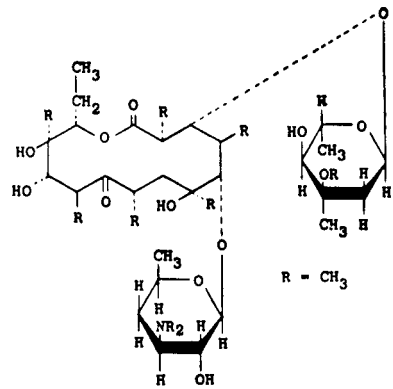
ERYTHROMYCIN

Therapeutic Function: Antibacterial

Chemical Name: See structural formula

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 114-07-8

Trade Name	Manufacturer	Country	Year Introduced
Ilotycin	Dista	U.S.	1952
Erythrocin	Abbott	U.S.	1952
E-Mycin	Upjohn	U.S.	1953
Robimycin	Robins	U.S.	1972
Kesso-Mycin	McKesson	U.S.	1973
Staticin	Westwood	U.S.	1980
Eryc	Faulding	U.S.	1980
I/T/S Ilotycin	Lilly	U.S.	1980
Ery Derm	Abbott	U.S.	1980
A/T/S	Hoechst	U.S.	1981
Ery-Tab	Abbott	U.S.	1981
T.Stat	Westwood	U.S.	1983
Erymax	Allergan	U.S.	1983
Abomacetin	Mochida	Japan	—
Adamycin	Lederle	—	—
Aknemycin	Hermal	W. Germany	—
Benzamycin	Dermik	U.S.	—
Bisolvanat	Thomae	W. Germany	—

Trade Name	Manufacturer	Country	Year Introduced
Clafanone	Roche	–	–
Dowmycin	Merrell-Dow	–	–
Endoeritrin	Lopez-Brea	Spain	–
Eritrobios	Nuovo Cons. Sanit. Naz.	Italy	–
Eritonormo	Normon	Spain	–
Erycinum	Schering	W. Germany	–
Ery-Max	Astra	Sweden	–
Erythro ST	Nippon Kayaku	Japan	–
Estromycin	Orion	Finland	–
Ilosone	Lilly	Italy	–
Marocid	Lifepharma	Italy	–
Mistral	Dessy	Italy	–
Orizina	Perga	Spain	–
Pediamycin	Ross	U.S.	–
Polarmicina	Medipolar	Sweden	–
Reciomycin	Recip	Sweden	–
Retcin	D.D.S.A.	U.K.	–
Rivotrocin	Rivopharm	Switz.	–
RP-Mycin	Reid-Provident	U.S.	–
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 U.S. 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.; U.S. Patent 2,823,203; February 11, 1958; assigned to Abbott Laboratories
Friedland, W.C., Denison, F.W. Jr. and Peterson, M.H.; U.S. Patent 2,833,696; May 6, 1958; assigned to Abbott Laboratories
Bunch, R.L. and McGuire, J.M.; U.S. Patent 2,653,899; September 29, 1953; assigned to Eli Lilly and Company

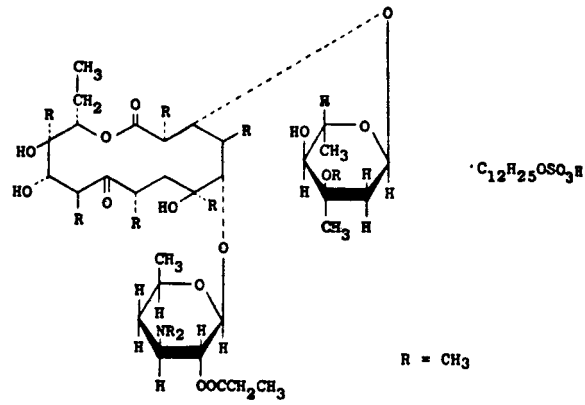
ERYTHROMYCIN ESTOLATE

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	U.S.	1958
Biomicron	Isa	Brazil	–
Chemthromycin	Chemo-Drug	Canada	–
Cimetrin	Cimex	Switz.	–
Dreimicina	Dreikehl	Spain	–
Endoeritrin	Lopez-Brea	Spain	–
Erimec	Isola-Ibi	Italy	–
Eriscel	Rachelle	U.S.	–
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	Barlowe Cote	Canada	–
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 monopropionylerythromycin 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.; U.S. 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: –

Structural Formula: See Erythromycin for structure of base

Chemical Abstracts Registry No.: 23067-13-2

Trade Name	Manufacturer	Country	Year Introduced
Ilotycin Gluceptate	Dista	U.S.	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.; U.S. 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: See Erythromycin for structure of base.

Chemical Abstracts Registry No.: 3847-29-8

Trade Name	Manufacturer	Country	Year Introduced
Erythrocin Lactobionate	Abbott	U.S.	1954
Erythrocin Piggyback	–	U.S.	–
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.; U.S. Patent 2,761,859; September 4, 1956; assigned to Abbott Laboratories

ERYTHROMYCIN STEARATE

Therapeutic Function: Antibacterial

Chemical Name: Erythromycin stearate

Common Name: –

Structural Formula: See Erythromycin for structure of base

Chemical Abstracts Registry No.: 643-22-1

Trade Name	Manufacturer	Country	Year Introduced
Erythrocin Stearate	Abbott	U.S.	1952
Bristamycin	Bristol	U.S.	1971
Ethril	Squibb	U.S.	1972
Erypar	Parke Davis	U.S.	1972
SK-Erythromycin	SKF	U.S.	1972
Qidmycin	Mallinckrodt	U.S.	1973
Pfizer-E	Pfizer	U.S.	1973
Dowmycin-E	Merrell Dow	U.S.	1974

Trade Name	Manufacturer	Country	Year Introduced
Erythromycin Stearate	Lederle	U.S.	1975
Wyamycin-S	Wyeth	U.S.	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.; U.S. Patent 2,862,921; December 2, 1958; assigned to The Upjohn Company

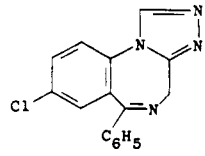
ESTAZOLAM

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-Takeda	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.; U.S. Patent 3,701,782; October 31, 1972; assigned to The Upjohn Co.

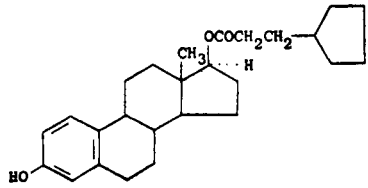
ESTRADIOL CYPIONATE

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

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 ml 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 20±2°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 benzene-petroleum 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.; U.S. 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: See Estradiol Cypionate for form of salt

Chemical Abstracts Registry No.: 979-32-8

Trade Name	Manufactuer	Country	Year Introduced
Delestrogen	Squibb	U.S.	1954
Lastrogen	Key	U.S.	1961
Reposo-E	Canfield	U.S.	1961
Estraval PA	Tutag	U.S.	1970
Androtardyl-Oestradiol	S.E.P.P.S.	France	—
Ardefem	Burgin-Arden	U.S.	—
Atladiol	I.C.I.	U.S.	—
Depogen	Sig	U.S.	—
Diol-20	Blaine	U.S.	—
Dioval	Keene	U.S.	—
Ditate	Savage	U.S.	—
Dura-Estate	Ries	U.S.	—
Dura-Estradiol	Myers-Carter	U.S.	—
Duratrad	Ascher	U.S.	—
Estate	Savage	U.S.	—
Estral-L	Pasadena	U.S.	—
Femogen	Fellows	U.S.	—
Femogex	Stickley	Canada	—
Menaval	Legere	U.S.	—
Oestrogynal	Asche	W. Germany	—
Ostrin Depo	I.E. Kimya	Turkey	—
Pelanin	Mochida	Japan	—
Primogyn-Depot	Schering	W. Germany	—
Progynon Depot	Schering	W. Germany	—
Progynova	Schering	W. Germany	—
Repestrogen	Spencer-Mead	U.S.	—
Repo-Estra	Central	U.S.	—
Retestrin	Rocky Mountain	U.S.	—
Span-Est	Scrip	U.S.	—

Trade Name	Manufactuer	Country	Year Introduced
Testaval	Legere	U.S.	–
Valergen	Hyrex	U.S.	–

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 U.S. 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 U.S. 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.; U.S. Patent 2,205,627; June 25, 1940; assigned to the Society of Chemical Industry in Basle, Switzerland
Miescher, K. and Scholz, C.; U.S. Patent 2,233,025; February 25, 1941; assigned to Ciba Pharmaceutical Products, Incorporated

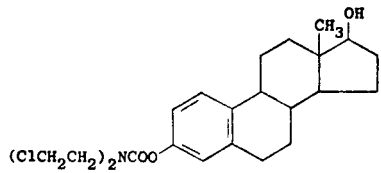
ESTRAMUSTINE PHOSPHATE

Therapeutic Function: Cancer chemotherapy

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

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 4891-15-0

Trade Name	Manufacturer	Country	Year Introduced
Estracyt	Bastian-Werk	W. Germany	1973
Estracyt	Lundbeck	U.K.	1977
Estracyt	Roche	France	1981
Estracyt	Roche	Italy	1981
Emcyt	Roche	U.S.	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(β-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.O.J.; U.S. Patent 3,299,104; Jan. 17, 1967; assigned to Leo AB, Sweden

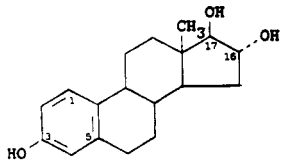
ESTRIOL SUCCINATE

Therapeutic Function: Estrogen

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

Common Name: 16α-hydroxyestradiol

Structural Formula:



(base)

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	Nourypharma	W. Germany	—
Synapause	Organon	France	—
Synapasa	Erco	Denmark	—

Raw Materials

Estriol
Succinic acid 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

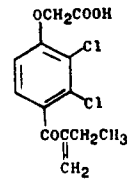
ETHACRYNIC ACID

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	U.K.	1966
Edecrin	MSD	U.S.	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 methylcyclohexane, 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.; U.S. Patent 3,255,241; June 7, 1966; assigned to Merck & Co., Inc.

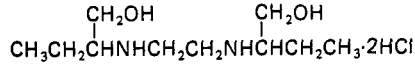
ETHAMBUTOL HYDROCHLORIDE

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	U.S.	1967
Myambutol	Cyanamid	W. Germany	1967
Myambutol	Lederle	U.K.	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	–

Trade Name	Manufacturer	Country	Year Introduced
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 Berun-Chemie	E. Germany	–
Tambutol	Atabay	Turkey	–
Tisiobutol	Capitol	Spain	–
Tuberol	Deva	Turkey	–

Raw Materials

2-Amino-1-butanol
Hydrogen chloride
Ethylene dichloride
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.; U.S. Patent 3,297,707; January 10, 1967; assigned to American Cyanamid Company

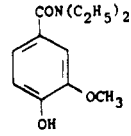
ETHAMIVAN

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.	U.S.	1961
Corivanil	Sirt-B.B.P.	Italy	—
Romecor	Benvegna	Italy	—
Vandid	Riker	U.K.	—
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.; U.S. Patent 2,641,612; June 9, 1953; assigned to Oesterreichishe Stickstoffwerke A.G. (Austria)

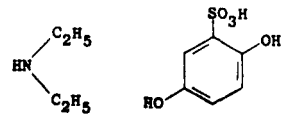
ETHAMSYLATE

Therapeutic Function: Hemostatic

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

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

Structural Formula:



Chemical Abstracts Registry No.: 88-46-0

Trade Name	Manufacturer	Country	Year Introduced
Dicynone	Delalande	France	1965
Dicynene	Delalande	Italy	1967
Altodor	Delalande	W. Germany	1967
Dicynene	Delalande	U.K.	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

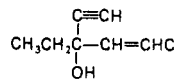
ETHCLORVYNOL

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	U.S.	1965
Arvynol	Pfizer	U.K.	–
Arvynol	Taito Pfizer	Japan	–
Nostel	Dainippon	Japan	–
Roeridorm	Pfizer-Roerig	–	–
Serenesil	Abbott	U.K.	–

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.; U.S. Patent 2,746,900; May 22, 1956; assigned to Chas. Pfizer & Co., Inc.

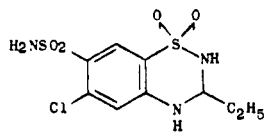
ETHIAZIDE

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	U.K.	–

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 diethyleneglycol dimethylether, 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

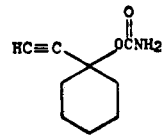
ETHINAMATE

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	U.S.	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.; U.S. Patent 2,816,910; December 17, 1957; assigned to Schering AG, Germany

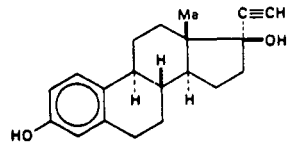
ETHINYLESTRADIOL

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	U.S.	1944
Lynoral	Organon	U.S.	1945
Eticyclol	Ciba	U.S.	1947
Ethinyl Oestradiol	Roussel	France	1950
Diogyn-E	Pfizer	U.S.	1953
Provest	Upjohn	U.S.	1964
Norlestrin	Parke Davis	U.S.	1964
Oracon	Mead Johnson	U.S.	1965
Feminone	Upjohn	U.S.	1970
Demulen	Searle	U.S.	–
Duramen	Leo	Sweden	–
Edrol	Virax	Australia	–
Ertonyl	Schering	–	–
Estigyn	Allen & Hanburys	U.K.	–
Etifollin	Nyegaard	Norway	–
Etivex	Leo	Sweden	–
Farmacyrol	Farmaryn	W. Germany	–
Follikoral	Arcana	Austria	–

Trade Name	Manufacturer	Country	Year Introduced
Gynetone	Schering	U.S.	–
Gynolett	Labopharma	W. Germany	–
Gynoral	Teva	Israel	–
Kolpi Gynaedron	Artesan	W. Germany	–
Metroval	Kwizda	Austria	–
Oradiol	Van Pelt & Brown	U.S.	–
Orestralyn	McNeil	U.S.	–
Ovahormon	Teikoku Zoki	Japan	–
Ovex	Ratiopharm	W. Germany	–
Progynon	Schering	W. Germany	–
Turisteron	Jenapharm	E. Germany	–
Ylestrol	Ferndale	U.S.	–

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.; U.S. Patent 2,265,976; December 9, 1941; assigned to Schering Corp.

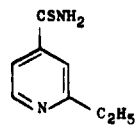
ETHIONAMIDE

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	U.S.	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 & Baker	U.K.	—
Tubenamide	Seiko	Japan	—
Tubermin	Meiji	Japan	—
Tuberoid	Sankyo	Japan	—
Tuberoson	Shionogi	Japan	—

Raw Materials

Methyl ethyl ketone
Ethyl oxalate
Hydrogen chloride
Phosphorus oxychloride
Phosphorus pentoxide
Ammonia
Cyanacetamid
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.

α-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

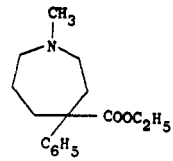
ETHOHEPTAZINE

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	U.S.	1957
Equagesic	Wyeth	U.S.	—
Mepro	Schein	U.S.	—
Panalgin	Padil	Italy	—
Zactipar	Wyeth	U.K.	—
Zactirin	Banyo	Japan	—

Raw Materials

Phenylacetonitrile
Sodium amide
Sulfuric acid
N-(2-Chloroethyl)dimethylamine
Trimethylene bromide
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.; U.S. Patent 2,666,050; January 12, 1954; assigned to American Home Products Corporation

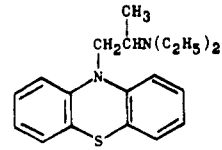
ETHOPROPAZINE HYDROCHLORIDE

Therapeutic Function: Antiparkinsonian

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

Common Name: Profenamin

Structural Formula:



(base)

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

Trade Name	Manufacturer	Country	Year Introduced
Parsidol	Warner Lambert	U.S.	1954
Parkin	Yoshitomi	Japan	1973
Parsidol	Sevenet	France	1981
Dibutil	Bayer	—	—
Lysivane	May & Baker	U.S.	—
Parsitan	Rhone-Poulenc	Canada	—
Parsotil	Rhodia Iberica	Spain	—
Rodipal	Deutsches Hydrierwerk	E. Germany	—

Raw Materials

Phenthiazine
Methyl iodide
2-Chloro-1-diethylamino propane
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 & 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.; U.S. Patent 2,607,773; August 19, 1952; assigned to Societe des Usines Chimiques Rhone-Poulenc, France

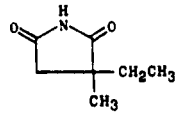
ETHOSUXIMIDE

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	U.S.	1960
Suxinutin	Parke Davis	W. Germany	1960
Zarontin	Parke Davis	U.K.	1960
Zarontin	Parke Davis	France	1965
Zarontin	Parke Davis	Italy	1966
Asamid	Pliva	Yugoslavia	–
Emeside	Lab. For Appl. Biol.	U.K.	–
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-methylpentanoate. 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.; U.S. Patent 2,993,835; July 25, 1961; assigned to Parke, Davis and Company