D

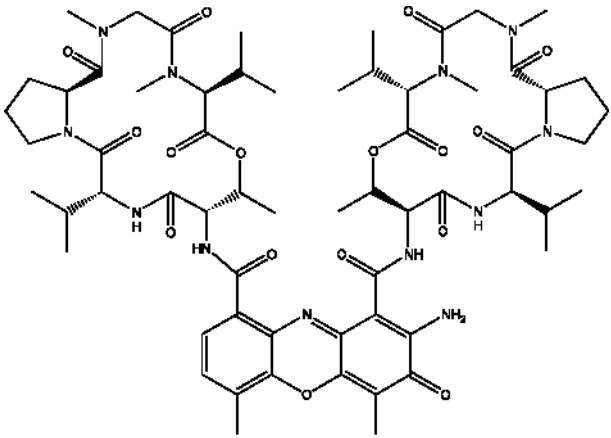
DACTINOMYCIN

Therapeutic Function: Cancer chemotherapy

Chemical Name: Actinomycin D

Common Name: Meractinomycin; Actinomycin D; Actinomycin A_{IV}

Structural Formula:



Chemical Abstracts Registry No.: 50-76-0

Trade Name	Manufacturer	Country	Year Introduced
Cosmegen	Merck Sharp and Dohme	US	1965
Lyovac	Merck Sharp and Dohme	W. Germany	1966
Cosmegen	Merck-Banyu	Japan	1969
Cosmegen	Merck Sharp and Dohme	Italy	1973

Raw Materials

Bacterium Actinomyces antibioticus
Nutrient medium

Manufacturing Process

An incubated culture of Actinomyces antibioticus was prepared using a medium consisting of 1% tryptone-peptone, 0.5% starch, 0.2% K_2HPO_4, 0.2% NaCl and 0.25% agar in distilled water, grown at a temperature of approximately 25° to 35°C, the incubation being complete after 6 to 10 days. 50 liters of this incubated culture are extracted approximately six times with ether, using 20 liters of ether for each extraction.

The final extract is faintly pale yellow in color, whereas the previous extracts are orange. The combined ether extracts are concentrated to dryness and about 3 grams of a reddish-brown residue is obtained. The residue is stirred with approximately 400 cc of petroleum ether for two to three hours, the solvent decanted and the residue treated again with approximately 400 cc of petroleum ether. A pale yellow oil constituting crude actinomycin B is recovered by evaporation from the petroleum ether.

The dark petroleum ether insoluble residue is dissolved in 1 liter of benzene with gentle heating. Usually a small amount of black amorphous material remains undissolved and is filtered off. The benzene solution is permitted to drop through a chromatographic tower (60 x 5 cm) packed with aluminum oxide (according to Brockman). The pigment is readily adsorbed. The column is washed with about 1 liter of benzene during which operation very little migration of the color bands occurs.

The column is then washed with benzene-acetone solution (15:85) whereby a chromatogram develops. By continued washing, light yellow colored pigments pass out of the column. When the main band (orange-red) reaches the lower end of the column, a solution of 30:70 acetone-benzene is passed through the column. The latter solvent elutes the pigment and when the eluate is very pale in color, washing is discontinued.

The eluate is concentrated to dryness under reduced pressure, taken up in 25 cc of hot acetone, filtered, and diluted with ether. The pigment which crystallizes as red-brick colored platelets is essentially pure but may be recrystallized if desired from hot ethyl acetate. An analysis of the product showed C = 59.01; H = 6.81; N = 13.38.

References

Merck Index 2792
Kleeman and Engel p. 265
PDR p. 1151
I.N. p. 282
REM p. 1148
Waksman, S.A. and Woodruff, H.B.; US Patent 2,378,876; June 19, 1945; assigned to Merck and Co., Inc.

DALTEPARIN SODIUM

Therapeutic Function: Anticoagulant, Antithrombotic

Chemical Name: Heparin, compounds, sodium salt

Common Name: Dalteparin sodium; Tedelparin 4-6

Structural Formula: Heparin, compounds, sodium salt

Chemical Abstracts Registry No.: 9041-08-1

Trade Name	Manufacturer	Country	Year Introduced
Fragmin	Vetter Pharma-Fertigung GmbH	Germany	-
Fragmin	Pharmacia and Upjohn	Belgium	-
LigoFragmin	Pfizer	Argentina	-

Raw Materials

Heparin
Starch-iodine paper
Sodium nitrate
Caustic soda

Manufacturing Process

Heparinic acid a highly acidic mucopolysaccharide formed of equal parts of sulfated D-glucosamine and D-glucuronic acid with sulfaminic bridges. The molecular weight ranges from six to twenty thousand. Heparin occurs in and is obtained from liver, lung, mast cells, etc., of vertebrates. Its function is unknown, but it is used to prevent blood clotting in vivo and vitro, in the form of many different salts.

In a self-regulated process for depolymerizing a heparin in an aqueous solution by providing about 0.02 to 0.1 M nitrous acid and a pH of about 2 to 3 in said solution, so that process occurs when all the nitrous acid has been consumed and mucopolysaccharides are produced from the heparin having an average molecular weight of less than 6,000. Heparin has molecular weight from 2000 to 50000. The products obtained by a below described method are constituted by a major part of species of molecular weight of about 2,000 to 8,000, which corresponds to structures having from about 8 to 40 saccharide entities (the molecular weights are measured by the HPLC method, by means, for example, of a 0.5 M sodium sulphate buffer).

Self-Regulated Depolymerization of Heparin and Production of MPS of Low Molecular Weight.

Into 15 liters of distilled water at +20°C, 1,500 grams of commercial heparin having a YW/USP ratio in the vicinity of 1 and a USP titer of 160 iu, are dissolved. 51.8 g of sodium nitrate dissolved in 300 ml of distilled water are added, and immediately the pH is lowered to 2.5 by pure hydrochloric acid.

The reaction then takes place and its progress is checked until the absence of nitrous ions. After 40 minutes, the presence or absence of nitrous ions is checked at regular intervals in the reaction medium. Starch-iodine paper, for example, is used, checking every 5 minutes. After about 60 minutes of reaction, the nitrous acid had been entirely consumed and no more NO_2^- ions remained in the reaction medium. The pH was then adjusted to 7 with pure caustic soda, and the products of the reaction were recovered by the addition of 31 liters of pure ethanol (2 volumes). The precipitate formed was collected by centrifugation, washed with ethanol and dried at 60°C under vacuum. 1,200 g of products having the following characteristics were collected: USP titer: 19 μ/mg; APTT titer: 13 μ/mg; Yin and Wessler titer: 202 μ/mg.

In 10 liters of distilled water, at room temperature (15°-20°C) 1,000 grams of commercial injectable heparin having a USP titer of 170 μ/mg and a YW titer of 160 μ/mg, are dissolved. 38 g of sodium nitrite (final molarity 0.055 M) dissolved in 200 ml of water, is added. The pH is immediately lowered to 2.5 by pure hydrochloric acid. The reaction is checked as above at regular intervals of time (5-10 minutes). After 30 minutes, NO_2^- ions are no longer detected in the reaction medium. The pH is then adjusted to 7 with 5 N soda; the products of the reaction are recovered by the addition of 21 liters of pure ethanol (2 volumes). The precipitate formed is collected by centrifugation, washed with ethanol and dried at 60°C under vacuum. Finally there are obtained 780 grams of white coloured powder having the following characteristics: USP Titer: 22 μ/mg; Yin and Wessler Titer: 260 μ/mg; APTT Titer: 10 μ/mg. Content of nitrites-nitrates: 5 ppm: <4 ppm. Average molecular weight: less than 6,000. Percentage of species whose molecular weight exceeds 10,000: less than 1%.

References

Lormeau J.-C. et al.; US Patent No. 5,019,649; May 28, 1991; Assigned to Choay S. A., Paris Cedex, France

DANAPAROID SODIUM

Therapeutic Function: Antithrombotic

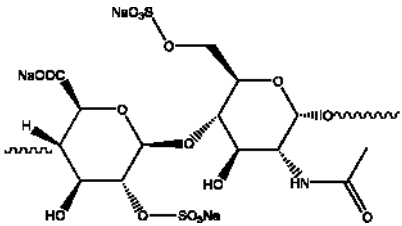
Chemical Name: Suleparoid sodium salt (ap. 84%), mixture with dermatan sulphate sodium (ap. 12%) and chondroitin sulphate sodium (ap. 4%)

Common Name: Danaparoid sodium; Dermatan sulfate

Chemical Abstracts Registry No.: 83513-48-8

Trade Name	Manufacturer	Country	Year Introduced
Danaparoid sodium	Organon	Netherlands	-
Orgaran	Organon	-	-

Structural Formula:



Raw Materials

Bovine lung or mucous
QAE Sephadex A50
Proteases of Bacillus subtilis
Proteolytic enzymes from pig pancreas

Manufacturing Process

Bovine lung (100 kg) was treated with proteolytic enzymes from pig pancreas. After 15 hours incubation at pH 8.5, 40°C, the mixture was filtered off. The clear filtrate was brought into contact with a strongly basic ion exchanger (QAE Sephadex A50) and stirred for 15 hours. Then the ion exchanger was filtered off and eluted with an aqueous solution of NaCl (200 g/L). Methanol was added to the eluate up to 50% v/v. The resultant precipitate was removed, after which methanol was added to the mother liquor up to 75% v/v. The precipitate was recovered, washed with 100% methanol and dried. The white amorphous powder (22.7 g) obtained had a galactosamine content of 0.45 mmol/g, a glucosamine content of 0.54 mmol/g, an average molecular weight of 6600 with an auxiliary peak at an average of 38,000 (determined with respect to dextrane), an $[\alpha]_D^{20}$ of +34.2°, a sulphur content of 5.7%, a nitrogen content of 2.6%, a content of ionic groups of 3.90 meq/g, a content of sulphamido groups of 0.69 mmol/g and an idose/glucose ratio of 2.1.

Pig intestinal mucous (100 kg) was treated with proteases of Bacillus subtilis at 35°C and pH 8.2 for 24 hours. The mixture was filtered and the clear filtrate was processed in a manner similar to that described above. The yield was 3.2 g of white amorphous powder with a galactosamine content of 0.38 mmol/g, a glucosamine content of 0.82 mmol/g, an average molecular weight of 6100 with an auxiliary peak at an average of 42,000 (determined with respect to dextrane), an $[\alpha]_D^{20}$ of +35.1°, a sulphur content of 5.9%, a nitrogen content of 2.7%, a content of ionic groups of 3.70 meq/g, a content of sulphamido groups of 0.73 mmol/g and an idose/glucose ratio of 1.9.

References

Sanders A. et al.; US Patent No. 4,438,108; Mar. 20, 1984; Assigned to Akzo N.V., Arnhem, Netherlands

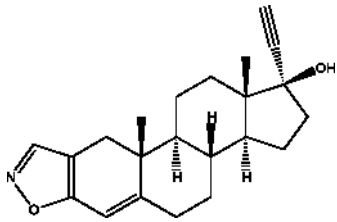
DANAZOL

Therapeutic Function: Anterior pituitary suppressant

Chemical Name: 17α-Pregna-2,4-dien-20-yno[2,3-d]isoxazol-17-ol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 17230-88-5

Trade Name	Manufacturer	Country	Year Introduced
Danol	Winthrop	UK	1974
Danocrine	Sterling Winthrop	US	1976
Winobanin	Winthrop	W. Germany	1976
Danatrol	Winthrop	Switz.	1976
Bonzol	Tokyo Tanabe	Japan	1983
Chronogyn	Winthrop	US	-
Cyclomen	Winthrop	Canada	-
Danatrol	Sterwin Espanola	Spain	-
Ladogal	Ross	US	-
Ladogar	Winthrop	-	-

Raw Materials

17α-Ethynyl-2-hydroxymethylene-4-androsten-17β-ol-3-one
Hydroxylamine
Sodium acetate
Acetic acid

Manufacturing Process

Danazol was prepared from 4.32 grams of 17α-ethynyl-2-hydroxymethylene-4-androsten-17β-ol-3-one, 1.00 gram of hydroxylamine hydrochloride, 1.12 grams of fused sodium acetate and 135 ml of acetic acid. To a 500 ml, 3-necked flask, equipped with a sealed Hershberg-type stirrer, a reflux condenser and a stopper, was added the above androstenone derivative in 300 ml of 95% ethanol. Stirring was commenced and a slurry of fused sodium acetate and hydroxylamine hydrochloride in glacial acetic acid was added.

The mixture was refluxed gently on a steam bath for 1½ hours. Fifteen minutes after initiating the reaction, the reaction mixture gave a negative ferric chloride test. Most of the ethanol and acetic acid were removed by distillation in vacuo, 300 ml of water and 300 ml of ether were added to the concentrate, and the mixture was shaken. The layers were separated, the aqueous layer extracted with fresh ether, and the combined ether extracts were washed with water, dried over anhydrous sodium sulfate, filtered and evaporated to dryness in vacuo. The residue was crystallized by trituration with ether, and the crystals were collected by filtration, washed with hexane and dried. The mother liquors were concentrated to dryness and dissolved in a minimum amount of acetone, whereupon a second crop was obtained. The two crops were combined, dissolved in ethyl acetate, decolorized with activated charcoal, and recovered by concentration.

There was thus obtained 2.35 grams of 17α-ethynyl-17β-hydroxy-4-androsteno[2,3-d]isoxazole, MP 224.2°-226.8°C (corr.) when recrystallized from acetone; $[\alpha]_D^{25}$= +7.5±0.2° (in 95% ethanol); ultraviolet maximum at 286 nm (E=11,300).

References

Merck Index 2799
Kleeman and Engel p. 266
PDR p. 1907
OCDS Vol. 2 p. 157 (1980)
DOT 11 (2) 52 (1975) and 18 (5) 223 (1982)
I.N. p. 283
REM p. 997
Clinton, R. and Hanson, A.; US Patent 3,135,743; June 2, 1964; assigned to Sterling Drug

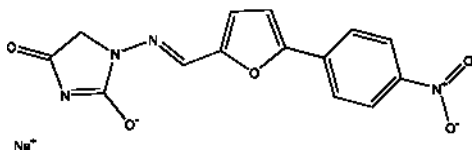
DANTROLENE SODIUM

Therapeutic Function: Muscle relaxant

Chemical Name: 1-[[[5-(4-Nitrophenyl)-2-furanyl]-methylene]amino]-2,4-imidazolidinedione sodium salt

Common Name: 1-[[5-(p-Nitrophenyl)furfurylidene]-amino]hydantoin sodium salt

Structural Formula:



Chemical Abstracts Registry No.: 28468-30-0; 7261-97-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Dantrium	Norwich Eaton	US	1974
Dantrium	Eaton	UK	1975
Dantamacrin	Roehm	W. Germany	1978
Dantrium	Oberval	France	1979
Dantrium	Yamanouchi	Japan	1981
Dantrium	Formenti	Italy	1981
Dantrix	S.I.T.	Italy	-

Raw Materials

5-(p-Nitrophenyl)-2-furaldehyde
1-Aminohydantoin hydrochloride
Sodium hydroxide

Manufacturing Process

5-(p-Nitrophenyl)-2-furaldehyde (40.0 grams, 0.2 mol) is dissolved in dimethylformamide. An aqueous solution of 1-aminohydantoin hydrochloride (30.0 grams, 0.2 mol) is added. The solution is chilled and diluted with water. The crude material is collected and recrystallized from aqueous dimethylformamide to yield 10.0 grams (16%). MP 279°-280°C. This compound is then converted to the sodium salt.

References

Merck Index 2803
Kleeman and Engel p. 266
PDR p. 1273
OCDS Vol. 2 p.242 (1980)
DOT 17 (9) 384 (1981)
I.N. p. 284
REM p. 922
Davis, C.S. and Snyder, H.R. Jr.; US Patent 3,415,821; December 10, 1968; assigned to The Norwich Pharmacal Company

DAPSONE

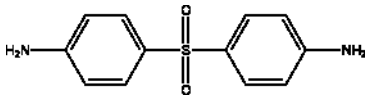
Therapeutic Function: Antibacterial (leprostatic)

Chemical Name: 4,4'-Sulfonylbisbenzamine

Common Name: Bis(4-aminophenyl)sulfone; Diaphenylsulfone

Chemical Abstracts Registry No.: 80-08-0

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Avlosulfon	Ayerst	US	1957
Dapsone	Jacobus	US	-
Disulone	Specia	France	-
Maloprim	Wellcome	UK	-
Protogen	Yoshitomi	Japan	-
Sulfona Oral	Esteve	Spain	-
Udolac	I.C.I.	UK	-

Raw Materials

p-Chloronitrobenzene
Stannous chloride
Acetamidobenzene sodium sulfonate
Hydrogen chloride

Manufacturing Process

p-Chloronitrobenzene is reacted with $NaSO_2C_6H_5NHCOCH_3$ to give as an intermediate, $O_2NC_6H_5SO_2C_6H_5NHCOCH_3$ which is then reduced and deacetylated to give the product, dapsone. Alternatively, benzene and sulfuric acid react to give phenyl sulfone which is nitrated, then reduced to give dapsone.

References

Merck Index 2808
Kleeman and Engel p. 267
PDR p. 951
OCDS Vol. 1 p. 139 (1977) and 2 p. 112 (1980)
I.N. p. 284
Weijiard, J. and Messerly, J.P.; US Patent 2,385,899; October 2, 1945; assigned to Merck and Co., Inc.

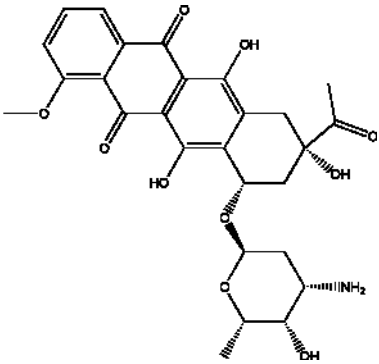
DAUNORUBICIN

Therapeutic Function: Cancer chemotherapy

Chemical Name: (8S-cis)-8-Acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione

Common Name: Rubidomycin; Antibiotic F.I. 1762

Structural Formula:



Chemical Abstracts Registry No.: 20830-81-3

Trade Name	Manufacturer	Country	Year Introduced
Cerubidine	Specia	France	1968
Daunoblastin	Farmitalia	W. Germany	1968
Daunoblastina	Farmitalia	Italy	1968
Daunomycin	Meiji Seika	Japan	1970
Cerubidin	May and Baker	UK	1971
Cerubidine	Ives	US	1979
Cerubidine	Rhone Poulenc	Canada	-
Ondena	Bayer	-	-
Rubomycin	Medexport	USSR	-

Raw Materials

Bacterium Streptomyces F.I. 1762
Glucose

Manufacturing Process

Two 300 ml Erlenmeyer flasks are prepared, each of them containing 60 ml of the following vegetative medium in tap water: 0.6% peptone, 0.3% dry yeast and 0.05% calcium nitrate. The pH after sterilization by heating in an autoclave to 120°C for 20 minutes is 7.2.

Each flask was inoculated with mycelium of Streptomyces F.I. 1762 whose quantity corresponds to one-fifth of a suspension in sterile water of the mycelium of a 10 day old culture growth in a test tube containing the following ingredients dissolved in tap water.

	Percent
Saccharose	2
Dry yeast	0.1
Potassium hydrogen phosphate	0.2

	Percent
Sodium nitrate	0.2
Magnesium sulfate	0.2
Agar	2

The flasks are incubated at 28°C for 48 hours on a rotary shaker with a stroke of 60 mm at 220 rpm. 2 ml of a vegetative medium thus grown are used to inoculate 300 ml Erlenmeyer flasks containing 60 ml of the following productive medium in tap water at pH 7.0.

	Percent
Glucose	4
Dry yeast	1.5
Sodium chloride	0.2
Potassium hydrogen phosphate	0.1
Calcium carbonate	0.1
Magnesium sulfate	0.01
Iron sulfate	0.001
Zinc sulfate	0.001
Copper sulfate	0.001

(The medium had been sterilized at 120°C for 20 minutes, the glucose being previously sterilized separately at 110°C for 20 minutes.) It is incubated at 28°C under the conditions described for the vegetative media. After 120 hours of fermentation a maximum activity corresponding to a concentration of 60 micrograms/ml is achieved.

References

Merck Index 2815
PDR p. 1944
DOT 16 (11) 371 (1980)
I.N. p. 285
REM p. 1148
British Patent 1,003,383; September 2, 1965; assigned to Sta Farmaceutical Italia, Italy

DAUNORUBICIN HYDROCHLORIDE

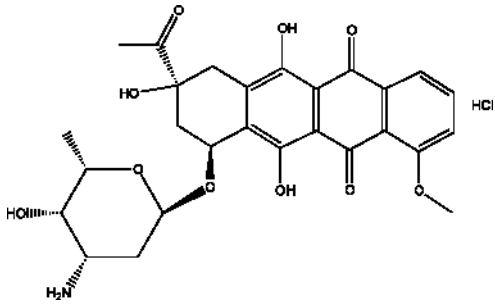
Therapeutic Function: Antineoplastic

Chemical Name: 5,12-Naphthacenedione, 8-acetyl-10-((3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy)-7,8,9,10-tetrahydro-6,8,11-trhydroxy-1-methoxy-, hydrochloride, (8S,10S)-

Common Name: Daunomicina cloridrato; Daunomycin hydrochloride; Daunorubucin hydrochloride; Rubidomycin hydrochloride

Chemical Abstracts Registry No.: 23541-50-6

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Cerubidin	Rhone-Poulenc Rorer	France	-
Cerubidine	Ben Venue Laboratories, Inc.	USA	-
Daunorubicin hydrochloride	LKT Laboratories, Inc.	USA	-
DaunoXome	Nexstar Pharmaceuticals Internetional	UK	-
DaunoXome	Gilead Sciences Inc.	USA	-
Rubilem	Sanital Pharmaceuticals	Pakistan	-

Raw Materials

Corn steep	Sucrose
Soya flour	Soya oil
Starch	Amberlite

Manufacturing Process

A 170 liter fermentation vessel is charged with:

Corn steep	2.400 kg
Sucrose	3.600 kg
Calcium carbonate	0.900 kg
Ammonium sulphate	0.240 kg
Water	to 100 liters

This culture medium has a pH of 6.15. It is sterilised by passage of steam at 122°C for 40 minutes. After cooling, the volume of the broth is 120 liters and the pH is 7.20. The medium is then seeded with 200 cc of a culture of the strain Streptomyces 31723. The culture is carried out for 27 hours at 26°-27°C with agitation and aeration with sterile air. It is then suitable for seeding the production culture. The production culture is carried out in an 800 liter formentation vessel charged with the following:

Soya flour	20 kg
Distillers' solubles	2.500 kg
Soya oil	2.500 liters
Sodium chloride	5 kg
Water	to 465 liters
Starch	10 kg

The pH of the medium thus obtained is adjusted to 7.20 with concentrated sodium hydroxide solution (400 cc). The medium is then sterilised by the passage of steam at 122°C for 40 minutes. After cooling, the volume of the broth is 500 liters and the pH is 6.75. It is then seeded with 50 liters of the culture from the 170 liter fermentation vessel. Culture is carried out at 28°C for 67 hours with agitation and aeration with sterile air. The pH of the medium is then 7.40 and the volume of the fermentation culture is 520 liters. The quantitiy of antibiotic present in the medium is 29 μ/cc.

The above fermentation culture (520 liters; activity 29 μ/cc) is placed in a vessel equipped with an agitator and the pH is adjusted to 1.8 with a concentrated solution of oxalic acid. Agitation is carried out for one hour and a filtration adjuvant (20 kg) then added. The mixture is filtered on a filter-press and the filter-cake washed with water (100 liters) acidified to pH 2 with oxalic acid. The filtrate (612 liters) is treated with concentrated sodium hydroxide solution until the pH is 4.5. The filtrate is then passed through a column containing Amberlite IRC 50 in hydrogen form (20 liters; diameter of column 15.2 cm, height of column 200 cm, height of resin at rest in column 110 cm). The filtrate passes through the bed of Amberlite from base to top at a rate of 40 liters/hour. The column is then washed with water (100 liters) at a rate of 50 liters/hour circulating from base to top and then with methanol (containing 10% water; 75 liters) circulating from top to base at a rate of 50 liters/hour. The washings are discarded and the column is then eluted with a solution having the following composition (per liter):

Sodium chloride	10 g
Water	100 cc
Methanol	to 1000 cc

The eluate (100 liters), which contains the major part of the antibiotic, is concentrated under reduced pressure at 35°C to 10 liters. The concentrate is extracted at pH 7.5 with chloroform (2 times 5 liters). The chloroformic extract is adjusted to pH 4 with a solution of acetic acid in chloroform (10:100 by volume) and then concentrated at 30°C under reduced pressure to 100 cc. The antibiotic is precipitated by the addition of hexane (1 liter), separated, washed and dried to give an amorphous red powder (9 g) of activity 1,400 μ/mg.

The crude antibiotic (17.1 g) obtained as above described (activity 1530 μ/mg) is dissolved with stirring in a mixture of methylene chloride (1.5 liters), carbon tetrachloride (0.3 liters) and water (1.8 liters). The pH is then adjusted to 3 by the addition of normal hydrochloric acid (8 cc). After decanting, the aqueous phase is treated with methylene chloride (7 liters) and 0.1 N sodium hydroxide solution (200 cc) to give a pH of 7.5. After decanting, the aqueous phase is again extracted at pH 7.5 with methylene chloride (3.5 liters). The methylene chloride extracts are combined and concentrated to 100 cc. After the addition of hexane (1 liter) to the concentrate, a product precipitates

which is filtered off, washed and dried at 30°C under reduced pressure to give the antibiotic 9865 RP (9.15 g) in the form of an amorphous orange-red powder of activity 2180 μ/mg.

9865 RP (500 mg), obtained as above described, is dissolved in normal sulphuric acid (100 cc) and the solution obtained is heated for 20 minutes on a water-bath. After cooling and extracting with ethyl acetate (3 times 200 cc), the organic extract is dried over anhydrous sodium sulphate, filtered and concentrated to a small volume, giving, after filtering, washing and drying, crystals (218.5 mg). These crystals (150 mg) are dissolved in chloroform (3 cc) and benzene (1.5 cc) and the solution obtained is chromatographed on 20 sheets of Arches No. 310 paper impregnated with a solution of acetone containing 20% formamide, and developed for 90 minutes by means of a 2:1 mixture of chloroform and benzene saturatd with formamide. The principal zone of R_f = 0.86 is cut out of each of the 20 sheets and the 20 zones thus cut out are comminuted in a mixer in the presence of methanol. The mixture obtained is filtered, concentrated, and water (10 volumes) added. The precipitate obtained is filtered off, washed and dried under reduced pressure to give crystals (120 mg). These crystals (170 mg) are dissolved in dioxan containing 20% water (15 cc) and water acidified to pH 4 with 0.1 N hydrochloric acid is added dropwise. The crystals formed are filtered off, washed and dried, thus giving the aglycone of 9865 RP (130 mg) in the form of orange-red needles, having a first melting point at 160°C and a second at 225°C-230°C.

Daudorubicin can be prepared by gene ingineering methods also.

References

Pinnert S. et al.; US Patent No. 3,989,598; Nov. 2, 1976; Assigned: Rhone-Poulenc S.A. (Paris, FR)
Hautchinson S.R. et al.; US Patent No. 5,364,781; Nov. 15, 1994; Assigned: Farmitalia Carlo ERBA S.r.l (Milan, IT)

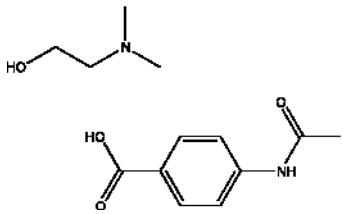
DEANOL ACETAMIDOBENZOATE

Therapeutic Function: Psychostimulant

Chemical Name: 4-(Acetylamino)benzoic acid compound with 2-(dimethylaminoethanol) (1:1)

Common Name:

Structural Formula:



Chemical Abstracts Registry No.: 3635-74-3

Trade Name	Manufacturer	Country	Year Introduced
Deaner	Riker	US	1958
Bimanol	Polfa	Poland	-
Cervoxan	S.M.B.	Belgium	-
Deanol	Kettelhack Riker	W. Germany	-
Diforene	Choay	France	-
Pabenol	Gentili	Italy	-

Raw Materials

p-Acetylaminobenzoic acid
2-Dimethylaminoethanol

Manufacturing Process

About 40 grams (0.223 mol) of p-acetylaminobenzoic acid was dissolved in 600 ml of absolute methanol, and the solution was heated to reflux temperature. Heating was discontinued, and, with mechanical stirring, 19.9 grams (0.223 mol) of 2-dimethylaminoethanol was added through a dropping funnel as fast as the exothermic nature of the reaction permitted. The reaction mixture was allowed to cool to room temperature (2.5-3 hours) under mechanical agitation, and the solution was suction-filtered through Celite filter aid. The filtrate was poured into 500 ml of anhydrous ethyl ether, seeded with a few crystals of 2-dimethylaminoethanol p-acetylaminobenzoate. The seeding crystals were obtained by introducing 3 to 6 drops of the filtered reaction mixture into a test tube containing 10 ml of anhydrous diethyl ether. The contents of the test tube were thoroughly shaken and allowed to stand at room temperature. The salt crystallized out within not more than 10-15 minutes.

The crude product (48.4 grams, 80.9% yield) was recrystallized from an absolute ethanol-ethyl acetate solvent system by suspending the salt in boiling anhydrous ethyl acetate and just enough absolute ethanol was gradually added to effect solution after which the solution was concentrated to about two-thirds of the original volume on the steam bath, charcoal treated, and suction-filtered through Celite filter aid. The white crystals of 2-dimethylaminoethanol p-acetylaminobenzoate obtained, dried at room temperature at a pressure of 0.08 mm Hg for 15 hours, melted at 159.0°-161.5°C.

References

Merck Index 2827
Kleeman and Engel p. 267
I.N. p. 285
REM p. 1136
British Patent 879,259; October 11, 1961; assigned to Riker Laboratories, Inc.

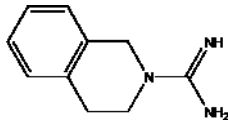
DEBRISOQUIN

Therapeutic Function: Antihypertensive

Chemical Name: 3,4-Dihydro-2(1H)-isoquinolinecarboximidamide

Common Name: Isocaramidine

Structural Formula:



Chemical Abstracts Registry No.: 1131-64-2; 581-88-4 (Sulfate)

Trade Name	Manufacturer	Country	Year Introduced
Declinax	Roche	UK	1967
Bonipress	Ikapharm	Israel	-
Redu-Pres	Protea	Australia	-
Tendor	Chinoin	Hungary	-

Raw Materials

1,2,3,4-Tetrahydroisoquinoline
2-Methyl-2-isothiourea sulfate

Manufacturing Process

27 g of 1,2,3,4-tetrahydroisoquinoline was added at room temperature to a solution of 28 g of 2-methyl-2-isothiourea sulfate in 80 ml of water. The resulting mixture was kept at room temperature with occasional shaking. After a short period of time, methylmercaptan began to escape, and the mixture warmed up slightly. After then standing for 24 hours, crystals formed. They were filtered off and rinsed with ice cold water. Recrystallization from approximately 100 ml of water yielded 1,2,3,4-tetrahydroisoquinoline-2-carboxamidine sulfate melting at 278°C to 280°C (uncorr.).

Another batch prepared in the same manner melted at 284°C to 285°C due to a minute difference in moisture content.

Both batches prepared above analyzed correctly for $(C_{10}H_{13}N_3)_2 \cdot H_2SO_4$.

References

Merck Index 2828
OCDS Vol. 1 p. 350 (1977) and 2 p. 374 (1980)
DOT 16 (4) 137 (1980)
I.N. p. 286

Wenner,W.; US Patent 3,157,573; November 17, 1964; assigned to Hoffmann-LaRoche, Inc.

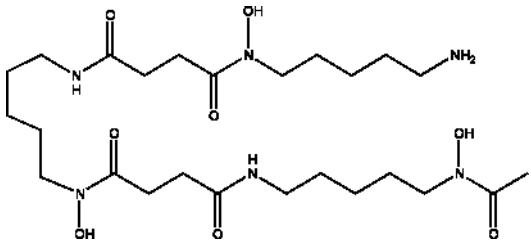
DEFEROXAMINE

Therapeutic Function: Pharmaceutic aid (chelating agent)

Chemical Name: Butanediamide, N'-(5-((4-((5-(acetylhydroxyamino)pentyl) amino)-1,4-dioxobutyl)hydroxyamino)pentyl)-N-(5-aminopentyl)-N-hydroxy-

Common Name: Deferoxamine; Desferrioxamine

Structural Formula:



Chemical Abstracts Registry No.: 70-51-9

Trade Name	Manufacturer	Country	Year Introduced
Deferoxamine	Novartis	Germany	-
Desferal	Ciba-Geigy	Switz.	-

Raw Materials

4-Cyanobutanal
Succinic anhydride
Acetic anhydride
Dicyclohexylcarbodiimide
Palladium on carbon
o-Benzylhydroxylamine hydrochloride
Sodium cyanoborohydride
Nickel Raney
Dimethylaminopyridine

Manufacturing Process

O-Benzylhydroxylamine hydrochloride (4.7 g, 29.7 mmol) was mixed with 5 ml of water and 11 ml of methanol at 0°C and the pH adjusted to 4.7 using 6 N KOH. The aldehyde, 4-cyanobutanal (2.6 mL, 27 mmol) was added to the hydroxylamine and the mixture allowed to warm to room temperature. The pH was maintained by addition of further 6 N KOH. After 1 h, the reaction was cooled to 0°C, and sodium cyanoborohydride (1.26 g, 20 mmol) was added. The pH was adjusted to 3 and maintained by addition of saturated HCl in methanol. When the pH stabilized, the reaction was warmed to room

temperature and stirred for 3 h at a PH of 3. The reaction mixture was then poured into ether and made basic with 6 N KOH. The aqueous layer was extracted with ether (3x50 mL). The extracts were combined, washed with brine, and dried over magnesium sulfate. The solvents were removed and the resulting liquid distilled at 150°-151°C (0.6 mm) to give 4.65 g (84% of O-benzyl-N-(4-cyanobutyl)hydroxylamine. 2.8 g (13.7 mmol) of the above prepared hydroxylamine in 23 ml of pyridine and 2.1 g (20.8 mmol) of succcinic anhydride, initially heated at 100°C for 1.5 h then allowed to cool to room temperature and stirred overnight. The pyridine was removed in vacuum and the residue was dissolved in a minimal amount of chloroform, and the residue was dissolved in ether, which was extracted three times with 20% potassium bicarbonate (3x50 mL). The aqueous solutions were combined, acidified, extracted with ether, dried, filtered and evaporated; the residue was then chromotagraphed on silica gel to give 4.12 g (98%) of N-(4-cyanobutyl-N-(benzyloxy)succinamic acid.

2.6 g (12.75 mmol) of O-benzyl-N-(4-cyanobutyl)hydroxylamine, 17.24 mL of pyridine and 17.2 mL of acetic anhydride were stirred under argon at room temperature for 24 h. Then the excess pyridine and acetic acid anhydride were removed by vacuum. The resulting oil was taken up in chloroform, which was extracted with 1 N HCl (2x50mL), washed with sodium bicarbonate and brine, dried, over sodium sulfate, filtered and evaporated to give 3.4 g (100%) of N-(4-cyanobutyl)-N-(benzyloxy)acetamide as a light oil. 1.4 g (5.7 mmol) of this product, 2.6 g Raney nickel, 15 ml of ammonia saturated methanol and 4 ml of saturated ammonium hydroxide were cooled in a ice bath and anhydrous ammonia was allowed to bubble through the solution for 10 min. The bottle was pressurized to 50 psi with hydrogen and shook for 3 h. Then the catalyst was filtered and the solvents evaporated. The crude material was chromatografed on silica gel to gave a 1.25 g (88%) of N-(5-aminopentyl)-N-(benzyloxy)acetamide.

1 g (4 mmol), of the above acetamide, 1.46 g (4.79 mmol) of N-(4-cyanobutyl-N-(benzyloxy)succinamic acid, 1.24 g (6 mmol) of DCC and 70 mg of DMAP was cooled to 0°C for 0.55 h in 28 mL of chloroform. The mixture was allowed to warm to room temperature and stirred 24 h. Then it was again cooled to 0°C, filtered and chromatografed to yield 2.1 g (98%) of N-(4-cyanobutyl)-3-[{5-N-benzyloxy)acetamido)pentyl}carbomoyl]-O-benzylpropionohydroxamic acid. This product (1 g) was hydrogeneted by analogue with N-(4-cyanobutyl)-N-(benzyloxy)acetamide using Nickel Raney as catalyst to give 1 g (88%) N-(5-aminopentyl)-3-[{5-(N -benzyloxyacetamido)pentyl}carbomoyl]-O-benzylpropionohydroxamic acid, which produced by the reaction with DCC described above 0.78 g (88%) of N-[5-[3-[{4-cyanobutyl)(benzyloxy)-carbomoyl]propionaminoamido]pentyl}-3-[{5-(N-bebzyloxyacetamido)pentyl]-carbomoyl]-O-benzylpropionohydroxamic acid. The purity of all products confirmed with1H-NMR and elemental analyses. The last compound (0.165 g, 0.2 mmol) was reduced in methanol, 2.7 mL of 0.1 N HCl and 0.27 g of 10% Pd on C. The hydrogenation was carried out at one atmosphere of hydrogene for 7.5 hrs. The solution was filtered, the solvents were removed and the residue was washed with cold methanol, and then chloroform to give 0.1 g (84%) of product. This material had melting point 167°-168°C [Prelog, supra] and was identical to an authentic sample by 300 MHz NMR [sample of deferrioxamine B supplied by dr. Heirich H. Peter at Ciba-Geigy, Basel, Switzerland].

References

Bergeron, R.J. et al.; EP0,347,163 A2; 20.12.89
Bickel, Helv. Chim. Acta., 43, 2129 (1960)
Helv. Chim. Acta., 45, 631 (1962)
Bergerson R.J. and Pegram J. J., J. Org. Chem., 53, 3131 (1988)

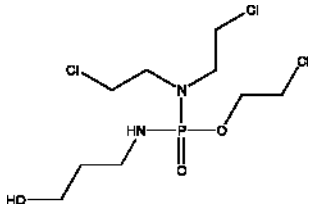
DEFOSFAMIDE

Therapeutic Function: Antineoplastic

Chemical Name: N,N,O-Tris-(β-chloroethyl)-N'-(γ-hydroxy-n-propyl)-phosphoric acid ester diamide

Common Name: Desmofosfamide; Trichlorethoxyphosphamide

Structural Formula:



Chemical Abstracts Registry No.: 3733-81-1

Trade Name	Manufacturer	Country	Year Introduced
Mitarson	Asta-Werke	W. Germany	1961

Raw Materials

N,N-Bis(β-chloroethyl)phosphoric acid amide dichloride
Ethylene chlorohydrin
1,3-Propanolamine

Manufacturing Process

A solution of 8 g of ethylene chlorohydrin and 10.2 g of triethylamine in 50 cc of absolute dioxane is slowly added dropwise to a solution of 25.9 g of N,N-bis-(β-chloroethyl)-phosphoric acid amide dichloride in 100 cc of absolute dioxane. The mixture is then heated for 2 hours at 60°C. After cooling, a solution of 7.5 g of 1,3-propanolamine and 10.2 g of triethylamine in 50 cc of absolute dioxane is added dropwise while stirring well and at a temperature up to 30°C. The mixture is left to stand for another 12 hours. The liquid is filtered off with suction from the precipitated triethyamine hydrochloride. The filtrate is filtered through carbon and concentrated by evaporation in water-jet vacuum at 40°C. The residue is dissolved in a little alcohol. Copious amounts

of ether are added and the solution is left overnight in a refrigerator. It is then again filtered through carbon, the ether is evaporated and the residual volatile fractions are removed under high vacuum at 55°C. The result is a yellowish, fairly viscous oil, which is insoluble in water.

References

Merck Index 2840
I.N. p. 288
Arnold, H., Bourseaux, F. and Brock, N.; US Patent 3,035,080; May 15, 1962; assigned to AstaWerke A.G. Chemische Fabrik (W. Germany)

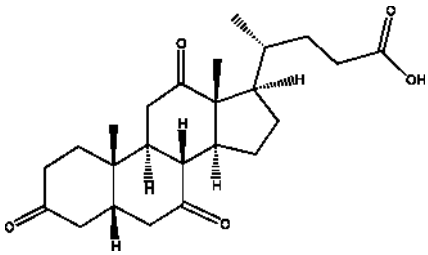
DEHYDROCHOLIC ACID

Therapeutic Function: Choleretic, Diuretic, Diagnostic aid

Chemical Name: Cholan-24-oic acid, 3,7,12-trioxo-, (5β)-

Common Name: Acide dehydrocholique; Acidum dehydrocholicum; Acidum trioxocholanicum; Dehydrocholic acid; Dehydrocholsaeure; Ketocholanic acid

Structural Formula:



Chemical Abstracts Registry No.: 81-23-2

Trade Name	Manufacturer	Country	Year Introduced
Dehydrocholic Acid	New Zealand Pharmaceuticals Limited (NZP)	-	-
Dehydrocholic Acid	ICE (Industria Chimica Emiliana)	-	-
Atrocholin	Glaxo	-	-

Raw Materials

Cholic acid
Sodium sulfite

Manufacturing Process

A.) Oxidation of cholic acid:

A solution, consisting of 15.40 g of cholic acid and 18.75 g of anhydrous sodium acetate in a solvent mixture of 20 ml of ethyl acetate, 30 ml of glacial acetic acid, and 30 ml of water, was prepared. This solution was cooled to 20°C. Chlorine gas was bubbled into the solution with vigorous stirring while the reaction temperature was maintained at 20°C. The chlorine was delivered at a constant rate of about 2.5 g per hour over a 4-hour period. The total amount of chlorine gas was 9.80 g which corresponds to about 3.68 moles per mole of cholic acid, or approximately a 23% excess. The solution temperature was maintained in the range of 16° to 20°C during the entire addition of chlorine. Initially the cholic acid solution was very dark-colored. As the reaction progressed, the solution became pale yellow and a precipitate of sodium chloride deposited. A considerable amount of product and sodium chloride precipitated during the latter stages of the reaction so that the final reaction mixture was a heavy slurry which was difficult to stir. After the addition of chlorine was complete, the slurry was aged one hour with stirring at 20°C. The excess chlorine was then discharged by dropwise addition of 10% aqueous sodium sulfite until the solution gave a negative test to starch-iodide paper. The semi-crystalline slurry was then diluted with water to raise the total volume to 225 ml. The water was added dropwise with stirring over a 1-hour period. The ethyl acetate was then distilled off at 65-88°C. The resulting crystalline slurry was cooled to below 70°C and filtered through a sintered-glass funnel of medium porosity. The filter cake was washed until the filtrate gave a negative halide test with silver nitrate solution and then was sucked partially dry on the funnel. Drying was completed in a drier at 110°C for 3 hours. The product was crude pale tan dehydrocholic acid. Yield 14.3 (95%); M.P. 225-231°C.

B.) Purification of dehydrocholic acid:

To a chromatographic column, packed with 6.67 g of charcoal ("Nuchar C") with layers of sea sand at either end, 75 ml of acetone was added to wet the carbon. The column was heated to 40°C, and 25 ml of acetone was drained off. A solution of 20 g of dry crude dehydrocholic acid in 500 ml of acetone was poured into a reservoir atop the column and maintained in this reservoir at 40°C. This solution was then allowed to drop through the column at a constant rate over a 3-hour period. The column was then washed with 250 ml of acetone flowing through the column at a constant rate over a 1-hour-period at 40°C. The column effluent and wash acetone were combined and concentrated to a residual volume of about 100 ml which resulted in the formation of a thick slurry. The slurry was cooled with stirring at 0° to 5°C and aged for 30 min at this temperature. The slurry was filtered and the filter cake washed with cold acetone. The filter cake of U.S.P. dehydrocholic acid was sucked partially dry on the filter and then dried at 110°C for 3 hours. Yield 15 g to 17 g (75% to 85%).

A second crop of crystals was obtained from the combined filtrate and wash liquid from the first crop filtration. This mixture, which initially had a volume of about 100 ml, was concentrated to 20 ml. 10 ml of water was added to the solution and 10 ml of acetone mixed with a small amount of water distilled off. The residual thick slurry of dehydrocholic acid was cooled to 0-5°C, aged at

this temperature with stirring for 30 min, and filtered. The filter cake was washed with acetone at 0°C, partially dried by suction on the filter, and then dried for three hours at 110°C. Yield 1 to 2 g (5% to 10%).

References

Merck Index, Monograph number: 2922, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Hinkley D. F., Singleton B.; US Patent No. 2,966,499; Dec. 27, 1960; Assigned to Merck and Co, Inc., Rahway, N.Y., a corporation of New Jersey

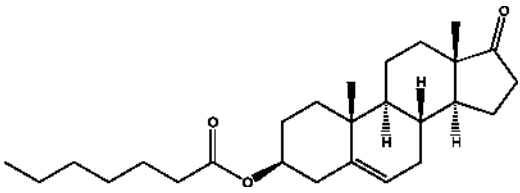
DEHYDROEPIANDROSTERONE ENANTHATE

Therapeutic Function: Glucocorticoid

Chemical Name: 3β-Hydroxyandrost-5-en-17-one heptanoate

Common Name: Dehydroepiandrosterone enanthate; Prasterone enanthate

Structural Formula:



Chemical Abstracts Registry No.: 23983-43-9

Trade Name	Manufacturer	Country	Year Introduced
Prasterone enanthate	Schering	-	-

Raw Materials

Dehydro-epi-androsterone
Sodium hydroxide
Oenanthic acid anhydride

Manufacturing Process

A mixture of 10.0 g of dehydro-epi-androsterone, 40 ml of pyridine and 20 ml of oenanthic acid anhydride was warmed for 2 h on a steam bath. About 10 ml of water were added and the mixture was warmed for a further 30 min. The reaction mixture was then subjected to a steam distillation. The resulting mixture was extracted with ether and the extract was successively washed with dilute sodium hydroxide solution, sodium carbonate solution and water.

The solution was dried over sodium sulfate and exaporated. 13.6 g of crude dehydro-epiandrosterone-3-oenanthate were obtained, melting point 70°-72°C (recrystallisation from methanol).

References

GB Patent No. 1,246,639; Sept. 15, 1971; Assigned: Schering Aktiengesellschaft, a Body Corporate, Germany

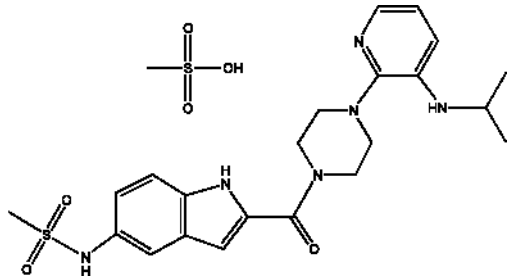
DELAVIRDINE METHANESULFONATE

Therapeutic Function: Antiviral, Anti-HIV virus agent

Chemical Name: Piperazine, 1-(3-((1-methylethyl)amino)-2-pyridinyl)-4-((5-((methylsulfonyl)amino)-1H-indol-2-yl)carbonyl)-, monomethanesulfonate

Common Name: Delavirdine mesylate

Structural Formula:



Chemical Abstracts Registry No.: 147221-93-0

Trade Name	Manufacturer	Country	Year Introduced
Delavirdine mesylate	Pfizer	USA	-
Rescriptor	Pharmacia and Upjohn	-	-
Rescriptor	Pfizer	USA	-

Raw Materials

1-(Ethyl)-3-(dimethylaminopropyl)carbodiimide
1-[3-(N-Isopropyl)amino-2-pyridinyl]piperazine
Methanesulfonyl chloride
5-Nitroindole-2-carboxylic acid
Palladium on carbon
Methanesulfonic acid

Manufacturing Process

5-Nitroindole-2-carboxylic acid (0.86 g), 1-[3-(N-isopropyl)amino-2-pyridinyl]piperazine (0.43 g), 1-(ethyl)-3-(dimethylaminopropyl)carbodiimide (0.45 g) and THF (4 ml), were stirred at 20-25°C for 3 hr; then the reaction mixture was dissolved in chloroform (50 ml) and extracted with saturated aqueous sodium bicarbonate, saline, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash column chromatography (200 g silica) eluting with ethyl acetate/hexane (50/50), the appropriate fractions were pooled and concentrated to give 1-[5-nitroindolyl-2-carbonyl]-4-[3-(1-methylethylamino)-2-pyridinyl]piperazine, mp 153°-154°C.

1-[5-Nitroindolyl-2-carbonyl]-4-[3-(1-methylethylamino)-2-pyridinyl]piperazine (1.0 g) was dissolved in ethanol (60 ml) and THF (60 ml) and palladium on carbon (10%, 0.15 g) was added. The reaction mixture was hydrogenated at 40 psi for 14 hr, then filtered through celite and concentrated under reduced pressure. Purification by flash chromatography, eluting with ethyl acetate/hexane (50/50) pooling and concentrating the appropriate fractions gave 1-[5-aminoindolyl-2-carbonyl]-4-[3-(1-methylethylamino)-2-pyridinyl]piperazine, mp 212°-214°C.

1-[5-Aminoindolyl-2-carbonyl]-4-[3-(1-methylethylamino)-2-pyridinyl]piperazine (0.075 mg) was dissolved in methylene chloride (0.4 ml) and pyridine (0.016 g) was added and the reaction is cooled to 0°C. Then methanesulfonyl chloride (0.023 g) was added. After 2.5 hr of stirring, the reaction was diluted with chloroform and washed with saturated aqueous sodium bicarbonate, saline, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The concentrate was dissolved in the minimum amount of chloroform and passed through a small plug of silica gel and then it is recrystallized with ethyl acetate/hexane to provide the 1-[5-methansulfoneamidolyl-2-carbonyl]-4-[3-(1-methylethylenamino)-2-pyridinyl]piperazine, mp 226°-228°C.

The mesylate salt may be formed by dissolving the free base in methanol and methanesulfonic acid (1 eq) is added.

References

Palmer J.R. et al.; US Patent No. 5,563,142; Oct. 8, 1996; Assigned: The Upjohn Company (Kalamazoo, MI)

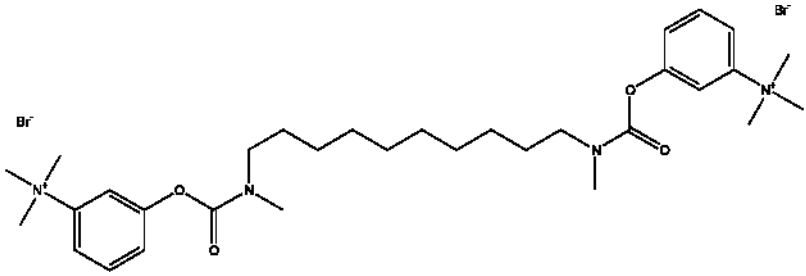
DEMECARIUM BROMIDE

Therapeutic Function: Cholinergic (ophthalmic)

Chemical Name: 3,3'-[1,10-Decanediylbis[(methylimino)carbonyloxy]]bis [N,N,N-trimethylbenzenaminium]dibromide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 56-94-0

Trade Name	Manufacturer	Country	Year Introduced
Humorsol	MSD	US	1959
Tonilen	Frumtost	Spain	-
Tosmilen	Chibret	France	-
Tosmilen	Chugai	Japan	-
Tosmilen	Linz	Austria	-
Tosmilen	Lentia	W. Germany	-
Tosmilen	Astra	UK	-

Raw Materials

N,N,N,N-Tetramethyldecamethylene diamine
m-Dimethylaminophenol
Methyl bromide
Phosgene
Sodium

Manufacturing Process

N,N,N,N'-tetramethyldecamethylene diamine is reacted with phosgene in toluene under agitation. The phosgene which escapes through an ascending cooling tube together with the evolved methyl chloride is condensed in a cold trap. As soon as immixture has been completed, the temperature is raised to 100°C and the phosgene recovered in the trap is vaporized and bubbled through the solution again, the escaping gas being recondensed and returned once more. The repeated passage through the reagents of the phosgene that has not yet reacted is continued for 7 hours. When the solution is cool it is passed through a filter, the remaining phosgene is removed from the clear solution by distillation and the remainder distilled in vacuo.

A solution of 11.9 parts of m-dimethylaminophenol in 90 parts of xylene (isomer mixture) is added to a solution of sodium methylate consisting of 2.0 parts of sodium and 25 parts of methanol. The methanol is then completely removed by distillation and the temperature raised until the boiling point of the xylene is reached. The decamethylene-bis-(N-methyl carbamic chloride) is added to the remainder which contains the sodium salt of m-

dimethylaminophenol in the form of solid crystals. The reagent mixture is heated and maintained at a temperature of 100°C and continuously agitated. After having been cooled it is washed three times in water, three times in a 5% solution of caustic soda, and another three times in water. The xylene is then evaporated in vacuo and the oily residue freed of any remaining traces of xylene by allowing it to stand in air when the product crystallized completely. In this manner 15.6 parts of decamethylene-bis-(N-methyl carbamic acid m-dimethylaminophenylester) are obtained, This is in turn reacted with methyl bromide to give the desired product. The decamethylene-bis-(N-methyl carbamic acid m-dimethylaminophenylesterbromomethylate) appears after precipitation from a solution in acetic acid with methyl ethyl ketone in the form of a finely crystalline powder with a micro melting point between 164° and 170°C.

References

Merck Index 2857
Kleeman and Engel p. 270
PDR p. 1182
I.N. p.290
REM p.898
Schmid, O.; US Patent 2,789,981; April 23, 1957; assigned to Oesterreichische Stickstoffwerke AG, Austria.

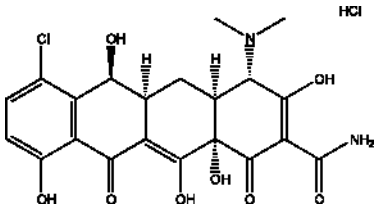
DEMECLOCYCLINE HYDROCHLORIDE

Therapeutic Function: Antibacterial

Chemical Name: 7-Chloro-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-1,11-dioxo-2-naphthacenecarboxamide

Common Name: 7-Chloro-6-demethyltetracycline

Structural Formula:



Chemical Abstracts Registry No.: 127-33-3; 64-73-3 (Hydrogen chloride)

Trade Name	Manufacturer	Country	Year Introduced
Declomycin	Lederle	US	1959
Ledermycine	Lederle	Japan	1970
Ledermycine	Lederle	France	1971

Trade Name	Manufacturer	Country	Year Introduced
Actaciclina	Courtois	Italy	-
Benaciclin	Jebena	Spain	-
Bioterciclin	Lisapharma	Italy	-
Clortetrin	Medosan	Italy	-
Compleciclin	Andromaco	Spain	-
Demebronc	Lederle	W. Germany	-
Demeplus	Boniscontro-Gazzone	Italy	-
Deme-Proter	Proter	Italy	-
Demetetra	Pierrel	Italy	-
Demetetraciclin	Bios	Italy	-
Demetraclin	Weles	Italy	-
Demetraciclina	Librac	Italy	-
Detracin	Sierochimica	Italy	-
Detravis	Vis	Italy	-
Dimeral	Panther-Osfa	Italy	-
D-Siklin	Dif-Dogu	Turkey	-
Duramycin	Ilsan	Turkey	-
Elkamicina	Biotrading	Italy	-
Fidocin	Farmaroma	Italy	-
Isodemetil	Isola-Ibi	Italy	-
Latomicina	Farber-R.E.F.	Italy	-
Ledermicina	Lederle	Italy	-
Magis-Ciclina	Tiber	Italy	-
Meciclin	Citobios	Switz.	-
Mexocine	Specia	France	-
Mirciclina	Francia	Italy	-
Neo-Cromaciclin	Panther-Osfa	Italy	-
Perciclina	Atral	Portugal	-
Provimicina	Lifasa	Spain	-
Temet	Coli	Italy	-
Tetradek	S.I.T.	Italy	-
Tollercin	Scalari	Italy	-
Veraciclina	A.F.I.	Italy	-

Raw Materials

Bacterium S. aureofaciens
Starch

Manufacturing Process

According to US Patent 2,878,289, a suitable medium for the preparation of inocula for the fermentation may be prepared with the following substances.

Sucrose, g/l	30
$(NH_4)_2SO_4$, g/l	2
$CaCO_3$, g/l	7
Corn steep liquor, ml/l	16.5

The pH of the medium thus prepared is about 6.8. An 8 ml portion is measured into an 8 inch Brewer tube and sterilized at 120°C for 20 minutes. The sterilized medium is then inoculated with 0.5 ml of an aqueous spore suspension of a strain of S. aureofaciens capable of producing chlorodemethyltetracycline, such as S-604, containing approximately 40-60 million spores per milliliter. The inoculated medium is incubated for 24 hours at 28°C on a reciprocating shaker operated at 110 cycles per minute.

A suitable fermentation medium contains water and a source of assimilable carbon and nitrogen and essential mineral salts. A typical medium suitable for production of chlorodemethyltetracycline is as follows:

Corn starch, g/l	55
$CaCO_3$, g/l	7
$(NH_4)_2SO_4$, g/l	5
NH_4Cl, g/l	1.5
$FeSO_4 \cdot 7H_2O$, mg/l	40
$MnSO_4 \cdot 4H_2O$, mg/l	50
$ZnSO_4 \cdot 7H_2O$, mg/l	100
$CoCl_2 \cdot 6H_2O$, mg/l	5
Corn steep liquor, g/l	30
Cottonseed meal, g/l	2
Lard oil, % v/v	2.0

According to US Patent 3,154,476, a culture of Streptomyces aureofaciens (ATCC 13900) is grown in approximately 50 ml of an aqueous medium containing, per 1,000 ml, 30 grams extraction process soybean meal, 1 gram sodium chloride, 50 grams glucose and 7 grams calcium carbonate in a 250 ml Erlenmeyer flask. The flask is agitated on a rotary shaker (280 cycles per minute) in a room maintained at 25°C for a period of 72 hours.

Ten percent of the resulting inoculum is then transferred to a 250 ml Erlenmeyer flask containing 50 ml of the medium employed above and the flask agitated a further 72 hours under the same conditions. One ml of the resulting inoculum is then employed for the inoculation of 10 ml of an aqueous medium containing, per 1,000 ml, 30 grams extraction process soybean meal, 1 gram sodium chloride, 50 grams glucose and 7 grams calcium carbonate, in a 1" x 6" test tube.

In addition, 1 mg of sterile S-2-hydroxyethyl-DL-homocysteine is added to the tube and the tube is shaken on a rotary shaker at 280 cycles per minute at 25°C for seven days. The contents of the tube were then acidified to pH 2 by the addition of sulfuric acid and centrifuged. Examination of the supernatant liquid by paper chromatography employing the methods of Bohonos et al, Antibiotics Annual (1953-4, page 49),demonstrates the presence of 7-chloro-6-demethyltetracycline,7-chlorotetracycline and tetracycline.

References

Merck Index 2858
Kleeman and Engel p, 270
PDR p. 1008
I.N. p. 290
REM p. 1204
McCormick, J.R.D., Hirsch, U., Jensen, E.R. and Sjolander, N.O.; US Patent 2,878,289; March 17, 1959; assigned to American Cyanamid Company
Szumski, S.A.; US Patent 3,012,946; December 12, 1961; assigned to American Cyanamid Company
Goodman, J.J. and Matrishin, M.; US Patent 3,019,172; assigned to American Cyanamid Company
Goodman, J.J.; US Patent 3,050,446; August 21, 1962; assigned to American Cyanamid Company
Neidleman, S. L.; US Patent 3,154,476; October 27, 1964; assigned to Olin Mathieson Chemical Corporation

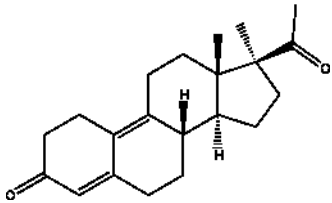
DEMEGESTONE

Therapeutic Function: Progestin

Chemical Name: 17-Methyl-19-norpregna-4,9-diene-3,20-dione

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 10116-22-0

Trade Name	Manufacturer	Country	Year Introduced
Lutionex	Roussel	France	1974

Raw Materials

3-Methoxy-19-nor-$\Delta^{(1,3,5(10),16)}$-pregnatetraene-20-one
Chromic acid
Ammonia
Methyl iodide
Acetic acid
Lithium
Bromine

Manufacturing Process

Step A: Preparation of 3-methoxy-17α-methyl-19-nor-$\Delta^{1,3,5(10)}$-pregnatriene-20-one - Under agitation and an inert atmosphere, 1.150 grams of lithium were introduced into one liter of ammonia cooled to a temperature of -70°C. For 15 minutes this reaction mixture was agitated, then, while maintaining the temperature at about -75°C, one liter of ether were added thereto, followed by 20 grams of 3-methoxy-19-nor-$\Delta^{1,3,5(10),16}$-pregnatetraene20-one. The mixture was allowed to stand for 2 hours at a temperature of -75°C under continued agitation and under continued inert atmosphere. Next, 160 cc of methyl iodide were added and the reaction mixture was again agitated for 2 hours at -75°C.

Thereafter, the ammonia was evaporated, 1 liter of water was added thereto and the aqueous phase was separated and extracted with ether. The ethereal phases now combined were washed with water until the wash waters were neutral, then dried over sodium sulfate, filtered and distilled to dryness to obtain 21 grams of product, which was dissolved in 210 cc of ethanol under reflux. Next, 21 cc of acetic acid and 21 grams of Girard's reactant T were added thereto. The mixture was agitated for 1½ hours under an atmosphere of nitrogen while maintaining the reflux. Thereafter, the reaction mixture was cooled to room temperature and then poured into 1,050 cc of water. Next, 155 cc of 2 N sodium hydroxide solution were added and finally the mixture was extracted with ether.

The combined ethereal phases were washed with water until the wash waters were neutral, dried over sodium sulfate, filtered and evaporated to dryness to obtain 16.80 grams of raw product which was purified by redissolving the product obtained in acetone under reflux and by recrystallization by heating and cooling.

13.185 grams of 3-methoxy-17α-methyl-19-nor-$\Delta^{1,3,5(10)}$-pregnatriene-20-one were thus obtained in the form of a colorless, solid product. The product was easily soluble in ether, soluble in alcohol, benzene and chloroform and insoluble in water. This product had a melting point of 109°C and a specific rotation of $[\alpha]_D^{20}$ = +75°+/-1° (c = 0.5% in chloroform). The starting compound, 3-methoxy-19-nor-$\Delta^{1,3,5(10),16}$-pregnatetraene-20-one, was obtained according to the process described by Burn, J. Chem. SOC.1962, page 364.

Step B: Preparation of 3-methoxy-17α-methyl-19-nor-$\Delta^{2,5(10)}$-pregnadiene-20-ol- 500 cc of ammonia and a solution of 20 grams of 3-methoxy-17α-methyl-19-nor-$\Delta^{1,3,5(10)}$-Pregnatriene-20-one were admixed with 400 cc of THF, and 10 cc of ethanol were added. The temperature was lowered to -35°C. 2.150 grams of lithium were added under an inert atmosphere and the reaction mixture was agitated for 15 minutes, after which 10 cc of ethanol and 2.150 grams of lithium were added. After agitating for 15 minutes, 30 cc of ethanol, then 2.150 grams of lithium were added. After maintaining the mixture at -35°C for 30 minutes, 30 cc of ethanol were added. The ammonia was evaporated by bringing the temperature to +20°C. 500 cc of water were added and the mixture was extracted with ether.

The aqueous phase was discarded and the combined ethereal phases were

washed with water, dried over sodium sulfate, filtered and distilled to dryness, to obtain 20.240 grams of 3-methoxy-17α-methyl-19-nor-$\Delta^{2,5(10)}$-pregnadiene-20-ol,which product was utilized as such for the next step. The compound occurred in the form of an amorphous product which was soluble in alcohol, ether, benzene and acetone and insoluble in water.

Step C: Preparation of 17α-methyl-19-nor-$\Delta^{5(10)}$-pregnene-20-ol-3-one - 20 grams of the compound prepared in Step B were dissolved in 35 cc of acetone, while agitating the solution for 15 minutes at room temperature. Thereafter, 300 cc of acetic acid containing 25% of water were added to the reaction mixture, which was then agitated for 3 hours and thereafter poured into a water-ether mixture and agitated for 10 minutes. The aqueous phase was separated after extracting with ether. The ethereal phases were washed first with an aqueous solution of sodium bicarbonate, then with water, dried over sodium sulfate, filtered and distilled to dryness to obtain 19,140 grams of 17α-methyl-19-nor-$\Delta^{5(10)}$-pregnene 20-ol-3-one. This product was utilized as such for the following step. The compound occurred in the form of a colorless, amorphous product which was soluble in alcohol, ether, benzene, acetone and chloroform and insoluble in water.

Step D: Preparation of 17α-methyl-19-nor-$\Delta^{5(10)}$-pregnene-3,20-dione - 20.5 grams of the compound prepared in Step C were dissolved in 615 cc of acetone under an atmosphere of nitrogen and under agitation. The solution obtained was cooled to -20°C. Next 21 cc of a solution of 54 grams of chromic acid anhydride and 46 cc of dilute sulfuric acid were added thereto. The solution was allowed to stand for 1 hour under agitation at about -10°C. It was then poured into 2 liters of a mixture of ice and water and extracted with benzene. The combined organic phases were washed first with water, then with a saturated solution of sodium bicarbonate and again with water. Next these phases were dried over magnesium sulfate and distilled to dryness.

20.40 grams of crude product were thus obtained, which was purified by subjecting it to chromatography through magnesium silicate and elution with benzene containing 2.5% of acetone, and recrystallization from isopropyl ether to obtain 8.50 grams of 17α-methyl-19-nor-$\Delta^{5(10)}$-pregnene-3,20-dione in the form of a colorless crystallized product. This product was soluble in alcohol, ether, acetone, benzene and chloroform and insoluble in water. This product had a melting point of 138°C, and a specific rotation of $[\alpha]_D^{20}$ = +168.5°+/-3.5° (c= 0.50% in chloroform).

Step E: Preparation of 17α-methyl-19-nor-$\Delta^{4,9}$-pregnadiene-3,20-dione - Under agitation and an atmosphere of nitrogen, 8.50 grams of the compound prepared in Step D were dissolved in 85 cc of pyridine and cooled to 0C. Next, 16.3 cc of a 29% bromine solution in methanol were added thereto. The agitation was continued for 30 minutes at the temperature of 0°C. Thereafter the temperature was raised to room temperature and the solution was allowed to stand for 16 hours under agitation. The solution was then poured into 850 cc of a mixture of ice and water and after 82 cc of hydrochloric acid were added, the mixture was extracted with methylene chloride. The combined organic phases were washed with water until the wash waters were neutral, then dried over magnesium sulfate and finally distilled to dryness to obtain 8.480 grams of a crude product which was purified by recrystallization from isopropyl ether. In this manner, 5.810 grams of 17α-methyl-19-nor-$\Delta^{4,9}$-pregnadiene-3,20-dione having a melting point of 106°C and a specific

rotation $[\alpha]_D^{20}$ = -270+/-4.5° (c = 0.5% in ethanol) were obtained.

References

Merck Index 2860
Kleeman and Engel p. 271
DOT 11 (4) 143 (1975)
I.N. p. 291
Vignau, M., Bucourt, R., Tessier, J., Costerousse, G., Nedelec, L., Gasc, J.-C., Joly, R., Warnant, J. and Goffinet, B.; US Patent 3,453,267; July 1, 1969; assigned to Roussel-Uclaf, France
Joly, R., Warnant, J. and Farcilli, A.; US Patent 3,547,959; December 15, 1970; assigned to Roussel-UCLAF, France

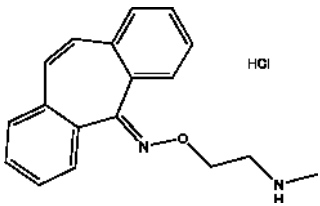
DEMEXIPTILINE HYDROCHLORIDE

Therapeutic Function: Antidepressant

Chemical Name: 5H-Dibenzo[a,d]cyclohepten-5-one-O-[2-(methylamino) ethyl]oxime hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 18059-99-9

Trade Name	Manufacturer	Country	Year Introduced
Deparon	Aron	France	1981

Raw Materials

5-Oximino-5H-dibenzo[a,d]cycloheptene
Methylaminoethyl chloride
Sodium
Hydrogen chloride

Manufacturing Process

1.15 g of Na are dissolved in 100 ml of absolute ethanol; 10 g of 5-oximino-5H-dibenzo[a,d]cycloheptene are introduced, followed by boiling under reflux

for 1 hour and evaporation to dryness. The residue is dissolved in dimethylformamide and part of the solvent is distilled off. The solution is now cooled to about 20°C and there are added 5.3 g of methylaminoethyl chloride which is prepared below 10°C from the corresponding hydrochloride by supersaturation with potassium carbonate. The mixture is then heated to 100°C for 1½ hours. Finally, the mixture is evaporated to dryness, the residue dissolved in ether/water and the ethereal phase washed with water. After drying of the ethereal phase with potassium carbonate, 8.5 g of the hydrochloride of 5-β-methylaminoethoxyimino-5H-dibenzo[a,d]cycloheptene (melting point 232°C to 233°C) are obtained.

References

Merck Index 2862
DFU 7 (1) 19 (1982)
DOT 17 (12) 548 (1981)
I.N.p.291
Schutz, S., Behner, O. and Hoffmeister, F.; US Patent 3,963,778; June 15, 1976; assigned to Bayer A.G. (W. Germany)

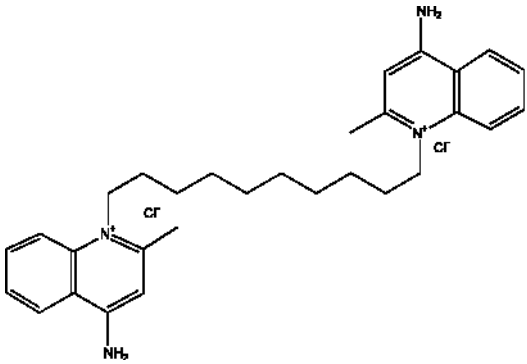
DEQUALINIUM CHLORIDE

Therapeutic Function: Antiseptic, Antifungal

Chemical Name: 1,1'-Decamethylenebis(4-aminoquinaldinium chloride)

Common Name: Dechalinium chloride, Dequalinium chloride

Structural Formula:



Chemical Abstracts Registry No.: 522-51-0

Trade Name	Manufacturer	Country	Year Introduced
Dequsan	Sante	-	-

Trade Name	Manufacturer	Country	Year Introduced
Colotin Troches	NeWai Chemical Industrial Co., Ltd.	-	-
Deliguo Lozenges	Solchem Italiana S.p.a.	-	-
Dequzlinum chloride	Shanghai abochem chemical co., Ltd.	-	-
Decatylen	Mepha	-	-
Dequadin Chloride	Allen and Hanburys	-	-
Dequadin Chloride	Roberts	-	-
Dequafungan	Kreussler	-	-
Dequavagyn	Kreussler	-	-
Eriosept	Kreussler	-	-
Evazol	Ravensberg	-	-
Labosept	L.A.B.	-	-

Raw Materials

4-Aminoquinaldine
Decamethylene diiodide

Manufacturing Process

a) 15 g of 4-aminoquinaldine, 15 g of decamethylene diiodide and 200 ml of methyl ethyl ketone were refluxed together for 400 hours. The mixture was allowed to cool, the precipitate filtered off, washed with methyl ethyl ketone, and 1,1'-decamethylenebis(4-aminoquinaldinium chloride) recrystallized from ethyl alcohol containing a little methyl alcohol.

b) 160 g of 4-aminoquinaldine, 174 g of decamethylene diiodide and 1,500 ml of methyl isobutyl carbinol were heated together at 120°C for 90 hours. The mixture was allowed to cool, the precipitate filtered off, washed with methyl ethyl ketone and 1,1'-decamethylenebis(4-aminoquinaldinium chloride) recrystallized from ethyl alcohol containing a little methyl alcohol.

The product obtained by both (a) and (b) consisted of a cream colored powder. Melting point 308-309°C (with decomposition).

References

Merck Index, Monograph number: 2959, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
GB Patent No. 745,956; Oct. 11, 1954; Assigned to Allen and Hanburys Limited, a British Co., of Three Colts Lane, Bethnal Green, London

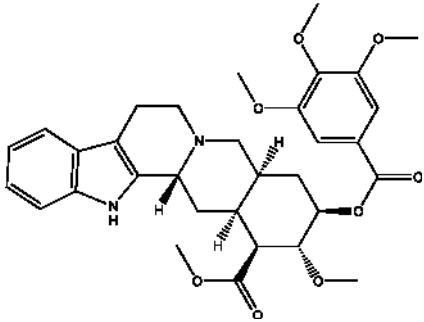
DESERPIDINE

Therapeutic Function: Antihypertensive

Chemical Name: 17a-Methoxy-18β-[(3,4,5-trimethoxybenzoyl)oxy]-3β,20α-yohimban-16β-carboxylic acid methyl ester

Common Name: 11-Desmethoxyreserpine

Structural Formula:



Chemical Abstracts Registry No.: 131-01-1

Trade Name	Manufacturer	Country	Year Introduced
Harmonyl	Abbott	US	1957
Enduronyl	Abbott	US	-
Harmonyl	Abbott	US	-
Harmonyl	Abbott	UK	-
Oreticyl	Abbott	US	-
Raunormine	Ono	Japan	-

Raw Materials

Rauwolfia roots
Methanol

Manufacturing Process

500 parts by weight of dried, finely ground roots of Rauwolfia canescens are extracted batchwise with methanol at its boiling point, using the following volumes and times, and filtering each extract while hot: 2,000 parts by volume, 1 hour; 1,000 parts by volume, 45 minutes; 1,000 parts by volume, 30 minutes; 1,000 parts by volume, 30 minutes. The extracts are combined and evaporated in vacuo to 75 parts by volume of a thick syrupy solution.

After the addition of 75 parts by volume of methanol and 150 parts by volume of acetic acid of 15% strength with adequate mixing, the solution is extracted with 2 portions each of 100 parts by volume of hexane. The combined hexane

extracts are extracted with 15 parts by volume of acetic acid of 15% strength. The latter extract is added to the above acetic acid phase which is then extracted with 3 portions each of 75 parts by volume and 1 portion of 50 parts by volume of ethylene chloride.

The first three extracts are combined and washed with 60 parts by volume of 2 N sodium carbonate solution and then with 60 parts by volume of distilled water. These washing solutions are saved and used for the washing of the 4th and final ethylene chloride extract. The combined ethylene chloride extracts are dried over sodium sulfate, filtered and evaporated in vacuo to a constant weight of a tan, frothy solid. One part by weight of this residue is dissolved in 1.5 parts by volume of warm methanol and the solution cooled to 5°C for 18 hours, whereby crystallization of a mixture containing principally reserpine sets in. After filtering this mixture and washing it with cool methanol, the filtrate is freed of solvent in vacuo.

Two parts by weight of the resulting red-brown solid froth are triturated with 2 portions each of 25 parts by volume of benzene and filtered each time. The benzene insoluble material is saved for further treatment. The benzene soluble fraction is poured on to a column of 40 parts by weight of activated alumina (Woelm, Activity Grade I) which is then eluted first with 3 portions each of 50 parts by volume of benzene and then with 6 portions each of 50 parts by volume of benzene-acetone (9:1), the first of which benzene-acetone portions had been used for extraction of the abovementioned benzene insoluble material. The second of the 6 benzene-acetone elution fractions on removal of the solvents gives a light tan solid froth which on crystallization from methanol gives colorless prismatic needles of slightly impure deserpidine. Rechromatographing of 1 part by weight of this substance on 20 parts by weight of activated alumina (Woelm, Activity Grade I) using benzene and benzene containing 0.1% methanol as eluting agents followed by crystallization from methanol gives colorless prismatic needles of pure deserpidine, melting at 228-232°C. Deserpidine obtained according to this example can be made up into pharmaceutical preparations.

References

Merck Index 2885
Kleeman and Engel p. 272
PDR pp. 515, 526, 543
OCDS Vol. 1 p. 320 (1977)
I.N. p. 296
REM p.909
Ulshafer, P.R.; US Patent 2,982,769; May 2, 1961; assigned to Ciba Pharmaceutical

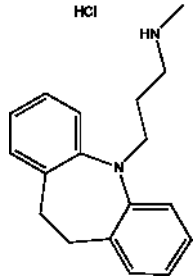
DESIPRAMINE HYDROCHLORIDE

Therapeutic Function: Psychostimulant

Chemical Name: 10,11-Dihydro-N-methyl-5H-dibenz-[b,f]azepine-5-propanamine hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 58-28-6; 50-47-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Pertofran	Geigy	UK	1963
Norpramine	Merrell	US	1964
Pertofrane	U.S.V.	US	1965
Pertofran	Ciba Geigy	Switz.	1965
Pertofran	Ciba Geigy	W. Germany	1965
Pertofran	Ciba Geigy	France	1966
Nortimil	Chiesi	Italy	1971
Deprexan	Unipharm	Israel	-
Nebril	Montpellier	Argentina	-
Norpolake	Lakeside	US	-
Petylyl	Arzneimittelwerk Dresden	E. Germany	-
Sertofren	Geigy	-	-

Raw Materials

o-Nitrotoluene
Hydrogen
N-(3-Chloropropyl)-N-methylbenzamine

Manufacturing Process

Oxidative coupling of o-nitrotoluene gives 4,4'-dinitrodibenzyl which is reduced with hydrogen to the diamine. The diamine is pyrolyzed to give dihydrobenzazepine. This is reacted with N-(3-chloropropyl)-N-methylbenzamine to give N-benzyldesipramine. This is debenzylated by reductive cleavage and then reacted with HCl.

References

Merck Index 2886

Kleeman and Engel p. 273
PDR pp. 1232,1819
OCDS Vol. 1 p. 402 (1977)
DOT 9 (6) 218 (1973)
I.N. p. 296
REM p. 1094
British Patent 908,788; October 24,1962; assigned to J.R. Geigy AG, Switzerland Biei, J.H. and Judd, C.I.; US Patent 3,454,554; July 8,1969; assigned to Colgate-Palmolive Co.

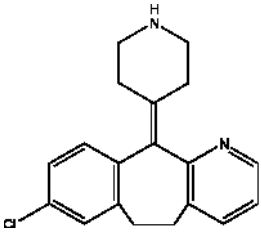
DESLORATADINE

Therapeutic Function: Antiallergic

Chemical Name: 5H-Benzo(5,6)cyclohepta(1,2-b)pyridine, 8-chloro-6,11-dihydro-11-(4-piperidinylidene)-

Common Name: Desloratadine

Structural Formula:



Chemical Abstracts Registry No.: 100643-71-8

Trade Name	Manufacturer	Country	Year Introduced
Delorta	Sarabhai Piramal Pharmaceuticals Ltd.	-	-
Desent	Indoco Remedies Ltd.	-	-
Deslor	Solares (A division of Sun)	-	-
DES-OD	Cadila Pharmaceuticals Ltd.	-	-
Dexly	Lyka Hetro Labs. Ltd.	-	-
Lorday	Cosme Healthcare	-	-
Loreta	Zuventus	-	-

Trade Name	Manufacturer	Country	Year Introduced
Nelora-5	Ochoa Laboratories (P) Ltd.	-	-
NUCOPE	Mankind Pharma Pvt. Ltd.	-	-
Rodera	Rexcel Pharmaceuticals	-	-
Aerius	Schering-Plough	-	-
Aerius	Essex Pharma	-	-
Azomyr	Schering-Plough	-	-
Azomyr	Essex Italia SPA	-	-
Neoclarityn	Schering-Plough	-	-
Opulis	Schering-Plough	-	-
Sch 34117	Schering-Plough HealthCare	-	-

Raw Materials

Ethylchloroformate
11-(N-Methyl-4-piperidylidene)-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine
Sodium hydroxide

Manufacturing Process

To a solution of 10.9 g (0.1 mole) of ethylchloroformate in 300 ml of anhydrous benzene is added dropwise, with stirring at room temperature, a solution of 16.2 g (0.05 M) of 11-(N-methyl-4-piperidylidene)-8-chloro-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine in 200 ml of benzene. The solution is stirred and is heated under reflux overnight (16-20 hours). The mixture is cooled and is poured into ice water and the organic layer is separated, washed with water, dried, and then concentrated to dryness. The residue is triturated with petroleum ether and a white solid of 8-chloro-6,11-dihydro-11-(1-ethoxycarbonyl-4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine having a melting point of 128-130°C is recrystallized from isopropyl ether after decolorization with decolorizing carbon.

To 12 g of sodium hydroxide in 30 ml ethyl alcohol (70%) add 6 g of 8-chloro-6,11-dihydro-11-(1-ethoxycarbonyl-4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine and reflux with stirring for 24 hours. After about the first 6-8 hours an additional 30 ml of 70% ethyl alcohol may be added. Remove about 50% of the solvent by distillation in vacuo. Add a small amount of ice water and acidify with glacial acetic acid. Extract with chloroform (6-8 times), since the product precipitates from the acetic acid solution as a thick emulsion which cannot be filtered. Concentrate the chloroform extracts to a small volume and precipitate the product with hexane to give crude 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine acetic acid salt, m.p. 197-200°C. Recrystallize from benzene-hexane to obtain the product, m.p. 199-200°C. Yield 4.0-4.5 g.

References

Vilani F.J.; US Patent No. 4,282,233; Aug. 4, 1981; Assigned to Schering Corporation (Kenilworth, NJ)
Villant F.J., Wong J.K.; US Patent No. 4,659,716; Apr. 21, 1087; Assigned to Schering Corparation, Madison, N.J.

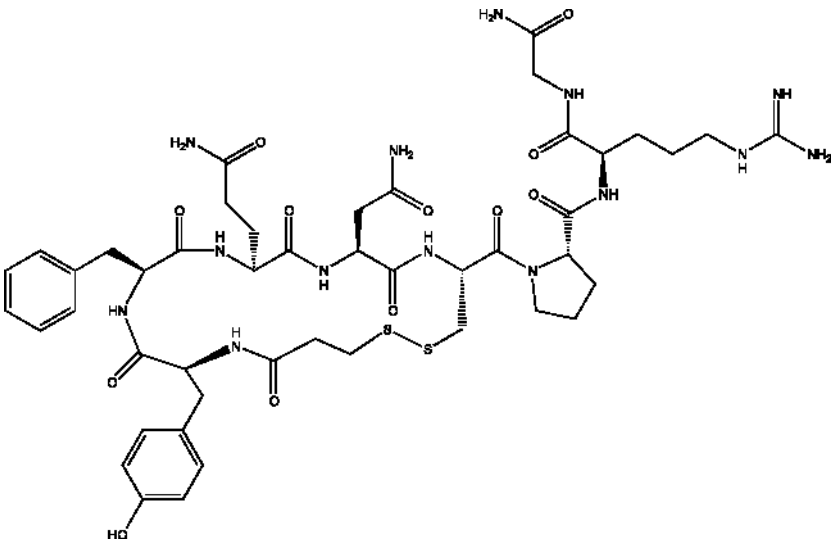
DESMOPRESSIN

Therapeutic Function: Antidiuretic

Chemical Name: 1-(3-Mercaptopropionic acid)-8-D-arginine vasopressin

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 16679-58-6; 16789-98-3 (Diacetate)

Trade Name	Manufacturer	Country	Year Introduced
DAV	Ritter	Switz.	1974
DDAVP	Ferring	UK	1975
Minirin	Ferring	W. Germany	1976
DDAVP	U.S.V.	US	1978
Desmopressin	Kyowa	Japan	1979
Minirin DDAVP	Valeas	Italy	1979
Adiuretin	Spofa	Czechoslovakia	-

Trade Name	Manufacturer	Country	Year Introduced
Defirin	Ferring	Sweden	-
Desurin	Ferring	Sweden	-
Minirin	Protea	Australia	-
Stimate	Armour	US	-

Raw Materials

β-Benzylmercaptopropionyl-L-tyrosyl-L-phenyalanyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-N-tosyl-D-arginyl glycinamide
Sodium
Ammonia
Acetic acid

Manufacturing Process

β-Benzylmercaptopropionyl-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-NG-tosyl-D-arginyl-glycinamide (0.5 g) is reduced with sodium in liquid ammonia. The liquid ammonia is then evaporated and the residue dissolved in 5% aqueous acetic acid (800 ml). The solution is filtered to remove the undissolved portion and the filtrate is adjusted to a pH of 6.5 to 7 by addition of aqueous sodium hydroxide and it is then oxidized by known procedure, cf. Kimbrough, R.D., Jr.; Cash, W.D.; Branda, L.A.; Chan, W.Y.; and Du Vigneaud, V.; J. Biol. Chem. 238,1411 (1963). The reaction mixture is thereupon adjusted to a pH of 4 to 4.5 by addition of acetic acid. The peptide is applied to a column of a carboxylate ion exchange resin, is eluted with 50% aqueous acetic acid and isolated by lyophilization (freeze-drying). The crude product is purified by known procedure using a carrier-free high-voltage electrophoresis, cf. Zaoral, M.; Sorm, F.; Collection Czechoslov. Chem Communs, 31, 310 (1966). Yield, 100 to 200 mg of 1-deamino-8-D-argine-vasopressin.

References

Merck Index 2888
Kleeman and Engel p. 274
PDR pp. 586, 1810
DOT 12 (1) 27 (1976) and 16 (10) 359 (1980)
I.N. p. 297
REM p. 958
Zaoral, M.,Vavra, I., Machova, A. and Sorm, F.; US Patent 3,497,491; February 24,1970; assigned to Ceskoslovenska Arademie Ved. (Czechoslovakia)
Ferring, A.B.; British Patents 1,539,317 and 1,539,318; both dated January 31, 1979

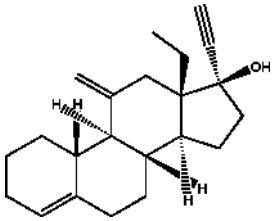
DESOGESTREL

Therapeutic Function: Progestin

Chemical Name: 13-Ethyl-11-methylene-18,19-dinorpregn-4-en-20-yn-17-ol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 54024-22-5

Trade Name	Manufacturer	Country	Year Introduced
Dicromil	Organol	W. Germany	1981
Marvelon	Organol	UK	1982

Raw Materials

11,11-Methylene-18-methyl-δ^4-estren-17-one
Potassium acetylide
Sulfuric acid

Manufacturing Process

A solution of 1.0 g of 11,11-methylene-18-methyl-delta4-estren-17-one in 33 ml tetrahydrofuran was added to a potassium-acetylide solution in tetrahydrofuran.

After 2 hours of stirring at 0°C to 5°C the reaction mixture was acidified with 2N $H_2SO_4$and processed further.

By a chromatographic treatment on silica gel and crystallization from pentane 0.7 g of 11,11-methylene-17α-ethynyl-18-methyl-δ^4-estren-17β-ol with a melting point of 109°C to 110°C and an $[\alpha]_D$ of +55°C ($CHCl_3$) was obtained.

References

Merck Index 2890
DFU 2 (12) 829 (1977)
DOT 18 (8) 361 (1982) and 19 (10) 570 (1983)
I.N.p.297 Van den Broek, A.J.; US Patent 3,927,046; December 16,1975; assigned to Akzona, Inc.

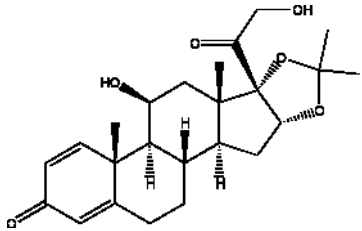
DESONIDE

Therapeutic Function: Antiinflammatory

Chemical Name: 11,21-Dihydroxy-16,17-[(1-methylethylidene)bis(oxy)] pregna-1,4-diene-3,20-dione

Common Name: Prednacinolone

Structural Formula:



Chemical Abstracts Registry No.: 638-94-8

Trade Name	Manufacturer	Country	Year Introduced
Tridesilon	Dome	US	1972
Tridesilon	Dome	UK	1972
Steroderm	De Angeli	Italy	1973
Tridesonit	Miles	France	1976
Tridesilon	Klinge	W. Germany	1978
Prenacid	Sifi	W. Germany	1979
Locapred	Alimedic	Switz.	1983
Sterax	Alcon	Switz.	1983
Apolar	A.L.	Norway	-
Locapred	Fabre	France	-
Prednol	Mustafa Nevzat	Turkey	-
Reticus	Farmila	Italy	-
Sine-Fluor	Made	Spain	-

Raw Materials

11β,16α,17α,21-Tetrahydroxy-1,4-pregnadiene-3,20-dione
Acetone

Manufacturing Process

Preparation of 11β,21-Dihydroxy-16α,17α-Isopropylidenedioxy-1,4-Pregnadiene-3,20-Dione: A solution of 11β,16α,17α,21-tetrahydroxy-1,4-pregnadiene-3,20-dione (40 mg) in acetone (10 ml) containing hydrochloric acid (three drops; d 1.19) is boiled 3n the steam bath for two minutes and

then allowed to stand for eighteen hours at room temperature. The reaction mixture is diluted with water (50 ml) and extracted with chloroform (3x25 ml), the combined extracts then being washed with water (30 ml) and dried over anhydrous sodium sulfate. The residue obtained by removal of solvent crystallized from ethyl acetate-petroleum ether as small plates (25 mg), melting point 257°-260°C.

References

Merck Index 2892
Kleeman and Engel p. 275
PDR p. 1261
OCDS Vol. 2 p. 179 (1980)
DOT 8 (6) 223 (1972)
I.N. p. 297
REM p. 972
Bernstein, S. and Allen, G.R., Jr.; US Patent 2,990,401; June 27, 1961; assigned to American Cyanamid Company
Diassi, P.A. and Principe, P.A.; US Patent 3,549,498; December 22, 1970; assigned to E.R. Squibb and Sons, Inc.

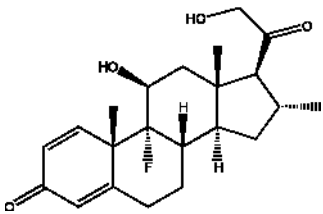
DESOXIMETASONE

Therapeutic Function: Antiinflammatory

Chemical Name: 9-Fluoro-11β,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione

Common Name: Desoxymethasone

Structural Formula:



Chemical Abstracts Registry No.: 382-67-2

Trade Name	Manufacturer	Country	Year Introduced
Topicorte	Roussel	France	1968
Topisolon	Hoechst	W. Germany	1974
Flubason	Albert Pharma	Italy	1974
Topicort	Roussel	Italy	1974
Topisolon	Hoechst	Switz.	1974

Trade Name	Manufacturer	Country	Year Introduced
Topicort	Hoechst	US	1977
Actiderm	Hoechst	-	-
Decolan	Hoechst	-	-
Dermo-Hidrol	Hoechst	-	-
Esperson	Hoechst	-	-
Ibaril	Hoechst	-	-
Topifram	Roussel	France	-
Topisolon	Cassella-Riedel	W. Germany	-

Raw Materials

Bacterium Curvularia lunata
16α-Methyldesoxycorticosterone
Bacterium Bacillus lentus
Glucose
Acetic anhydride
Hydrogen fluoride

Manufacturing Process

(a) Production of 16α-Methyl-4-Pregnene-11β,21-diol-3,20-Dione (= 16α-Methylcorticosterone): A fermenter of stainless steel having a 50 liter capacity is charged with 30 liters of a nutrient solution containing:

	Percent
Glucose (starch sugar)	4/4
Malt extract	1.0
$NaNO_3$	0.3
KH_2PO_4	0.1
KCl	0.05
$MgSO_4$	0.05
$FeSO_4$	0.002
Corn steep	0.5

sterilized for ½ hour at 120°C and after cooling, inoculated with a spore suspension of Curvularia lunata which is obtained by rinsing a seven day corn culture (15 grams corn) with approximately 100 cc of physiological sodium chloride solution.

After two days of culturing at 25°C under stirring (220 revolutions per minute) and ventilating (1.65 m3/hr), 18 liters of the obtained culture are removed under sterile conditions and introduced into a fermenter of the same size charged with 28.2 liters of a nutrient solution containing:

	Percent
Glucose (starch sugar)	4.4
Malt extract	1.0
$NaNO_3$	0.3
KH_2PO_4	0.1

After 24 hours cultivation under stirring and ventilation as described above, 7.5 grams of 16α-methyldesoxycorticosterone, obtained by saponification of the corresponding 21-acetate and melting at 102-104°C, in 200 cc of ethanol are added and fermented under the same conditions for 28 hours.

The course of the fermentation is tested by removal of samples, which are extracted with methyl isobutyl ketone. The extract is analyzed by paper chromatography in a system of dioxane + toluene/propylene glycol.

After the end of the fermentation (28 hours) the culture broth is filtered off by suction over a large suction filter. The mycel residue is washed with water several times. The filtrate is extracted three times, each time with 10 liters of methyl isobutyl ketone. The extract is concentrated under vacuum in a circulating evaporator and in a round flask carefully dried under vacuum. The residue is crystallized from acetone/isopropyl ether. The melting point is 157-158°C (fermentation yield = 60%). The pure product yield obtained after a second crystallization and chromatography of the mother liquor on silica gel amounts to 53% of the theoretical.

(b) 16α-Methyl-9α-Fluoro-Δ^4-Pregnene-11β,21-Diol-3,20-Dione: 7.5 grams of 16α-methyl-9α-fluoro-Δ^4-pregnene-21-ol-3,20-dione-21-acetate, obtained from Step (a) by acetylating with acetic anhydride in pyridine followed by reaction with HF in pyridine at 0°C, are fermented for 36 hours with Curvularia lunata (Mutant NRRL 2380), whereby the 21-acetate group is simultaneously saponified, and then further worked up. The residue is extracted with MIBK, subjected to chromatography on silica gel and there is obtained from chloroform/ethyl acetate (2:1) an eluate containing the 11β-hydroxy compound, which is further dehydrogenated as the crude product.

(c) 16α-Methyl-9α-Fluoro-$\Delta^{1,4}$-Pregnadiene-11β,21-Diol-3,20-Dione: 16α-methyl-9α-fluoro-β^4-pregnene-11β,21-diol-3,20-dione obtained as the crude product under Step (b) above, is fermented with Bacillus lentus for 30 hours and further worked up. The residue is extracted with methyl isobutyl ketone and there is obtained as the crude product 16α-methyl-9α-fluoro-$\Delta^{1,4}$-pregnadiene-11β,21-diol-3,20-dione.

References

Merck Index 2894
Kleeman and Engel p. 277
PDR p. 946
I.N. p. 297
REM p. 972
Kieslich, K., Kerb, U. and Raspe, G.; US Patent 3,232,839; February 1,1966; assigned to Schering AG, Germany

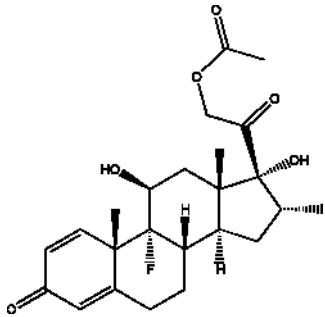
DEXAMETHASONE ACETATE

Therapeutic Function: Glucocorticoid

Chemical Name: 9-Fluoro-11β,17-dihydroxy-21-acetoxy-16α-methylpregna-1,4-diene-3,20-dione

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 1177-87-3; 50-02-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Dexacen	Central	US	1977
Decadron-La	MS and D	US	1974
Dalalone	O'Neal Jones	US	1982
Decasterolone	Biopharma	Spain	-
Decoderm	Igoda	Spain	-
Delladec	O'Neal Jones	US	-
Deronil	Essex Espana	Spain	-
Dexacortisyl	Roussel	-	-
Fortecortin	E. Merck	-	-
Panasone	Norbrook	UK	-
Solurex	Hyrex	US	-

Raw Materials

9β,11β-Epoxy-17α-hydroxy-21-acetoxy-16α-methyl-$\Delta^{1,4}$-pregnadiene-3,20-dione
Hydrofluoric acid

Manufacturing Process

The preparation of dexamethasone acetate is described in US Patent 3,007,923 as follows. 1.5 cc of dimethylformamide and 1.5 cc of anhydrous hydrofluoric acid are admixed and treated with 480 mg of 9β,11β-epoxy-17α-hydroxy-21-acetoxy-16α-methyl-$\Delta^{1,4}$-pregnadiene-3,20-dione (prepared according to E.P. Oliveto et al, J. Am. Chem. Soc., 80, 44331, 1958). The steroid dissolves in about 15 minutes. The reaction mixture is shaken for two hours at a temperature between 0 and +5°C, and then poured into 75 cc of

water containing in suspension, 7.5 grams of sodium bicarbonate. The mixture is vacuum filtered, the filter cake washed and then dried at 100°C, yielding 460 mg of crude hexadecadrol contaminated with a small amount of the starting material. A single recrystallization from methylene chloride yields 370 mg of the pure product having a melting point of 170°C and 229°C. The mother liquor yields 62 mg of the starting material, and a remainder constituting a mixture of starting and final materials with little other contamination.

References

Merck Index 2906
Kleeman and Engel p. 278
PDR pp.695, 928, 1156, 1286, 1569,1 606, 1723
OCDS Vol. 1 p. 199 (1977)
I.N. p. 299
REM p. 972
Fried, J.; US Patent 2,852.511; September 16, 1958; assigned to Olin Mathieson Chemical Corporation
Muller, G., Bardoneschi, R. and Jolly, J.; US Patent 3,007,923; November 7, 1961; assigned to Les Laboratories Francais de Chimiotherapie, France

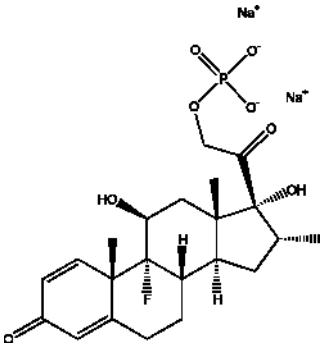
DEXAMETHASONE PHOSPHATE

Therapeutic Function: Glucocorticoid

Chemical Name: 9-Fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione-21-phosphate disodium salt

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 312-93-6; 2392-39-4 (Disodium salt)

Trade Name	Manufacturer	Country	Year Introduced
Decadron Phosphate	MS and D	US	1959
Hexadrol Phosphate	Organon	US	1965
Maxidex	Alcon	US	1975
Dexacen 4	Central	US	1977
Aacidexam	Aaciphar	Belgium	-
Cebedex	Chauvin-Blache	France	-
Cebefrasone	Chauvin-Blache	France	-
Chibro-Cardon	Chibret	France	-
Colvasone	Norbrook	UK	-
Cortcetine	Chauvin-Blache	France	-
Dalaron	O'Neal Jones	US	-
Decaderm	Frosst	Australia	-
Decadron	Banyu	Japan	-
Decalibour	MSD	France	-
Decort	Deva	Turkey	-
Delladec	O'Neal Jones	US	-
Desalark	Farm. Milanese	Italy	-
Dexacort	Ikapharm	Israel	-
Dexaderme	Chauvin-Blache	France	-
Dexa-Helvacort	Helvepharm	Switz.	-
Dexamed	Medice	W. Germany	-
Dexasone	Legere	US	-
Eta-Cortilen	S.I.F.I.	Italy	-
Megacort	Lancet	Italy	-
Orgadrone	Sankyo	Japan	-
Penthasone	Pentagone	Canada	-
Savacort	Savage	US	-
Soldesam	Farm. Milanese	Italy	-
Solone	Liade	Spain	-
Soludecadron	MSD	France	-
Solyrex	Hyrex	US	-
Spersadex	Dispersa	Switz.	-
Vasodex	Smith, Miller and Patch	Puerto Rico	-

Raw Materials

Phosphoric acid
Triethylamine
9α-Fluoro-11β,17α,21-trihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 21-methanesulfonate
Sodium methoxide

Manufacturing Process

A solution of bis-triethylamine phosphate was prepared by slowly adding 2.36 ml of 85% phosphoric acid to 20 ml of acetonitrile containing 9.9 ml of triethylamine at 20°C. This solution was added to a stirred solution of 4.70 g of 9α-fluoro-11β,17α,21-trihydroxy-16α-methyl-1,4-pregnadiene-3,2-dione 21-methanesulfonate and 20 ml of acetonitrile. The mixture was heated under reflux for four hours and then evaporated under reduced pressure to a volume of 12 ml. This mixture was a concentrated solution of 9α-fluoro-11β,17α,21-trihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 21-phosphate triethylamine salt with some inorganic phosphate.

The mixture was cooled, 25 ml of methanol added, and the cooled mixture treated with 33 ml of 1.89 N methanolic sodium methoxide solution. The precipitated inorganic phosphates were removed by suction filtration and washed thoroughly with methanol. The combined filtrates were evaporated under reduced pressure to a volume of 12 ml and treated with 30 ml of methanol. The resulting cloudy solution was clarified by filtration through diatomaceous earth. The volume of the filtrate was brought to 40 ml by the addition of methanol, and 120 ml of ether was added with stirring. The precipitated product, which was 9α-fluoro-11β,17α,21-trihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 21-phosphate sodium salt, was collected by suction filtration, and washed with acetone and then with ether. The weight of the air-dried material was 3.06 g.

References

Merck Index 2906
Kleeman and Engel p. 281
PDR p. 1033
OCDS Vol. 1 p. 199 (1977)
I.N. p. 300
REM p. 965
Chemerda, J.M., Tull, R.J. and Fisher, J.F.; US Patent 2,939,873; June 7, 1960; assigned to Merck and Co., Inc.

DEXAMETHASONE-21-LINOLEATE

Therapeutic Function: Topical antiinflammatory

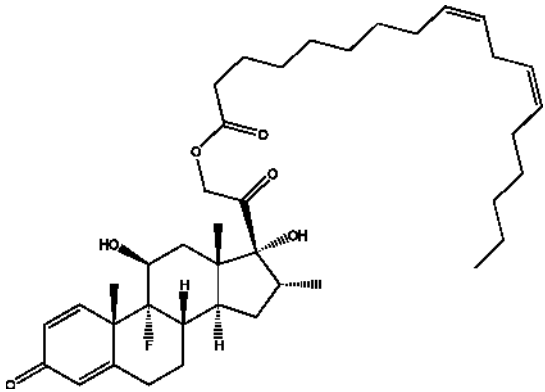
Chemical Name: 9α-Fluoro-11β-17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione-21-(octadeca-cis-9,cis-12-dienoate)

Common Name: -

Chemical Abstracts Registry No.: 39026-39-6

Trade Name	Manufacturer	Country	Year Introduced
Topolyn	I.S.F.	Italy	1979

Structural Formula:



Raw Materials

9α-Fluoro-11β,17,21-trihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione
Methanesulfonyl chloride
Potassium octadeca-cis-9,cis-13-dienoate

Manufacturing Process

To a stirred solution of 9α-fluoro-11β,17,21-trihydroxy-16α-methyl-pregna-1,4-diene-3,20-dione (10g, 25.5 mmol) in 20 ml pyridine and 12 ml acetone at -10°C, a cold solution of methanesulfonyl chloride (3 ml, 38.5 mmol) in 8 ml acetone was added dropwise. The addition was completed within about 3 hours and the mixture was then left standing in the cold for a further 1½ hours after which 200 ml cold water were added. The resulting precipitate was separated by filtration and washed with water to give 11.5 g (96% of theoretical yield) of dexamethasone 21-mesylate, melting point 208°C to 210°C (decomposition).

The dexamethasone 21-mesylate (11.5 g, 24.5 mmol) prepared as described was added in a nitrogen atmosphere to a stirred slurry of potassium octadeca-cis-9, cis-12-dienoate (7.81 g, 24.5 mmol) in 70 ml DMF. After stirring for 1½ hours at 50°C and evaporating the solvent in vacuo at the same temperature, the residue was washed by slurrying it into water and was then redissolved in methylene chloride, dried and the solvent evaporated. The residue was purified by chromatography on an inactivated (10% water) silica gel column (470 g) by using an ethyl acetate/hexane mixture (7:3) to give a very good yield of an oily product.

References

Merck Index 2906
DFU 1 (7) 316 (1976)
Kleeman and Engel p. 281
OCDS Vol. 1 p. 199 (1977)
I.N. p. 300

Piffer, G. and Pinza, M.; British Patent 1,292,785; October 11, 1972; assigned to I.S.F. SpA (Italy)

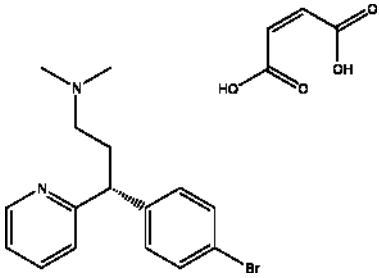
DEXBROMPHENIRAMINE MALEATE

Therapeutic Function: Antihistaminic

Chemical Name: d-2-[4-Bromo-α-(2-dimethylaminoethyl)benzyl]pyridine maleate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 2391-03-9; 132-21-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Disomer	White	US	1959
Dexbrom	Zenith	US	-
Disophrol	Schering	US	-
Drixoral	Schering	US	-
Ebalin	Allergo Pharma	W. Germany	-

Raw Materials

3-(2-Pyridyl)-3-p-chlorophenyl-N,N-dimethylpropylamine
d-Phenylsuccinic acid
Potassium carbonate
Maleic acid

Manufacturing Process

The following is taken from US Patent 3,061,517. Sixteen grams of racemic 3-(2-pyridyl)-3-p-bromophenyl-N,N,-dimethylpropylamine and 9.7 grams of d-phenylsuccinic acid are dissolved in 150 ml of absolute alcohol and kept at room temperature until crystallization is effected. The crystals are filtered,

washed with absolute ethyl alcohol, and recrystallized from the same solvent using 5 ml there of per gram of solid. Three subsequent crystallizations from 80% alcohol give d-3-(2-pyridyl)-3-p-bromophenyl-N,N-dimethylpropylamine-d-phenylsuccinate; MP 152-154°C; $[\alpha]_D^{25}$ 91 (concentration, 1% in dimethylformamide).

The free base, d-3-(2-pyridyl)-3-p-bromophenyl-N,N-dimethylpropylamine, is obtained from this salt with diethyl ether and aqueous potassium carbonate; $[\alpha]_D^{25}$ +42.7 (concentration, 1% in dimethylformamide). The free base is then reacted with maleic acid.

References

Merck Index 2907
Kleeman and Engel p. 283
PDR p. 999
OCDS Vol. 1 p.77 (1977)
I.N. p. 302
REM p. 1132
Walter, L.A.; US Patents 3,030,371; April 17, 1962; and 3,061,517; October 30, 1962; both assigned to Schering Corporation

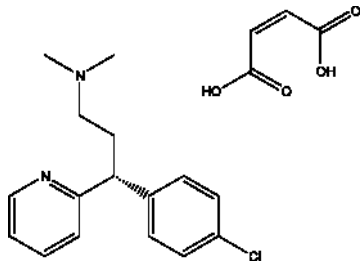
DEXCHLORPHENIRAMINE MALEATE

Therapeutic Function: Antihistaminic

Chemical Name: d-2-[p-Chloro-α-(2-dimethylaminoethyl)benzyl]pyridine maleate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 2438-32-6; 25523-97-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Polaramine	Schering	US	1958
Celestamine	Cetrane	France	-
Destral	Tiber	Italy	-
Dexchlor	Schein	US	-
Phenamin	Nyegaard	Norway	-
Polaramin	Aesca	Austria	-
Polaramin	Essex	Italy	-
Polaramine	Schering-Shionogi	Japan	-
Polaronil	Byk-Essex	W. Germany	-
Sensidyn	Medica	Finland	-

Raw Materials

3-(2-Pyridyl)-3-p-chlorophenyl-N,N-dimethylpropylamine
d-Phenylsuccinic acid
Potassium carbonate
Maleic acid

Manufacturing Process

Twenty grams of d-phenylsuccinic acid and 28 grams of 3-(2-pyridyl)-3-p-chlorophenyl-N,N-dimethylpropylamine are dissolved in 400 ml of absolute ethyl alcohol and allowed to stand at room temperature until crystallization is effected. The crystals are filtered, washed with absolute ethyl alcohol and recrystallized from 300 ml of this solvent in the same manner. The crystals are recrystallized twice from 80% ethyl alcohol using 3.5 ml per gram of compound in the manner described above and pure d-3-(2-pyridyl)-3-p-chlorophenyl-N,Ndimethylpropylamine-d-phenylsuccinate is obtained, melting point 145-147°C.

This salt is shaken with 100 ml of diethyl ether and 50 ml of 20% aqueous potassium carbonate; the ether layer is separated, dried over anhydrous potassium carbonate, filtered and the ether is removed in vacuo. The d-3-(2-pyridyl)-3-p-chlorophenyl-N,N-dimethylpropylamine so obtained is a mobile oil.

4.3 grams of the above base and 1.8 grams of maleic acid are dissolved in 20 ml isopropyl acetate and kept at room temperature until crystallization is complete. The crystals are filtered, washed with ethyl acetate and recrystallized from 15 ml of this solvent in the same manner. The crystalline d-3-(2-pyridyl)-3-p-chlorophenyl-N,N-dimethylpropylamine maleate so formed is then filtered off and dried. MP 113-115°C from US Patent 3,030,371.

References

Merck Index 2908
Kleeman and Engel p. 284
PDR pp. 1606, 1648
OCDS Vol.1 p.77 (1977)
I.N.p. 302

REM p. 1127
Walter, L.A.; US Patents 3,061,517; October 30, 1962; and 3,030,371; April 17, 1962; both assigned to Schering Corporation

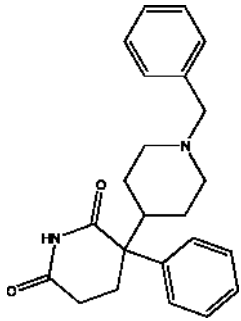
DEXETIMIDE

Therapeutic Function: Anticholinergic

Chemical Name: (+)-1-Benzyl-4-[(2,6-dioxo-3-pheny1)-3-piperidyl] piperidine

Common Name: Dexbenzetimide; Dextrobenzetimide; Benzetimide

Structural Formula:



Chemical Abstracts Registry No.: 21888-98-2

Trade Name	Manufacturer	Country	Year Introduced
Tremblex	Brocades	Italy	1981
Tremblex	Janssen	Switz.	-

Raw Materials

dl-1-Benzyl-4-(1,3-dicyano-1-phenylpropyl)piperidine HCl
Sulfuric acid
Hydrogen chloride

Manufacturing Process

400 parts glacial acetic acid are cooled to 10°C to 20°C. Then there are added first dropwise 300 parts concentrated sulfuric acid followed by portionwise addition of 50 parts dl-1-benzyl-4-(1,3-dicyano-1-phenylpropyl)-piperidine hydrochloride at the same temperature. After the addition is complete, the whole is heated to 125°C in the course of 15 to 20 minutes. This temperature is then maintained for 10 minutes. After cooling, the reaction mixture is

poured into ice, alkalized with NH_4OH at a temperature < 20°C and extracted with chloroform. The chloroform layer is first washed twice with a K_2CO_3 5% solution, and then washed twice with water, dried over $MgSO_4$, filtered and evaporated. The residue is dissolved in a mixture of 320 parts acetone and 600 parts diisopropylether, filtered and HCl gas is introduced into the filtrate. The solid hydrochloride is filtered off and dried, to yield 43 parts less pure l-benzyl-4-(2.6-dioxo-3-phenyl-3-piperidyl)-piperidine hydrochloride, melting point 283°C to 294°C.

A sample of 4 parts is recrystallized from a boiling mixture of 80 parts isopropanol, 40 parts methanol and 500 parts water. The whole is filtered and after cooling the filtrate overnight at -20°C, 1-benzyl-4-(2,6-dioxo-3phenyl-3-piperidyl)-piperidine hydrochloride is obtained, melting point 299°C to 301.5°C, as a white amorphous powder.

The dextro-isomer may be separated via the dextro-camphorsulfonate of the base.

References

Merck Index 2909
OCDS Vol. 2 p. 393 (1980)
DOT 9 (5) 170 (1975) and 9 (6) 247 (1975)
I.N. p. 302
Janssen, P.A.J.; US Patent 3,125,578; March 17, 1964; assigned to Research Laboratorium Dr. C. Janssen NV (Belgium)

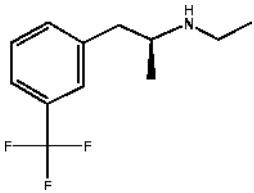
DEXFENFLURAMINE

Therapeutic Function: Antiobesity

Chemical Name: Phenethylamine, N-ethyl-α-methyl-m-(trifluoromethyl)-, (αS)-

Common Name: Fenfluramine; Phenfluoramine; Trifluethamine

Structural Formula:



Chemical Abstracts Registry No.: 3239-44-9

Trade Name	Manufacturer	Country	Year Introduced
Dexfenfluramine	Interneuron Pharmaceuticals (Lexington, Mass), for Wyeth Laboratories Inc	-	-
Diomeride	Servier	Bolivia	-
Redux	Southwood Pharm	-	-

Raw Materials

1-(3-Trifluoromethylphenyl)-2-aminopropane
Lithium aluminum hydride
Tartaric acid, dibenzoate, (-)-
Acetic anhydride
Hydrodiboric acid

Manufacturing Process

To 10.65 parts acetic anhydride there were added, with cooling, 8 parts 1-(3-trifluoromethylphenyl)-2-aminopropane and 100 parts water. The mixture was neutralized with 30 parts sodium carbonate. The organic layer was extracted twice with 50 parts ether. The ether solutions were washed with 25 parts water and dried over potassium carbonate. On distillation there were obtained 9 parts 1-(3-trifluoromethylphenyl)-2-acetyl-aminopropane. 9 parts of it were reduced in solution in 100 parts ether with 1.7 parts lithium and aluminium hydride with 20 parts ether. The suspension was refluxed for 4 hours, hydrolysed with 2 parts water, 2 parts 4 N sodium hydroxide and then 6 parts water. The precipitate was drained washed with 50 parts ether, the filtrate was extracted twice with 50 parts 0.5 N sulfuric acid. The acidic layers were separated by sedimentation and neutralized with 100 parts 4 N sodium hydroxide, the separated amine was extracted with 200 parts ether. There were obtained 6 parts 1-(3-trifluoromethylphenyl)-2-ethylaminopropane (boiling point 108°-112°C at 12 mm). The hydrochloride thereof was recrystallized from mixture of ethyl alcohol and ether (melting point 166°C).

S-Isomer was prepared the next way. To a solution of 160 parts of dibenzoyl d-tartaric acid in 1600 parts of anhydrous ethanol were added for 15 minutes 80 parts of dl-1-(3-trifluoromethylphenyl)-2-ethylaminopropane. After 15 additional minutes, 90.5 parts of crystalline solid were isolated. When this product was recrystallized from 1300 parts of anhydrous ethanol, there was obtained 70 parts of dibenzoyl d-tartarate acid salt of L-1-(3-trifluoromethylphenyl)-2-ethylaminopropane. This salt was treated with 500 parts of 4 N NaOH. The mixture was extracted with 2x200-part portions of diethyl ether and the ether extract was re-extracted with 100 parts of 4 N hydrodiboric acid. After treatment with 120 parts of 4 N NaOH, the free amine amounting to 25 parts distills at 105°-107°C (17.5 mm.). $[\alpha]_D^{25}$: - 9.6° (c=8% in ethanol).

References

Beregi L.G. et al.; US Patent No. 3,198,833; Aug. 3, 1965; Assigned to Science-Union and Compagnie-Societe Francaise de Recherches Medicales, Surenes, France, a French society

Beregi L.G. et al.; US Patent No. 3,198,834; Aug. 3 1965; Assigned to Science Union et Cie, Societe Francaise de Recherches Medicales, Surenes, France, a French society

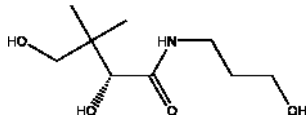
DEXPANTHENOL

Therapeutic Function: Gastrointestinal drug

Chemical Name: (R)-2,4-Dihydroxy-N-(3-hydroxypropyl)-3,3-dimethylbutanamide

Common Name: Panthenol; Pantothenyl alcohol

Structural Formula:



Chemical Abstracts Registry No.: 81-13-0

Trade Name	Manufacturer	Country	Year Introduced
Bepanthene	Roche	France	1951
Ilopan	Warren Teed	US	1957
Cozyme	Travenol	US	1958
Motilyn	Abbott	US	1960
Beducene	Roche	-	-
Dexol	Legere	US	-
Intrapan	Elkins-Sinn	US	-
May-Vita	Mayrand	US	-
Pantene	Shionogi	Japan	-
Pantenyl	Kay	US	-
Panthenol-Drobena	Drobena	W. Germany	-
Panthoderm	U.S.V.	US	-
Pantol	Toa-Eiyo-Yamanouchi	Japan	-
Thenalton	Fulton	Italy	-
Tonestat	A.V.P.	US	-
Urupan	Merckle	W. Germany	-

Raw Materials

d(-)-α-Hydroxy-β,β-dimethyl-γ-butyric acid lactone
3-Hydroxypropylamine

Manufacturing Process

130 parts by weight of d(-)-α-hydroxy-β,β-dimethyl-gamma-butyric acid lactone are dissolved in 150 parts by volume of methyl alcohol. 75 parts by weight of 3-hydroxypropylamine are added, in one portion, to the solution and the mixture is well stirred. While the reaction sets in, the temperature of the mixture gradually rises by itself to about 50°C and then drops again after about two hours. To cause completion of the reaction, the mixture is allowed to stand at room temperature for 24 hours. The so obtained (d+)-α,γ-dihydroxy-β,β-dimethyl-butyric-acid-(3'-hydroxypropyl)-amide is freed from methyl alcohol in vacuo. It is a colorless, viscous oil, easily soluble in water. It boils under a pressure of 0.02 mm between 118° and 120°C.

References

Merck Index 2910
Kleeman and Engel p. 284
PDR pp. 563, 872, 1033, 1083
I.N. p. 302
REM p. 813
Schnider. O.; US Patent 2,413,077; December 24, 1946; assigned to Hoffmann-La Roche Inc.

DEXTRAN 40

Therapeutic Function: Plasma extender

Chemical Name: See structure

Common Name: -

Structural Formula: Polymeric glucose of molecular weight 40,000

Chemical Abstracts Registry No.: 9004-54-0

Trade Name	Manufacturer	Country	Year Introduced
LMD 10%	Abbott	US	1967
Rheomacrodex	Pharmacia	US	1967
Fruidex	Polfa	Poland	-
Gentran 40	Travenol	US	-
Lomodex 40	Fisons	UK	-
Longasteril	Fresenius	W. Germany	-
Perfadex	Pharmacia	Sweden	-
Plander R	Pierrel	Italy	-
Reohem	Zdravlje	Yugoslavia	-
Rheoslander	Roger Bellon	France	-
Rheotran	Pharmachem	US	-
Soludeks	Pliva	Yugoslavia	-

Raw Materials

Sucrose
Bacterium Leuconostoc mesenteroides

Manufacturing Process

Sucrose is subjected to the action of the bacterium Leuconosfoc mesenteroides B 512 and the crude, high-molecular weight dextran thus formed is hydrolyzed and fractionated to an average molecular weight of about 40,000 as measured by light-scattering techniques.

References

Merck Index 2911
PDR p. 1428
I.N. p. 303
REM p.820
Gronwall, A.J.T. and Ingelman, B.G.A.; US Patent 2,644,815; July 7, 1953; assigned to Aktiebolaget Pharmacia, Sweden
Shurter, R.A.; US Patent 2,717,853; September 13, 1955; assigned to Commercial Solvents Corp.
Behrens, U. and Ringpfeil, M.; US Patent 3,044,940; July 17, 1962; assigned to Vebserum-Werk Bernburg (W. Germany)
Novak, L.J. and Stoycos, G.S.; US Patent 2,841,578; July 1, 1958; assigned to Commonwealth Eng. Co. of Ohio
Novak, L.J. and Witt, E.E.; US Patent 2,972,567; February 21,1961; assigned to Commonwealth Eng. Co. of Ohio

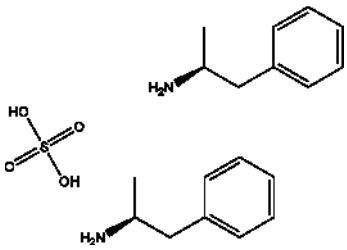
DEXTROAMPHETAMINE SULFATE

Therapeutic Function: Central stimulant

Chemical Name: (S)-α-Methylbenzeneethanamine sulfate

Common Name: d-β-Phenylisopropylamine sulfate

Structural Formula:



Chemical Abstracts Registry No.: 51-63-8

Trade Name	Manufacturer	Country	Year Introduced
Dexedrine Sulfate	SKF	US	1944
Domofate	Haag	US	1954
Dexalme	Meyer	US	1954
Amsusatain	Key	US	1954
Evrodex	Evron	US	1955
Cendex	Dentral	US	1956
D-Ate	Lemmon	US	1957
Perke One	Ascher	US	1966
Dexaspan	U.S.V.	US	1969
Dexa Sequels	Lederle	US	1970
Dexamplex	Lemmon	US	1976
Adiparthrol	Syntex-Medical	Switz.	-
Amfe-Dyn	Pharma-Dyn	Italy	-
d-Amfetasul	Pitman-Moore	US	-
Curban	Pasadena	US	-
Dexamine	Streuli	Switz.	-
Obetrol	Rexar	US	-
Simpamina	Recordati	Italy	-
Stil-2	Castillon	Spain	-

Raw Materials

dl-α-Methylphenethylamine
Sodium hydroxide
Tartaric acid, D-
Sulfuric acid

Manufacturing Process

Two mols, for example, 270 grams, of racemic α-methylphenethylamine base are reacted with one mol (150 grams) of d-tartaric acid, thereby forming dl-α-methylphenethylamine d-tartrate, a neutral salt. The neutral salt thus obtained is fully dissolved by the addition of sufficient, say about 1 liter, of absolute ethanol, and heating to about the boiling point. The solution is then allowed to cool to room temperature with occasional stirring to effect crystallization. The crystals are filtered off and will be found to contain a preponderance of the levo enantiomorph.

The residual solid in the mother liquors is repeatedly and systematically crystallized, yielding a further fraction of 1-α-methylphenethylamine d-tartrate which may be purified by recrystallization. d-α-Methylphenethylamine may be readily recovered from the mother liquors by the addition of tartaric acid thereto for the formation of acid tartrates and separation of d-α-methylphenethylamine d-bitartrate by crystallization.

The free base of either optical isomer may be obtained by addition to the d-tartrate in the case of the levo isomer and the d-bitartrate in the case of the dextro isomer of alkali in excess, as, for example, by the addition of an aqueous solution of caustic soda, which will cause the base to separate as an

oil which may be recovered and purified by any well-known procedure. The base is exactly neutralized with sulfuric acid to give the sulfate.

References

Merck Index 2918
PDR pp. 1450, 1711
OCDS Vol. 1 p. 70 (1977)
I.N. p. 301
REM p. 881
Nabenhauer, F.P.; US Patent 2,276,508; March 17, 1942; assigned to Smith, Kline and French Laboratories

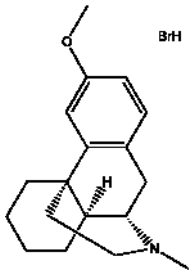
DEXTROMETHORPHAN HYDROBROMIDE

Therapeutic Function: Antitussive

Chemical Name: d-3-Methoxy-N-methylmorphinan hydrobromide

Common Name: Racemethorphan hydrobromide

Structural Formula:



Chemical Abstracts Registry No.: 510-53-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Symptom 1	Parke Davis	US	1977
Romilar HBR	Block	US	1954
Methorate	Upjohn	US	1958
Dormethan	Dorsey	US	1958
Tusasade	Westerfield	US	1964
Benylin	Parke Davis	US	1978
Delsym	Pennwalt	US	1982
Cremacoat	Vicks	US	1983
Agrippol	Herdt and Charton	Canada	-
Albatussin	Bart	US	-
Ambenyl-D	Marion	US	-

Trade Name	Manufacturer	Country	Year Introduced
Balminil-DM	Rougier	Canada	-
Broncho-Grippol	Herdt and Charton	Canada	-
Calmasan	Syntex-Pharm	Switz.	-
Calmerphan-L	Siegfried	Switz.	-
Cardec	Schein	US	-
Codimal	Central	US	-
Comtrex	Bristol-Myers	US	-
Congespirin	Bristol-Myers	US	-
Contratuss	Eri	Canada	-
Coryban D	Pfipharmecs	US	-
Co Tylenol	McNeil	US	-
Coughcon	Santen	Japan	-
Demo-Cineol	Sabex	Canada	-
Dextphan	Hishiyama	Japan	-
Extuson	Ferrosan	Denmark	-
Histalet DM	Reid-Rowell	US	-
Husmedin	Toho	Japan	-
Hustenstiller	Roha	W. Germany	-
Hustep	S.S. Pharm	Japan	-
Kibon S	Sawai	Japan	-
Koffex	Rougier	Canada	-
Methorcon	Kowa	Japan	-
Neo-DM	Neo	Canada	-
Nycoff	Dover	US	-
Pedia Care	McNeil	US	-
Pulmex-DM	Therapex	Canada	-
Quelidrine	Abbott	US	-
Rivodex	Rivopharm	Switz.	-
Robidex	Robins	US	-
Scot-Tussin	Scot-Tussin	US	-
Sedatuss	Trianon	Canada	-
Sedotus	Farge	Italy	-
Sisaal	Towa	Japan	-
Sorbutuss	Dalin	US	-
St. Joserph Cough Syrup	Plough	US	-
Testamin	Toyama	Japan	-
Triaminicol	Dorsey	US	-
Trimpus	Zensei	Japan	-
Tussar D.M.	U.S.V.	US	-
Tussidyl	Tika	Sweden	-
Tussi-Organidin	Wallace	US	-
Val-Atux	Farm. Milanese	Italy	-

Raw Materials

D,L-3-Hydroxy-N-methyl-morphinan
Phenyl trimethyl ammonium chloride
Tartaric acid, D-
Sodium carbonate
Hydrogen bromide

Manufacturing Process

The methylation of 51.4 parts by weight of D,L-3-hydroxy-N-methyl-morphinan is carried out with a methylating solution obtained from 51.5 parts by weight of phenyl-trimethylammonium-chloride. The D,L-3-methoxy-N-methyl-morphinan is isolated in the form of its hydrobromide, which melts with 1 mol of water at 92°-94°C,without water at 239°-240°C. The base isolated from the aqueous solution by means of sodium carbonate melts at 81°-83°C.

27.1 parts by weight of D,L-3-methoxy-N-methyl-morphinan base are dissolved with 15.0 parts by weight of D-tartaric acid in 150 parts by volume of hot alcohol. The solution is cooled and seeded with (+)-3-methoxy-N-methyl-morphinan-tartrate.The (+)-form which is difficultly soluble in alcohol separates, is filtered by suction and washed with a little alcohol.

[The (-)-form may be crystallized from the residue obtained by concentrating the mother liquor, separating therefrom as much as possible of the (+)-form and adding acetone].

The (+)-3-methoxy-N-methyl-morphinan-tartrate melts with 1 mol of water at 195°-196°C $[\alpha]_D^{20}$ =+30.6° (c = 1.5 in water). The (+) base melting at 108°-109°C may be obtained from the tartrate by means of sodium carbonate. The corresponding hydrobromide melts at 122°-124°C $[\alpha]_D^{20}$ =+27.6° (c = 1.5 in water).

References

Merck Index 8009
PDR pp.552, 654, 688, 727, 784, 829, 847, 851, 993, 1074, 1084, 1404, 1447, 1454, 1562, 1606, 1662, 1824, 1868, 1886, 1972
I.N. p. 304
REM p. 870
Schnider, O. and Grussner, A,; US Patent 2,676,177; April 20, 1954; assigned to Hoffmann-La Roche Inc.

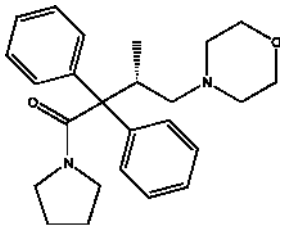
DEXTROMORAMIDE

Therapeutic Function: Narcotic analgesic

Chemical Name: Pyrrolidine, 1-(2,2-diphenyl-3-methyl-4-morpholinobutyryl)-, (+)-

Common Name: Destromoramide; Dextrodiphenopyrine; Dextromoramide; D-moramide; Pyrrolamidol

Structural Formula:



Chemical Abstracts Registry No.: 357-56-2

Trade Name	Manufacturer	Country	Year Introduced
Palfium	ACE Pharmaceuticals B.V.	-	-
Palfium	Purdue Frederick	-	-
Jetrium	Hek	-	-

Raw Materials

Diphenylacetylpyrrolidine
Sodium oxide
1-(2-Chloropropyl)morpholine

Manufacturing Process

1 mol diphenylacetylpyrrolidine was added to a suspension of 1,1-1,3 mol sodium oxide in 700 ml of toluene. The mixture was refluxed for a few hours until the sodium compounds of the acetamide derivative were formed completely. Then a slight excess of 1-(2-chloropropyl)morpholine was slowly added, dissolved in an equal volume of toluene or xylene. This mixture was refluxed for 6-8 hours. The reaction mixture was treated with water. The organic layer was then extracted with dilute hydrochloric acid and this extract was again made alkaline and extracted with ether. The extract was dried with potassium carbonate. A small amount of diphenylacetylpyrrolidine crystallizes from the ether. This is filtered off, petroleum ether is added and mixture is placed in refrigerator. After some days the 1-(4-N-morpholino-4-methyl-2,2-diphenylbutyryl)pyrrolidine is separated from this extract. M.P. 109-111°C.

References

Merck Index, Monograph number: 2997, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
GB Patent No. 822,055; Oct. 23, 1956; Assigned to N.V. Nederlandsche Commbinate voor Chemische Industrie, Amsterdam, and Labotratoria Pharmaceutica Dr. Janssen N.V., a Belgian Limited Liability Company

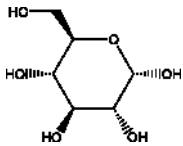
DEXTROSE

Therapeutic Function: Sugar supplement

Chemical Name: D-Glucose

Common Name: Corn sugar; Dekstroz; Dextrose; Glicose; Glucosa; Glucose; Glukose; Glycosum; Grape sugar; Nutritive Sugar; Saccharum amylaceum; Saccharum uveum; Starkezucker; Starch sugar; Traubenzucker

Structural Formula:



Chemical Abstracts Registry No.: 50-99-7

Trade Name	Manufacturer	Country	Year Introduced
Dextrose	Wockhardt Ltd.	India	-
Glucose	Hemofarm	Serbia and Montenegro	-
Glucosteril	Fresenius	Germany	-

Raw Materials

Dextrose monohydrate
Glucose

Manufacturing Process

D-Glucose is naturally occurring and is found in fruits and other parts of plants in its free state. It is used therapeutically in fluid and nutrient replacement.

Dehydration of Dextrose Monohydrate.

1. Dehydration with Fluid-bed Dryer

Dextrose monohydrate was brought in a fluid bed dryer (Retsch Type TG1) wherein the ratio of air (in kg) to product (in kg) is 0.77. The product which contained about 9% of moisture was dried to obtain dehydrated dextrose monohydrate which contained less than 0.5% water. The total driving time was about 25 to 70 minutes at a temperature of the incoming air of between 90°C and 120°C.

2. Dehydration with Turbo-dryer

Dextrose monohydrate was brought in a horizontal-placed turbo-dryer (VOMM, Mailand, Italy). The dehydration occurred at a temperature of between 90° to 150°C in a stream of air of 5 Normalised m^3/kg (i.e volume of gas at 0°C and 1 mbar) dextrose and a rotation speed of 1200 min^{-1}.

Dehydration of Glucose Syrup (Dextrose Content 96%).

A glucose syrup (C*SWEET D 02763 Cerestar) (dry substance ca. 70%) was sprayed at a flow rate of 7 kg/h at 70°C into a Niro FSD pilot plant spray dryer. For powdering ca. 9 kg coarsely milled dried product at a ratio liquid/solid of 1:2 was added. The atomising conditions were as follows:

Air temperature:	20°C
Air pressure:	3 bar
Air flow:	20 kg/h
Diameter nozzle:	2 mm
Air valve position:	-0.5 mm

The drying chamber was operated at:

Pressure chamber:	-10 mm WG
Pressure difference first cyclone:	90 mm WG
Air flow:	520 kg/h
Air inlet temperature:	146°C
Air outlet temperature:	81°C

The fluid bed was adjusted to:

Pressure difference air inlet pipe:	22 mm WG
Air flow:	120 kg/h
Air inlet temperature:	79°C
Powder temperature:	75°C
Powder bed pressure:	60-75 mm WG

References

Hopcke R. et al.; US Patent No. 6,646,112 B2; Nov. 11, 2003; Assigned to Cerestar Holding, B.V., LA Sas van Gent (NL)

DEXTROTHYROXINE SODIUM

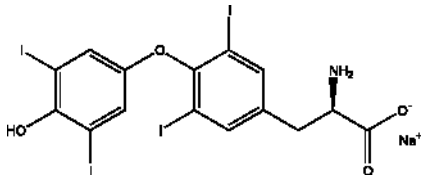
Therapeutic Function: Thyroid hormone, Anticholesteremic

Chemical Name: D-Tyrosine, O-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodo-, monosodium salt

Common Name: Dextrothyrosine sodium; Sodium dextrothyroxine; D-Thyroxine sodium

Chemical Abstracts Registry No.: 51-49-0 (Base); 137-53-1

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Choloxin	Knoll	-	-
Choloxin	Abbott	-	-
Oroxine	Sigma	-	-
Levothyrox	Merck Lipha Sante	-	-

Raw Materials

Benzenesulfonyl chloride
4-Methoxyphenol
Acetic anhydride
Nickel Raney
Phosphorus
Iodine
Formic acid
Methylamine
3-Iodo-5-nitro-4-hydroxybenzaldehyde
Pyridine
Sodium
Sodium nitrite
Potassium iodide
Brucine
Acetaldehyde

Manufacturing Process

The synthesis of dextrothyroxine includes 10 steps:

1. 3-Iodo-5-nitro-4- [4-methoxy-phenoxy]benzaldehyde

A suspension of 106 g 3-iodo-5-nitro-4-hydroxybenzaldehyde in 370 ml dry pyridine was stirred with 70 g benzenesulfonyl chloride for 2 hours at 20°C, whereupon 90 g 4-methoxyphenol was added and boiled for 1 hour. Pyridine was distilled off in vacuum and 2 N HCl was added to the residue and 3 times extracted with ether. The reminder was washed with 2 N NaOH, water and recrystallized from butyl ether. Yield 98 g; MP: 101°C.

2. 2-Methyl-4-[3-iodo-5-nitro-(4-methoxy-phenoxy)-benzylidene]-4-H-oxazol-5-one

40 g above prepared derivate was heated with 12 g acetic acid and 10 g dry sodium acetate in 70 ml acetic anhydride for 2.5 hours at 100°C. On cooling the oxazolone precipitated. It was filtered off, washed with CCl_4 and water; next it was recrystallized from benzene. Yield 35 g. MP: 205°-206°C.

3. Methyl ester 3-iodo-5-nitro-4- [4-methoxy-phenoxy]-α-acetylaminocinnamonic acid

20 g the product from an item 2 was stirred with a solution of 1.2 g sodium in

200 ml methanol at 20°C. Soon the desirable ester began to fall. It was filtered off after adding of 5 ml 95% acetic acid and recrystallized from 95% acetic acid. Yield 18 g; MP: 216°C.

4. Methyl ester 3-iodo-5-amino-4- [4-methoxy-phenoxy]-α-acetylaminocinnamonic acid

25 g Raney nickel was added to the suspension of 67 g above nitro ester in 450 ml methanol. Whereupon about 8.55 L hydrogen was passed (2 hours), the hydrogenation product crystallized. It was filtered off. The catalyst was removed by dissolving in tetrahydrofuran and repeated filtration. The solvent was removed in vacuum. Yield 38 g; MP: 184°C (recrystallized from methanol).

5. Methyl ester 3,5-diiodo-4- [4-methoxy-phenoxy]-α-acetylaminocinnamonic acid

5 g the product from item 4 in 20 ml 95% acetic acid and 30 ml conc. H_2SO_4 was dropwise added to the solution of 1.1 g sodium nitrite in 15 ml conc. H_2SO_4 and 30 ml conc. acetic acid. After 30 minutes the solution of diazonium salt was added to the mixture of 3.5 g KI, 5.2 g I_2 and 2.0 g urea in 250 ml water and 30 ml $CHCl_3$.

The excessive iodine was removed with $NaHSO_3$, an organic layer was separated and distilled off to dryness. The residue was recrystallized from acetic acid to yield 3.9 the desired product. MP: 209°C.

6. DL-3,5-Diiodothyronine

150 ml acetaldehyde was dropwise added to 150 ml HI (d 1.70) by ice cooling. Then 0.1 g $FeSO_4$ and 18 g red phosphorous was added to 27 g diiodo-derivate from the step 5. The mixture was heated to reflux about 20 minutes. Simultaneously methyl iodide was distilled off. Red phosphorous was filtered off. The clear filtrate was distilled to dryness. The residue was dissolved in 150 ml of hot water and 100 ml 2 N HCl. The conc. NH_3 was added. Precipitated product was washed with water, methanol and acetone and dried. Yield 20.7 g (86%). MP: 256°C (decomp.).

7. DL-N-Formyl-3,5-diiodothyronine

100 g DL-3,5-Diiodothyronine was added to the mixture of 100 ml dry formic acid and 50 ml acetic anhydride by stirring at ambient temperature to give the clean solution. Soon DL-N-formyl-3,5-diiodothyronone begun to crystallize. Yield 95 g. MP: 225°-230°C.

8. (-)-D-N-Formyl-3,5-diiodothyronine

The above prepared DL-N-formyl-3,5-diiodothyronine was in 1500 ml of dry isopropanol heated on a steam bath heated and the hot solution of 300 g dry brucine in 1500 ml dry isopropanol was added. On cooling (+/-)-D- N-formyl-3,5-diiodothyronone-brucine salt precipitated during 3 hours. 290 g this salt was recrystallized from a mixture of 1 L dimethylformamide and 2.5 L

isopropanol. MP: 271°C. It was dropped into 750 ml 2 N NH_3, four times with methylene chloride extracted for brucine removing. Water-basic solution was acidified to pH 2 with conc. HCl. (-)-D-N-Formyl-3,5-diiodothyronine precipitated on cooling. Yield 140 g (96.5 %). MP: 186°C.

9. (-)-D-3,5-Diiodothyronine

It was prepared from 100 g (-)-D-N-formyl-3,5-diiodothyronine and mixture of 1 L 48% HBr and water (1:2). Yield 80.5 g MP: 252°C (decomp.). $[\alpha]_D^{20}$: -25.0° (c=5, in 1 N HCL/95% ethanol 1:2)

10. (-)-D-3,5,3',5'-Tetraiodothyronine (dextrothyroxine)

9 g (-)-D-3,5-diiodothyronine was dissolved in 80 ml 40% methylamine by stirring at room temperature. 34 ml 1 N iodine/KI was added slowly to this solution. After 1.5 hours stirring, 150 ml NaCl solution was added and a sodium salt precipitated. It was dissolved in mixture of 200 ml methanol and 20 ml 2 N HCl, and heated with an animal coal. The coal was filtered off and neutralized with solution sodium acetate to pH 6. The precipitated was filtered off, washed with methanol and acetone and dried. Yield of desired product 6.2 g; MP: 235°C; $[\alpha]_D^{25}$:- 14.6° (c=5, in 1 N HCl/95% ethanol 1:2).

References

Nahm H., Siedel W.; Chem. Ber.; v 96, No 1, 1-9; 1963
Nahm H., Siedel W.; D.B. Patent No. 1,067,826; Dec. 24, 1955
Siedel W. et al.; D.B. Patent No. 1,077,673; Aug. 1958

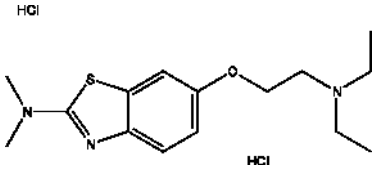
DIAMTHAZOLE DIHYDROCHLORIDE

Therapeutic Function: Antifungal

Chemical Name: 6-(2-Diethylaminoethoxy)-2-dimethylaminobenzathiazole dihydrochloride

Common Name: Dimazole dihydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 136-96-9; 95-27-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Aterola	Roche	US	1951
Aterola	Roche	-	-
Aterola	Roche	-	-
Aterola	Roche	-	-
Kesten	Roche	-	-
Mycotol	Syntofarma	Poland	-

Raw Materials

2-Dimethylamino-6-hydroxybenzothiazole
1-Diethylamino-2-chloroethane
Sodium hydroxide
Hydrogen chloride

Manufacturing Process

19.4 g of 2-dimethylamino-6-hydroxybenzothiazole (MP 245°C) were sludged in a 500 cc three-necked flask with 250 cc of chlorbenzene. Then 4.4 g of sodium hydroxide flakes were added and the mixture heated with agitation to 90°C. 4 cc of water were dropped in, and the mixture then heated slowly to the boil while about 500 cc of the water-containing chlorbenzene were distilled off. 50 cc of dry chlorbenzene were then added and the distillation was continued until about 30 cc of the chlorbenzene were distilled off. The residue was the sodium salt of thiazole in chlorbenzene. To the residue were added at 90°C, 15 g of fresh distilled 1-diethylamino-2-chloroethane. The mixture was then refluxed at 133°C for three hours, then cooled to 35°C. 75 cc of water and 5 cc of (40% by volume) sodium hydroxide solution were added and the mixture stirred for one hour. The chlorbenzene layer which contained the reaction product was separated from the aqueous layer in a separatory funnel. The chlorbenzene solution was then dried with sodium sulfate for twelve hours. It was then filtered and HCl gas was passed into the chlorbenzene solution until saturated, while cooling and stirring. The dihydrochloride precipitated as a white crystalline, sandy powder. The precipitate was filtered and washed on the funnel with benzene and finally washed with ether. The filter cake was dried at 80°C to 90°C. The 2-dimethylamino-6-(β-diethylaminoethoxy)-benzothiazole dihydrochloride thus obtained is a white crystalline powder, MP 240°C to 243°C. It can be recrystallized from ethanol and ether, or methanol or acetone.

The free base, which is an oil, can be obtained from the aqueous solution of the dihydrochloride by adding dilute sodium hydroxide or sodium carbonate solution. The base is soluble in ether, methanol, ethanol, benzene and the like, but slightly soluble in water.

References

Merck Index 2955
Kleeman and Engel p. 313
I.N. p. 333
Steiger, N. and Keller,O.; US Patent 2,578,757; December 18, 1951; assigned to Hoffmann - La Roche, Inc.

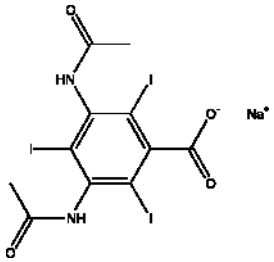
DIATRIZOATE SODIUM

Therapeutic Function: Diagnostic aid (radiopaque medium)

Chemical Name: 3,5-Bis(acetylamino)-2,4,6-triiodobenzoic acid sodium salt

Common Name: Amidotrizoate sodium

Structural Formula:



Chemical Abstracts Registry No.: 737-31-5 (Sodium salt); 117-96-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Hypaque Sodium	Winthrop	US	1955
MD-50	Mallinckrodt Inc.	US	1980
Urovist Sodium	Berlex	US	1983
Trignost	Teva	Israel	-
Urovison	Schering	W. Germany	-
Visotrast	Fahlberg-List	E. Germany	-

Raw Materials

3,5-Dinitrobenzoic acid
Sodium hydroxide
Acetic anhydride
Hydrogen
Iodine monochloride

Manufacturing Process

3,5-Dinitrobenzoic acid (15.9 g) was dissolved in an equivalent amount of sodium hydroxide solution, and the solution was diluted to 310 ml with water. The solution was refluxed with Raney nickel for fifteen minutes, filtered, and the filtrate was hydrogenated at elevated pressure using platinum oxide catalyst. After the amount of hydrogen calculated to reduce both nitro groups had been absorbed, the mixture was filtered, and the filtrate was acidified with an equal volume of concentrated hydrochloric acid. Iodine monochloride (17 ml) in 100 ml of 6N HCl was then added with stirring. The reaction mixture was allowed to stand for two and one-half hours at room temperature, then diluted with an equal amount of water with vigorous stirring, and the solid material was collected by filtration and recrystallized

from dilute methanol, giving 18.5 g of 3,5-diamino-2,4,6-triiodobenzoic acid, MP about 135°C with decomposition. The 18.5 g of 3,5-diamino-2,4,6-triiodobenzoic acid was suspended in 150 ml of acetic anhydride containing 5 drops of 70% perchloric acid, and the mixture was heated on a steam bath for three and one-half hours. The reaction mixture was poured into 300 ml of ice water, and then heated on a steam bath until crystallization took place. The solid material was collected by filtration, dissolvedin dilute sodium hydroxide solution, filtered, and hydrochloric acid was added to the filtrate to reprecipitate the acid product. The latter was again dissolved in sodium hydroxide and reprecipitated with acid, giving 9 g of 3,5-diacetamido-2,4,6-triiodobenzoic acid, MP above 250°C.

The acid may be used as the sodium salt or as the meglumate.

References

Merck Index 2965
Kleeman and Engel p. 38
I.N. p.68
REM p. 1268
British Patent 782,313; September 4, 1957; assigned to Mallinckrodt Chemical Works
Larsen, A. A.; US Patent 3,076,024; January 29, 1963; assigned to Sterling Drug, Inc.

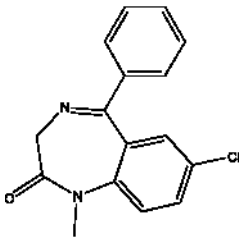
DIAZEPAM

Therapeutic Function: Tranquilizer

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

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 439-14-5

Trade Name	Manufacturer	Country	Year Introduced
Valium	Roche	Italy	1962
Valium	Roche	US	1963
Valium	Roche	W. Germany	1963
Valium	Roche	UK	1963
Valium	Roche	France	1964
Novazam	Genevrier	France	1984
Aliseum	Zova	Italy	-
Amiprol	US Vitamin	Argentina	-
Anksiyolin	Saglik	Turkey	-
Ansiolin	Scharper	Italy	-
Ansiolisina	Effepi	Italy	-
Anxium-5	Ethica	Canada	-
Anzepam	Arislo	India	-
Apaurin	Krka	Yugoslavia	-
Apozepam	A.L.	Norway	-
Armonil	Alet	Argentina	-
Assival	Assia	Israel	-
Atensine	Berk	UK	-
Avex	Spemsa	Italy	-
Bensedin	Galenika	Yugoslavia	-
Betapam	Be-Tabs	S. Africa	-
Calmpose	Ranbaxy	India	-
Canazepam	Paul Maney	Canada	-
Cercine	Takeda	Japan	-
Ceregulart	Kaken	Japan	-
Condition	Nagataki	Japan	-
Diaceplex	Salvat	Spain	-
Dialag	Lagap	Switz.	-
Diapam	Orion	Finland	-
Diapam	Dincel	Turkey	-
Diatran	Protea	S. Africa	-
Diaz	Taro	Israel	-
Diazem	Deva	Turkey	-
Diazemuls	Kabi Vitrum	Sweden	-
Diempax	Lafi	Brazil	-
Dipam	Alkaloid	Yugoslavia	-
Dizam	Pharmador	S. Africa	-
Domalium	Valderrama	Spain	-
Doval	Ormed	S. Africa	-
Drenian	Ern	Spain	-
Ducene	Sauter	Australia	-
Duksen	Kobanyai	Hungary	-
E-Pam	I.C.N.	Canada	-
Eridan	UCB-Smit	Italy	-

Trade Name	Manufacturer	Country	Year Introduced
Erital	Eri	Canada	-
Euphorin	Dojin	Japan	-
Eurosan	Mepha	Switz.	-
Evacalm	Unimed	UK	-
Faustan	Arzneimittelwerk Dresden	E. Germany	-
Grewacalm	Heilmittelwerke Wien	Austria	-
Githitan	Toyama	Japan	-
Horizon	Yamanouchi	Japan	-
Lamra	Merckle	W. Germany	-
Lembrol	Gerardo Ramon	Argentina	-
Levium	Sodelco	Netherlands	-
Liberetas	Galup	Spain	-
Lizan	Nobel	Turkey	-
Meval	Medic	Canada	-
Neo-Calme	Neo	Canada	-
Nervium	Saba	Turkey	-
Neurolytril	Dorsch	W. Germany	-
Noan	Ravizza	Italy	-
Notense	Rio Ethicals	S. Africa	-
Novodipam	Novopharm	Canada	-
Pacipam	Cox	UK	-
Pacitran	Grossmann	Mexico	-
Pacitran	Lafi	Brazil	-
Pax	Lennon	S. Africa	-
Paxel	Elliott-Marion	Canada	-
ProPam	Protea	Australia	-
Psychopax	Sigmapharm	Austria	-
Quetinil	Dompe	Italy	-
Quievita	Vita	Italy	-
Relivan	Scruple	S. Africa	-
Renborin	Nippon Chemiphar	Japan	-
Rival	Riva	Canada	-
Saromet	Sintyal	Argentina	-
Scriptopam	Propan-Lipworth	S. Africa	-
Sedapam	Duncan Flockhart	UK	-
Sedaril	Kodama	Japan	-
Sedipam	Medica	Finland	-
Seduxen	Gedeon Richter	Hungary	-
Serenack	Nordic	Canada	-
Serenamin	Medimpex	Hungary	-
Serenamin	Toyo Jozo	Japan	-
Serenzin	Sumitomo	Japan	-
Solis	Galen	UK	-
Somasedan	Celtia	Argentina	-

Trade Name	Manufacturer	Country	Year Introduced
Sonacon	Delmar	Canada	-
Sonacon	Chugai	Japan	-
Stresolid	Dumex	Denmark	-
Stress-Pam	Sabex	Canada	-
Tensium	D.D.S.A.	UK	-
Tensium	D.D.S.A.	UK	-
Tensopam	Pharmacal	Finland	-
Tranquase	Azuchemie	W. Germany	-
Tranquo-Puren	Klinge	W. Germany	-
Tranquo-Tablinen	Sanorania	W. Germany	-
Umbrium	Kwizda	Austria	-
Valibrin	Mulda	Turkey	-
Valitran	Firma	Italy	-
Vatran	Valeas	Italy	-
Vival	A.L.	Norway	-
Vivol	Horner	Canada	-
Zepam	Aksu	Turkey	-
Valium	Roche	Italy	1962
Valium	Roche	US	1963
Valium	Roche	W. Germany	1963
Valium	Roche	UK	1963
Valium	Roche	France	1964
Novazam	Genevrier	France	1983
Aliseum	Zova	Italy	-
Amiprol	U.S.V.	Argentina	-
Anksiyolin	Saglik	Turkey	-
Ansiolin	Scharper	Italy	-
Ansiolisina	Effepi	Italy	-
Anxium-5	Ethica	Canada	-
Anzepam	Arislo	India	-
Apaurin	Krka	Yugoslavia	-
Apozepam	A.L.	Norway	-
Armonil	Alet	Argentina	-
Assival	Assia	Israel	-
Atensine	Berk	UK	-
Avex	Spemsa	Italy	-
Bensedin	Galenika	Yugoslavia	-
Betapam	Be-Tabs	S. Africa	-
Calmpose	Ranbaxy	India	-
Canazepam	Paul Maney	Canada	-
Cercine	Takeda	Japan	-
Cereguiart	Kaken	Japan	-
Condition	Nagataki	Japan	-
Diaceplex	Salvat	Spain	-

Trade Name	Manufacturer	Country	Year Introduced
Dialag	Lagap	Switz.	-
Diapam	Orion	Finland	-
Diapam	Dincel	Turkey	-
Diatran	Protea	S. Africa	-
Diaz	Taro	Israel	-
Diazem	Deva	Turkey	-
Diazemuls	Kabi Vitrum	Sweden	-
Diempax	Lafi	Brazil	-
Dipam	Alkaloid	Yugoslavia	-
Dizam	Pharmador	S. Africa	-
Domalium	Valderrama	Spain	-
Doval	Ormed	S. Africa	-
Drenian	Ern	Spain	-
Ducene	Sauter	Australia	-
Duksen	Kobanyai	Hungary	-
E-Pam	I.C.N.	Canada	-
Eridan	UCB-Smit	Italy	-
Erital	Eri	Canada	-
Euphorin	Dojin	Japan	-
Eurocan	Mepha	Switz.	-
Evacalm	Unimed	UK	-
Faustan	Arzneimittelwerk Dresden	E. Germany	-
Grewacalm	Heilmittelwerke Wien	Austria	-
Githitan	Toyama	Japan	-
Horizon	Yamanouchi	Japan	-
Lamra	Merckle	W. Germany	-
Lembrol	Gerardo Ramon	Argentina	-
Levium	Sodelco	Netherlands	-
Liberetas	Galup	Spain	-
Lizan	Nobel	Turkey	-
Meval	Medic	Canada	-
Neo-Calme	Neo	Canada	-
Nervium	Saba	Turkey	-
Neurolytril	Dorsch	W. Germany	-
Noan	Ravizza	Italy	-
Notense	Rio Ethicals	S. Africa	-
Novodipam	Novopharm	Canada	-
Pacipam	Cox	UK	-
Pacitran	Grossmann	Mexico	-
Pacitran	Lafi	Brazil	-
Pax	Lennon	S. Africa	-
Paxel	Elliott-Marion	Canada	-
Pro-Pam	Protea	Australia	-
Psychopax	Sigmapharm	Austria	-

Trade Name	Manufacturer	Country	Year Introduced
Quetinil	Dompe	Italy	-
Quievita	Vita	Italy	-
Relivan	Scruple	S. Africa	-
Renborin	Nippon Chemiphar	Japan	-
Rival	Riva	Canada	-
Saromet	Sintyal	Argentina	-
Scriptopam	Propan-Lipworth	S. Africa	-
Sedapam	Duncan Flockhart	UK	-
Sedaril	Kodama	Japan	-
Sedipam	Medica	Finland	-
Seduxen	Gedeon Richter	Hungary	-
Serenack	Nordic	Canada	-
Serenamin	Medimpex	Hungary	-
Serenamin	Toyo Jozo	Japan	-
Serenzin	Sumitomo	Japan	-
Solis	Galen	UK	-
Somasedan	Celtia	Argentina	-
Sonacon	Delmar	Canada	-
Sonacon	Chugai	Japan	-
Stresolid	Dumex	Denmark	-
Stress-Pam	Sabex	Canada	-
Tensium	D.D.S.A.	UK	-
Tensopam	Pharmacal	Finland	-
Tranquase	Azuchemie	W. Germany	-
Tranquo-Puren	Klinge	W. Germany	-
Tranquo-Tablinen	Sanorania	W. Germany	-
Umbrium	Kwizda	Austria	-
Valibrin	Mulda	Turkey	-
Valitran	Firma	Italy	-
Vatran	Valeas	Italy	-
Vival	A.L.	Norway	-
Vivol	Horner	Canada	-
Zepam	Aksu	Turkey	-

Raw Materials

Chloroacetyl chloride
Phosphorus trichloride
Diazomethane
2-Amino-6-chlorobenzophenone-β-oxime
Sodium hydroxide

Manufacturing Process

Into a stirred, cooled (10°-15°C) solution of 26.2 grams (0.1 mol) of 2-amino-5-chlorobenzophenone β-oxime in 150 ml of dioxane were introduced in small

portions 12.4 grams (0.11 mol) of chloracetyl chloride and an equivalent amount of 3 N sodium hydroxide. The chloracetyl chloride and sodium hydroxide were introduced alternately at such a rate so as to keep the temperature below 15°C and the mixture neutral or slightly alkaline. The reaction was completed after 30 minutes. The mixture was slightly acidified with hydrochloric acid, diluted with water and extracted with ether. The ether extract was dried and concentrated in vacuum. Upon the addition of ether to the oily residue, the product, 2-chloroacetamido-5-chlorobenzophenone β-oxime, crystallized in colorless prisms melting at 161°-162°C.

20 ml of 1 N sodium hydroxide were added to a solution of 6.4 grams (20 mmol) of 2chloroacetamido-5-chlorobenzophenone β-oxime. After 15 hours the mixture was diluted with ice cold 1 N sodium hydroxide and extracted with ether. The ether extract was discarded. The alkaline solution was acidified with hydrochloric acid and extracted with methylene chloride. The methylene chloride solution was concentrated to a small volume and then diluted with petroleum ether to obtain 7-chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one 4-oxide.

To a stirred suspension of 10 grams (35 mmol) of 7-chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one 4-oxide in approximately 150 ml of methanol was added in portions an excess of a solution of diazomethane in ether. After about one hour, almost complete solution had occurred and the reaction mixture was filtered. The filtrate was concentrated in vacuum to a small volume and diluted with ether and petroleum ether. The reaction product, 7-chloro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one 4-oxide, crystallized in colorless prisms. The product was filtered off and recrystallized from acetone, MP 188°-189°C.

A mixture of 3 grams (0.01 mol) of 7-chloro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one 4-oxide, 30 ml of chloroform and 1 ml of phosphorus trichloride was refluxed for one hour. The reaction mixture was then poured on ice and stirred with an excess of 40% sodium hydroxide solution. The chloroform was then separated, dried with sodium sulfate, filtered and concentrated in vacuo. The residue was dissolved in methylene chloride and crystallized by the addition of petroleum ether. The product, 7-chloro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one, was recrystallized from a mixture of acetone and petroleum ether forming colorless plates melting at 125°-126°C.

The manufacturing procedure above is from US Patent 3,136,815. Purification of diazepam is discussed in US Patent 3,102,116.

References

Merck index 2967
Kleeman and Engel p. 288
PDR pp. 1506, 1517, 1999
OCDS Vol. 1 p. 365 (1977) and 2 p. 452 (1980)
DOT 9 (6) 236 (1973); 18 (8) 380 (1982) and 19 (3) 170 (1983)
I.N. p. 309
REM p. 1062
Chase, G.; US Patent 3,102,116; August 27, 1963; assigned to Hoffmann-La Roche Inc.

Reeder, E. and Sternbach, L.H.; US Patent 3,109,843; November 5, 1963; assigned to Hoffmann-La Roche Inc.
Reeder, E. and Sternbach, L.H.; US Patent 3,136,815; June 9, 1964; assigned to Hoffmann-La Roche Inc.
Reeder, E. and Sternbach, L.H.; US Patent 3,371,085; February 27, 1968; assigned to Hoffmann-La Roche Inc.

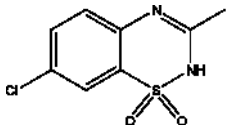
DIAZOXIDE

Therapeutic Function: Antihypertensive

Chemical Name: 7-Chloro-3-methyl-2H-1,2,4-benzothiadiazine-1,1-dioxide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 364-98-7

Trade Name	Manufacturer	Country	Year Introduced
Eudemine	Allen and Hanburys	UK	1970
Hyperstat	Schering	US	1973
Hypertonalum	Byk-Essex	W. Germany	1973
Hyperstat	Essex	Switz.	1973
Proglicem	Byk-Essex	W. Germany	1974
Proglicem	Cetrane	France	1974
Proglicem	Essex	Italy	1975
Hyperstat	Cetrane	France	1976
Diapressin	Medica	Finland	-
Proglicem	Aesca	Austria	-
Proglycem	Schering	US	-

Raw Materials

Benzyl chloride
Ammonia
Acetic anhydride
Chlorine
Orthoanilamide
2,4-Dichloronitrobenzene
Ethyl orthoacetate
Thiourea
Iron

Manufacturing Process

One route is described in US Patent 2,986,573: Mix 63 grams of benzyl chloride, 38 grams of thiourea, 3 drops of concentrated ammonium hydroxide solution, and 250 ml of 95% ethanol. Reflux the mixture for 3 hours. Cool and add a solution containing 96 grams of 2,4-dichloro-nitrobenzene in 200 ml of ethanol. Heat the mixture to reflux and then add drop-wise a solution of 70 grams of potassium hydroxide in 500 ml of ethanol. Continue refluxing for 2 hours, and then cool and filter the solids produced. Wash the solid with aqueous ethanol and dry. There is thus produced 2-benzylthio-4-chloro-nitrobenzene. Suspend 50 grams of 2-benzylthio-4-chloronitrobenzene in 1,000 ml of 33% aqueous acetic acid. Bubble chlorine gas through the suspension during a period of 2 hours, while maintaining the suspension at a temperature in the range of about 0°-5°C.

Extract the mixture 3 times with 400 ml each of chloroform, pool the extracts, and wash the chloroform solution with water. Dry the chloroform solution with anhydrous sodium sulfate and filter.

Evaporate the dried chloroform solution to a residue, add to the residue 400 ml of liquid ammonia, stir and allow the excess ammonia to evaporate, triturate the residue with hexane to form a crystalline solid, continue trituration with water, and filter the solid to yield substantially pure 2-sulfamyl-4-chloro-nitrobenzene. Recrystallize from aqueous methanol. Mix together 4.4 grams of ammonium chloride, 18 ml of methanol, 9 ml of water and 3.0 grams of 2-sulfamyl-4-chloro-nitrobenzene. Heat the mixture to reflux. Add portionwise 4.4 grams of iron filings during a period of about 1½ hours. Cool the mixture and filter. Concentrate the filtrate to a residue. Triturate the residue with 15 ml of water and filter the solid. Recrystallize the solid from aqueous methanol to yield substantially pure 2-sulfamyl-4-chloroaniline.

Heat a mixture of 6 grams of 2-sulfamyl-4-chloroaniline and 15 ml of ethyl orthoacetate at 100°-110°C for 1½ hours. Cool and filter the solids. Recrystallize from aqueous ethanol yielding 3-methyl-7-chloro-1,2,4-benzothiadiazine-1,1-dioxide. This substance is a white crystalline solid melting at 330°C.

Another route is described in US Patent 3,345,365: A mixture containing 10 grams of orthoanilamide, 10 cc of pyridine and 20 cc of acetic anhydride is heated for 3 hours at 50°-60°C and allowed to stand overnight. The solids obtained are filtered and crystallized from ethanol to yield 10.73 grams of N,N'-diacetyl-o-anilamide, MP 199°-200°C.

To a mixture of 3.0 grams of N,N'-diacetyl-o-anilamide and 20 ml of acetic acid is added a previously prepared solution of 1.5 grams of chlorine in 31 cc of acetic acid. The reaction mixture is allowed to stand at room temperature for 3 hours and is then evaporated to dryness on a steam bath under reduced pressure. The resulting solid residue is recrystallized from ethanol, yielding the intermediate N,N'-diacetyl-2-sulfamyl-4-chloroaniline. The intermediate compound is fused in an oil bath at 250-260°C for 15 minutes, cooled and the product so obtained is crystallized from 80% ethanol yielding 3-methyl-7-chloro-1,2,4-benzothiadiazine-1,1-dioxide, MP 330°C.

References

Merck Index 2975
Kleeman and Engel p. 290
PDR pp. 1130, 1630
OCDS Vol. 1 P. 355 (1977) and 2 p. 395 (1980)
DOT 9 (11) 458 (1973)
I.N. p. 310
REM p.847
Topliss, J.G., Sperber, N. and Rubin, A.A.; US Patent 2,986,573; May 30, 1961; assigned to Schering Corporation
Topliss, J.G., Sperber, N. and Rubin, A.A.; US Patent 3,345,365; October 3, 1967; assigned to Schering Corporation

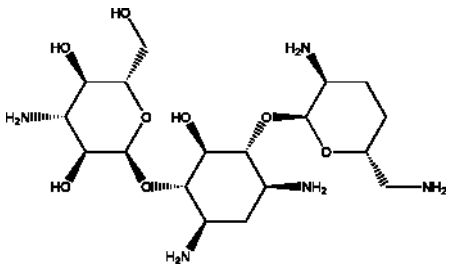
DIBEKACIN

Therapeutic Function: Antibacterial

Chemical Name: O-3-Amino-3-deoxy-α-D-glucopyranosyl-(1-->6)-O-[2,6-diamino-2,3,4,6-tetradeoxy-α-D-erythrohexopyranosyl(1-->4)]-2-deoxy-D-streptamine

Common Name: Dideoxykanamycin

Structural Formula:



Chemical Abstracts Registry No.: 34493-98-6; 60594-69-6 (Sulfate)

Trade Name	Manufacturer	Country	Year Introduced
Panimycin	Meiji Seika	Japan	1975
Orbicin	Pfizer	W. Germany	1978
Kappabi	Farmitalia	Italy	1980
Ioacine	Bristol	France	1981
Decabicin	Lefa	Spain	-
Debekacyl	Meiji	Japan	-
Duramycin	Pfizer-Roerig	-	-

Trade Name	Manufacturer	Country	Year Introduced
Klobamicina	Admirall	Spain	-
Nipocin	Pliva	Yugoslavia	-
Panimycin	Gerardo Ramon	Argentina	-

Raw Materials

penta-N-Benzyloxycarbonyl-2"-O-benzylsulfonyl-3',4'-dideoxy-3'-eno-kanamycin B
Sodium
Ammonia
Hydrogen

Manufacturing Process

Penta-N-benzyloxycarbonyl-2"-O-benzylsulfonyl-3',4'-dideoxy-3'-eno-kanamycin B (61 mg) was dissolved in about 18 ml of liquid ammonia at -50°C, followed by addition of about 120 mg of metal sodium. The mixture was gently stirred at -50°C for 1 hour, followed by addition of methanol to consume up the excess of the metal sodium. The reaction mixture was allowed to slowly raise up to ambient temperature while permitting the ammonia to evaporate. The residue so obtained was dissolved in water, and the aqueous solution was admixed with 4 ml of a cation-exchange resin, Dowex 50WX2 (H cycle) (a product of Dow Chemical Co., USA) under stirring. The admixture comprising the resin was placed on the top of a column of 3,5 ml of the same resin. Dowex 50WX2, and the whole resin column was well washed with water and then eluted using 1 M aqueous ammonia as the developing solvent. The eluate was collected in fractions, and such fractions which gave positive reaction with ninhydrin were combined together and concentrated to dryness, affording 3',4'-dideoxy-3'-eno-kanamycin B in the form of its monocarbonate. The yield was 23,8 mg (97%).

The product (12.1 mg) obtained in the above step was dissolved in 0.3 ml of water, to which was then added a catalytic quantity (about 5 mg) of platinum oxide. Hydrogenation was made with hydrogen gas at a pressure of 3.5 kg/cm^2 for 1½ hours. The reaction solution was filtered to remove the catalyst, and the filtrate was concentrated to dryness, giving the desired product 3',4'-dideoxykanamycin B in the form of its monocarbonate. The yield was 11.5 mg (95%). $[\alpha]_D^{25}$ +110° (c 1, water). The overall yield of 3',4'-dideoxykanamycin B based on the starting kanamycin B was 57%.

References

Merck Index 2976
Kleeman and Engel p. 290
DOT 12 (5) 211 (1976)
I.N.p.311
Umezawa, H., Umezawa, S. and Tsuchiva,T.; US Patent 4,169,939; October 2, 1979: assigned to Zaidan Hojin Biselbutsu Kagaku Kenkyu Kai (Japan)

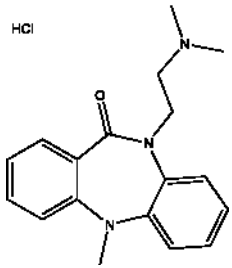
DIBENZEPIN HYDROCHLORIDE

Therapeutic Function: Psychostimulant

Chemical Name: 10-[2-(Dimethylamino)ethyl]-5,10-dihydro-5-methyl-11H-dibenzo[b,e][1,4]diazepin-11-one hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 315-80-0; 4498-32-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Noveril	Wander	Switz.	1965
Noveril	Wander	W. Germany	1965
Noveril	Sandoz	France	1967
Noveril	Wander	Italy	1968
Noveril	Wander	UK	1970
Noveril	Morishita	Japan	1975
Ansiopax	Andrade	Portugal	-
Deprex	Novo	-	-
Ecatril	Sandoz	France	-
Neodit	Wander	-	-
Victoril	Unipharm	Israel	-

Raw Materials

5-Methyl-11-hydroxy-5H-dibenzo[b,e][1,4]diazepine
Sodium amide
β-Dimethylaminoethyl chloride
Hydrogen chloride

Manufacturing Process

4.48 grams of 5-methyl-11-hydroxy-5H-dibenzo[b,e][1,4]diazepine and 0.86

gram of sodium amide were boiled for one hour in 50 ml of absolute dioxane. After adding a concentrated benzenic solution of β-dimethylamino-ethyl chloride freshly prepared from 3.75 grams of the hydrochloride with concentrated sodium hydroxide solution, taking up in benzene and drying the solution with potash, the mixture was boiled for 16 hours under reflux, whereupon the reaction mixture was concentrated to dryness and the residue distributed between ether and water. By exhaustive extraction of the basic fractions with dilute acetic acid, precipitation with ammonia, taking up the base in ether and working up the ethereal solution, there was obtained 5.05 grams (85% of the theoretical) of 5-methyl-10-β-dimethylamino-ethyl-10,11-dihydro-11-oxo-5H-dibenzo[b,e][1,4]diazepine in the form of a viscous yellowish resin with the boiling point 185°C/0.01mm Hg. The base was crystallized from acetone-petroleum ether, MP 116°-117°C. Melting point of the monohydrochloride (from ethanol-ether) 234°-240°C.

References

Merck Index 2979
Kleeman and Engel p. 291
OCDS Vol. 1 p. 405 (1977) and 2 pp. 424, 471 (1980)
DOT 2 (1) 4 (1966)
I.N. p. 311
British Patent 961,106; June 17, 1964; assigned to Dr. A. Wander AG, Switzerland
Schmutz, J. and Hunziker, F.; US Patent 3,419,547; December 31, 1968; assigned to Dr. A. Wander, S.A. (Switzerland)

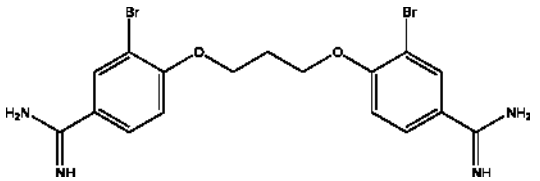
DIBROMPROPAMIDINE

Therapeutic Function: Antiprotozoal

Chemical Name: 4,4'-(Trimethylenedioxy)bis(3-bromobenzamidine)

Common Name: Dibromopropamidine; Dibrompropamidine

Structural Formula:



Chemical Abstracts Registry No.: 496-00-4

Trade Name	Manufacturer	Country	Year Introduced
Dibrompropamidine	Aventis Pharma AS	-	-

Raw Materials

2,2'-Dibromo-4,4'-dicyano-α,γ-diphenoxypropane
Hydrogen chloride
Ammonia

Manufacturing Process

2,2'-Dibromo-4,4'-dicyano-α,γ-diphenoxypropane (3.0 g) and anhydrous ethanol (3.0 ml) were dissolved in anhydrous chloroform (40 ml). The solution was saturated at 0°C with dry hydrogen chloride and set aside for 7 day. The iminoether hydrochloride which crystallised out, was filtered off and washed with light petroleum. The solid was added to 12% ammoniacal ethanol (47 c.c.) and the mixture was heated at 60°C for 6 hours. Solution was obtained after 3 hours and the amidine hydrochloride began to cryistallise. The mixture was ice-cooled, and the white crystalline solid was filtered off, washed with 2 N hydrochloric acid, and recrystallised twice from 0.5 N hydrochloric acid.

2,2'-Dibromo-4,4'-diamidino-α,γ-diphenoxypropane dihydrochloride (2.1 g) [another name: 4,4'-(Trimethylenedioxy)bis(3-bromobenzamidine)] separated as white prisme. Melting point 309°C. (decomp.).

References

Berg S.S., GB Patent No. 598,911; March 22, 1945; Assigned to May and Bakker Limited, a British Co., Dagenham, Essecs.

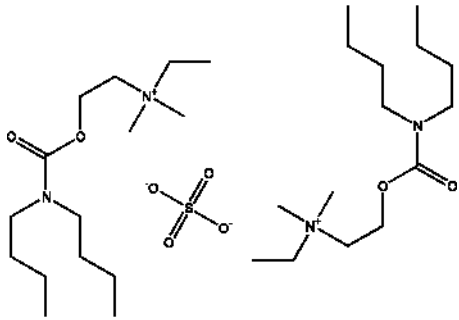
DIBUTOLINE SULFATE

Therapeutic Function: Anticholinergic

Chemical Name: Bis[ethyl(2-hydroxyethyl)dimethylammonium]sulfate-bis(dibutylcarbamate)

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 532-49-0

Trade Name	Manufacturer	Country	Year Introduced
Dibuline Sulfate	MSD	US	1952

Raw Materials

β-Chloroethyl-di-n-butylcarbamate
Silver sulfate
Dimethylamine
Ethyl iodide

Manufacturing Process

About 55.5 g of β-chloroethyl-di-n-butylcarbamate and about 22.6 g of dimethylamine are placed in a container, firmly sealed, and heated at about 95°C for about 16 hours. To the resulting crude mixture is added ethyl ether and the mixture filtered to remove dimethylamine hydrochloride formed during the course of the reaction. The ethereal solution is then extracted with 12 N hydrochloric acid. Under a fresh layer of ether and at a temperature under 10°C the aqueous acid extract is first neutralized with sodium carbonate and then made strongly alkaline with sodium hydroxide. The supernatant ethereal solution is then separated and dried over potassium hydroxide. The ethereal solution is finally concentrated and the residue obtained is fractionally distilled under vacuum. The β-dimethylaminoethyl-di-n-butylcarbamate is found to distill undecomposed at about 128°C to 130°C under approximately 2 mm pressure.

A mixture of about 100 g of β-dimethylaminoethyl-di-n-butylcarbamate and about 188 cc of ethyl iodide is held at about 25°C for two hours. The temperature is kept about 25°C by occasional cooling in an ice bath during the first half hour. About 1,600 cc of anhydrous ethyl ether is then added causing the precipitation of a dense white product. After standing for about 16 hours at 0°C the product is filtered off, washed thoroughly with anhydrous ether, and dried under diminished pressure at room temperature over sulfuric acid. The β-(dimethyl ethyl ammonium iodide)-ethyl-di-n-butylcarbamate thus obtained is a white crystalline powder, slightly hygroscopic with a melting point of about 76°C to 77°C.

A mixture of about 150 g of β-(dimethyl ethyl ammonium iodide)-ethyl-di-n-butylcarbamate, 90 g of silver sulfate, 750 cc of water and 750 cc of ethanol is stirred at about 30°C for approximately 45 minutes. The silver iodide formed is removed and the excess silver remaining in solution is removed by bubbling in hydrogen sulfide for five minutes followed by filtration to remove the precipitated silver sulfide. The filtrate is concentrated to a thick syrup under vacuum and about one liter of benzene is added which is distilled off with stirring to atmospheric pressure to remove the last traces of water. The residual benzene is removed under vacuum and the product granulated by stirring with one liter of anhydrous ether for two hours. The product is removed, washed with anhydrous ether, and dried under diminished pressure over phosphorous pentoxide at 25°C. The β-(dimethyl ethyl ammonium sulfate)-ethyl-di-n-butylcarbamate thus obtained is a very hygroscopic white solid having a melting point of about 166°C with decomposition.

References

Merck Index 3012
I.N. p. 313
Swan, K.C. and White, N.G.; US Patent 2,432,049; December 2, 1947

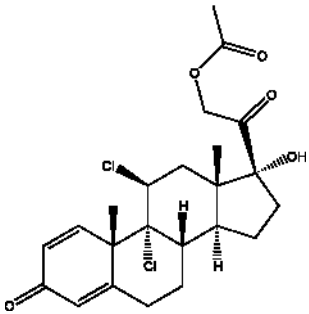
DICHLORISONE ACETATE

Therapeutic Function: Antipruritic

Chemical Name: 9α,11β-Dichloro-1,4-pregnadiene-17α,21-diol-3,20-dione-21-acetate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 79-61-8; 7008-26-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Diloderm	Schering	US	1960
Astroderm	Aristochimica	Italy	-
Dermaren	Areu	Spain	-
Diclasone	Liberman	Spain	-
Disoderm	Schering	-	-

Raw Materials

1,4,9(11)-Pregnatriene-17α,21-diol-3,20-dione-21-acetate
N-Chlorosuccinimide

Manufacturing Process

A solution of 1.0 g of 1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione-21-acetate and 5.0 g of lithium chloride in 40 ml of glacial acetic acid is treated

with 0.410 g of N-chlorosuccinimide, followed by 0.104 g of anhydrous hydrogen chloride dissolved in 2.5 ml of tetrahydrofuran. The reaction mixture is stirred for 2 hours and poured into ice water. The crude product is filtered and washed with water to give 1.12 g of solid material, which is recrystallized from acetone-hexane to give substantially pure 9α,11β-dichloro-1,4-pregnadiene-17α,21-diol-3,20-dione-21-acetate; MP 246°C to 253°C (dec.).

References

Merck Index 3030
Kleeman and Engel p. 292
OCDS Vol. 1 p. 203 (1977)
I.N. p. 314
Gould, D.H., Reimann, H. and Finckenor, L.E.; US Patent 2,894,963; July 14, 1959; assigned to Schering Corp.

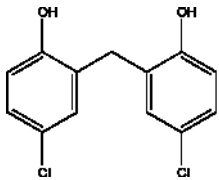
DICHLOROPHEN

Therapeutic Function: Antiseptic, Anthelmintic, Antifungal

Chemical Name: Phenol, 2,2'-methylenebis(4-chloro-

Common Name: Dichlorophen

Structural Formula:



Chemical Abstracts Registry No.: 97-23-4

Trade Name	Manufacturer	Country	Year Introduced
Dichlorophen	Aquapharm	-	-
Difelen	Teknofarma	-	-

Raw Materials

4-Chlorophenol
Sulfuric acid
Formaldehyde

Manufacturing Process

2.520 g of sulfuric acid (93%) is stirred and cooled to 0°C. A solution of 552 g

of p-chlorophenol in 305 g of methyl alcohol is run into the acid, the temperature being kept below 10°C. The mixture is cooled to -5°C and a solution of 170 g of aqueous formaldehyde solution (37% CH_2O in water) in 332 g of methyl alcohol is introduced at a more or less uniform rate over a period of 4 hours. The temperature of the reaction mixture is not allowed to rise above 0°C. After all of the formaldehyde-containing solution has been added, the batch is stirred for 3 hours longer at a temperature of -5°-0°C.

Enough ice is then added to the contents of the reaction chamber in order to reduce the sulfuric acid concentration to 70%. 2,2'-Dihydroxy-5,5'-dichloro-diphenyl methane is extracted from the resulting mixture with a mixture of 1.069 g of isopropyl ether and 1.575 g of toluene. Ice is added until the acid concentration is about 30%. The acid layer is removed and the solvent layer is washed acid-free. Most of the isopropyl ether is removed by atmospheric distillation with a fractionating column, the temperature of the escaping vapors not being permitted to exceed 90°C. From the residue, about 280 g of pure 2,2'-dihydroxy-5,5'-dichloro-diphenyl methane, MP: 177°-178°C, crystallize. The product is filtered, washed with toluene and dried at about 100°C. By concentrating the mother liquor remaining after the foregoing crystallization and filtration, another 225 grams of substantially pure 2,2'-dihydroxy-5,5'-dichloro-diphenyl methane are obtained. This latter crop may be crystallized from toluene in order to convert it into 2,2'-dihydroxy-5,5'-dichlorodiphenyl methane of melting point of 177°-178°C.

References

Gumpet W.S. et al.; US Patent No. 2,334,408; Nov. 16, 1943; Assigned to Burton T Bush, Inc., New York, N.Y., a corporation of New Jersey

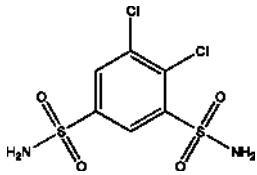
DICHLORPHENAMIDE

Therapeutic Function: Carbonic anhydrase inhibitor, Antiglaucoma

Chemical Name: 4,5-Dichloro-m-benzenedisulfonamide

Common Name: Diclofenamid

Structural Formula:



Chemical Abstracts Registry No.: 120-97-8

Trade Name	Manufacturer	Country	Year Introduced
Daranide	MSD	US	1958
Oratrol	Alcon	US	1960
Dicloferenamid	Mann	W. Germany	1976
Antidrasi	I.S.F.	Italy	-
Barastonin	Santen	Japan	-
Fenamide	Farmigea	Italy	-
Glajust	Hotta	Japan	-
Glaucol	Star	Finland	-
Glauconide	Llorens	Spain	-
Glaumid	S.I.F.I.	Italy	-
Hipotensor Oftalmico	C.M.C.	Spain	-
Netex	C.M.C.	Spain	-
Tensodilen	Frumtost	Spain	-

Raw Materials

Chlorosulfonic acid
O-Chlorophenol
Phosphorus pentachloride
Ammonia

Manufacturing Process

In a 2 liter round-bottomed flask equipped with stirrer and dropping funnel is placed 1,585 grams (880 cc; 13.6 mols) of chlorosulfonic acid. To this is added dropwise with stirring during 5 hours 218 grams (1.7 mols) of o-chlorophenol. The mixture is allowed to stand 1 hour at room temperature and then is heated 1 hour on a steam bath. The mixture is then poured on ice.

A product consisting largely of 5-chloro-4-hydroxybenzene-1,3-disulfonyl chloride separates as a gum which solidifies on standing for about 1 hour. The solid product is collected on a Buchner funnel, washed with water and thoroughly dried in air at room temperature.

A mixture of this crude product (approximately 302 grams, 0.92 mol) and 480 grams (2.3 mols) of phosphorus pentachloride is heated for 1 hour at 120°-140°C in a 2 liter round-bottomed flask. The resulting clear solution is poured on ice. 4,5-Dichlorobenzene-1,3-disulfonyl chloride separates immediately as a solid. It is collected by filtration and washed with water. While still moist, it is added in portions during about 20 minutes to 1 liter of concentrated ammonia water contained in a 3 liter beaker surrounded by a cold water bath. The reaction mixture is then allowed to stand for 1 hour without cooling after which it is heated on a steam bath for about 30 minutes while air is bubbled through it, in order to remove some of the excess ammonia. It is then filtered, acidified with concentrated hydrochloric acid and chilled.

The product separates as a gum from which the supernatant liquid is decanted, and the gum is triturated with 250 cc of water in order to induce crystallization. The crude product thus obtained is recrystallized from 3,200 cc

of boiling water and then from 40% aqueous isopropyl alcohol yielding 4,5-dichlorobenzene-1,3-disulfonamide as a white solid, MP 228.5° to 229.0°C.

References

Merck Index 3062
Kleeman and Engel p. 294
PDR p. 1155
OCDS Vol. 1 p. 133 (1977)
I.N. p. 316
REM p.936
Schultz, E.M.; US Patent 2,835,702; May 20,1958; assigned to Merck and Co., Inc.

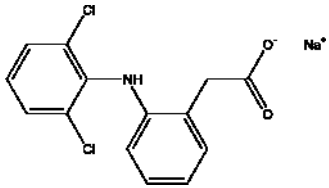
DICLOFENAC SODIUM

Therapeutic Function: Antiinflammatory

Chemical Name: 2-[(2,6-Dichlorophenyl)amino]benzeneacetic acid monosodium salt

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 15307-79-6; 15307-86-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Voltaren	Fujisawa	Japan	1974
Voltaren	Ciba Geigy	Italy	1975
Voltarene	Ciba Geigy	France	1976
Voltaren	Geigy	W. Germany	1976
Voltarol	Ciba Geigy	UK	1978
Adefuronic	Taiyo	Japan	-
Blesin	Sawai	Japan	-
Dichronic	Toyo	Japan	-
Docell	Nippon Kayaku, Co.	Japan	-
Irinatolon	Tatumi	Japan	-
Kriplex	Alfa Farm.	Italy	-
Neriodin	Teikoku	Japan	-

Trade Name	Manufacturer	Country	Year Introduced
Shignol	Taisho	Japan	-
Sofarin	Nippon Chemiphar	Japan	-
Sorelrnon	Towa Yakuhin	Japan	-
Thicataren	Isei	Japan	-
Tsudohmin	Toho	Japan	-
Valetan	Tobishi	Japan	-

Raw Materials

N-Chloroacetyl-N-phenyl-2,6-dichloroaniline
Aluminum chloride
Sodium hydroxide

Manufacturing Process

Four grams of N-chloroacetyl-N-phenyl-2,6-dichloroaniline and 4 grams of aluminum chloride are well mixed together and heated for 2 hours at 160°C. The melt is cooled and poured onto about 50 grams of ice while it is still warm. The oil which separates is dissolved in 50 ml of chloroform, the chloroform solution is washed with 10 ml of water, dried over sodium sulfate and concentrated under 11 torr. The residue is distilled. The 1-(2,6-dichlorophenyl)-2-indolinone melts at 126°-127°C.

A solution of 186 grams of 1-(2,6-dichlorophenyl)-2-indolinone in 660 ml of ethanol and 660 ml of 2 N sodium hydroxide solution is refluxed for 4 hours. The solution is then cooled and left to stand for 4 hours at 0°-5°C. The crystals which form are filtered off and recrystallized from water. The sodium salt of 2-(2,6-dichloroanilino)-phenylacetic acid melts at 283°-285°C. The yield is 97% of theoretical, according to US Patent 3,558,690.

References

Merck Index 3066
Kleeman and Engel p. 293
OCDS Vol. 2 p. 70 (1980)
DOT 9 (9) 369 (1973) and 11 (3) 106 (1975)
I.N. p. 316
Sallmann, A. and Pfister, R.; US Patent 3,558,690; January 26, 1971; assigned to Geigy Chemical Corporation
Sallmann, A. and Pfister, R.; US Patent 3,652,762; March 28, 1972; assigned to Ciba-Geigy Corporation

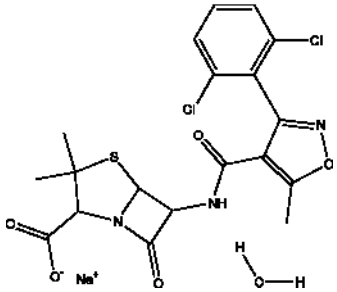
DICLOXACILLIN SODIUM

Therapeutic Function: Antibacterial

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

Common Name: 3-(2,6-Dichlorophenyl)-5-methyl-4-isoxazolylpenicillin

Structural Formula:



Chemical Abstracts Registry No.: 13412-64-1; 3116-76-5 (Acid)

Trade Name	Manufacturer	Country	Year Introduced
Dynapen	Bristol	US	1968
Veracillin	Ayerst	US	1968
Pathocil	Wyeth	US	1968
Diclocil	Bristol	France	1968
Diclocil	Bristol	Italy	1971
Dycill	Beecham	US	1975
Clocil	Bristol Banyu	Japan	-
Combipenix	Toyo Jozo	Japan	-
Constaphyl	Gruenenthal	W. Germany	-
Diclex	Meiji	Japan	-
Diclo	Firma	Italy	-
Diclomax	Pulitzer	Italy	-
Dicloxapen	Magis	Italy	-
Novapen	I.B.P.	Italy	-
Soldak	Ariston	Argentina	-
Staphicillin	Banyu	Japan	-
Totocillin	Bayer	W. Germany	-

Raw Materials

6-Aminopenicillanic acid
3-(2',6'-Dichlorophenyl)-5-methylisoxazole-4-carbonyl chloride
Sodium bicarbonate

Manufacturing Process

A suspension of 6-aminopenicillanic acid (216 grams) in water (2 liters) was adjusted to pH 6.8 by the addition of N aqueous sodium hydroxide (approximately 1 liter) and the resulting solution was stirred vigorously while a solution of 3-(2',6'-dichlorophenyl)-5-methylisoxazole-4-carbonyl chloride (290 grams) in acetone (1.5 liters) was added in one portion.

The temperature rose to 26°C and as reaction proceeded the free acid form of the penicillin separated as a white solid. After 30 minutes the suspension was cooled to 10°C and stirring was continued at this temperature for 1 hour more. The mixture was then cooled to 0°C, centrifuged, and the solid product washed with aqueous acetone (250 ml) and finally dried in an air oven at 30°C. The product (440 grams, 94%) had $[\alpha]_D^{20}$ +106.3° (c 1 in EtOH) and was shown by alkalimetric assay to be 97.5% pure.

The salt was prepared by dissolving the free acid form of the penicillin in the equivalent amount of aqueous sodium bicarbonate and freeze drying the resulting solution. The hydrated salt so obtained was shown by alkalimetric assay to be 94% pure and to contain 6% water.

References

Merck Index 3068
Kleeman and Engel p. 295
PDR pp.697, 993, 1606, 1967
OCDS Vol. 1 p. 413 (1977)
DOT 2 (2) 50 (1966)
I.N. p.316
REM p. 1196 |
Nayler, J.H.C.; US Patent 3,239,507; March 8, 1966; assigned to Beecham Group Limited, England

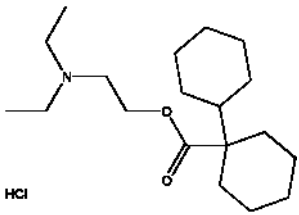
DICYCLOMINE HYDROCHLORIDE

Therapeutic Function: Spasmolytic

Chemical Name: (Bicyclohexyl)-1-carboxylic acid 2-(diethylamino)ethyl ester hydrochloride

Common Name: Dicycloverin hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 67-92-6; 77-19-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Bentyl	Merrell National	US	1950

Trade Name	Manufacturer	Country	Year Introduced
Dyspas	Savage	US	1974
Dicen	Mallard	US	1980
Neoquess	O'Neal Jones	US	1981
A-Spas	Hyrex	US	1983
Ametil	Corvi	Italy	-
Atumin	Merrell	W. Germany	-
Babyspasmil	Lacefa	Argentina	-
Benacol	Cenci	US	-
Bentomine	Darby	US	-
Bentylol	Inibsa	Spain	-
Clomin	S.C.S. Pharmalab.	S. Africa	-
Cyclobec	Pharbec	Canada	-
Dicycol	Ohio Medical	US	-
Esentil	Erba	Italy	-
Formulex	I.C.N.	Canada	-
Icramin	Toho Iyaku	Japan	-
Incron	Seiko	Japan	-
Kolantyl	Merrill	UK	-
Lomine	Riva	Canada	-
Mamiesan	Kyowa	Japan	-
Merbantal	Vitrum	Sweden	-
Merbenyl	Merrell	UK	-
Mydocalm	Lennon	S. Africa	-
Nomocramp	Salusa	S. Africa	-
Notensyl	C.T.S.	Israel	-
Or-Tyl	Ortega	US	-
Panakiron	Sato	Japan	-
Protylol	Pro Doc	Canada	-
Spascol	Vangard	US	-
Spasmoban	Trianon	Canada	-
Viscerol	Medic	Canada	-

Raw Materials

1-Phenylcyclohexane cyanide
Sodium
Ethanol
β-Diethylaminoethanol
Sulfuric acid
Hydrogen

Manufacturing Process

155 grams of 1-phenylcyclohexanecyanide, 350 cc of concentrated sulfuric acid and 1,130 cc of ethyl alcohol are refluxed vigorously for 48 hours. The remaining alcohol is then removed by vacuum distillation and the residue is poured into 1 liter of ice water. An oil separates which is extracted 3 times with 200 cc portions of petroleum ether, the extracts are combined and

heated on a steam bath to remove the ether. The resulting crude ester may be used directly for the reesterification operation or it may be distilled to purify it first. A mixture of the ester so obtained, 155 grams of β-diethylaminoethanol and 800 cc of dry xylene are placed in a reaction vessel with about 2 grams of sodium. The vessel is heated in an oil bath at 150°-160°C. A xylene-ethanol azeotrope distills over at about 78°-82°C over a period of 2 to 3 hours. The distillate is cooled and shaken with about 3 times its volume of water, the decrease in volume of the distillate being considered a measure of the amount of alcohol formed. When 80-90% of the theoretical amount of alcohol is obtained in the distillate the reaction mixture is subjected to vacuum distillation to remove most of the xylene and unreacted diethylaminoethanol. The residue is poured into 500 cc of benzene which is then extracted 3 times with 500 cc portions of water.

The washed benzene layer is diluted with an equal volume of ether and alcoholic hydrochloric acid is added until the mixture is acid to Congo red. A white crystalline solid forms which is dissolved in 300-400 cc of alcohol and diluted with ether to the point where precipitation starts. A few drops of butanone are added, the solution is cooled to -10°C, and filtered to recover the crystals which separate. The product is obtained in the form of white needles melting at 159°-160°C, in good yield.

13 parts of β-diethylaminoethyl 1-phenylcyclohexanecarboxylate hydrochloride, 125 parts of glacial acetic acid and 0.3 part of Adams' catalyst are heated to 70°C and shaken with hydrogen at 50 lb pressure until 90-100% of the theoretical hydrogen is absorbed. The acetic acid is then removed by distillation and the residue recrystallized from butanone, giving the above product as a crystalline hydrochloride melting at 165°-166°C, in good yields. This product may also be prepared by reacting cyclohexyl bromide with cyclohexyl cyanide with the use of sodium amide followed by alcoholysis and reesterification.

References

Merck Index 3083
Kleeman and Engel p. 295
PDR pp. 830, 986, 993
OCDS Vol. 1 p. 36 (1977)
I.N. p. 317
REM p. 915
Van Campen, M.G. Jr. and Tilford, C.H.; US Patent 2,474,796; June 28, 1949; assigned to The Wm. S. Merrell Company

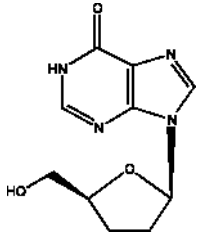
DIDANOSINE

Therapeutic Function: Antiviral

Chemical Name: Inosine, 2',3'-dideoxy-

Common Name: Didanosine; Dideoxyinosine

Structural Formula:



Chemical Abstracts Registry No.: 69655-05-6

Trade Name	Manufacturer	Country	Year Introduced
ddI	Bristol-Myers Squibb	USA	-
Didanosine	Bristol-Myers Squibb	USA	-
Didanosine	Cipla Limited	India	-
Videx	Bristol-Myers Squibb	USA	-
Videx EC	Bristol-Myers Squibb	USA	-

Raw Materials

Yeast extract	Peptone
Meat extract	Tris-HCl
Agar	One platinum loop of each microorganism

Manufacturing Process

In a 500 ml flask with a shoulder was separately charged 50 ml of medium (pH 7.0) containing 0.5 g/dl of yeast extract, 1.0 g/dl of peptone, 1.0 g/dl of meat extract and 0.5 g/dl of NaCl followed by sterilization. One platinum loop of each microorganism shown in Table which had been preincubated in bouillon agar medium at 30°C for 16 hours was inoculated on the medium followed by shake culture at 30°C for 16 hours. After the cells were isolated from the obtained culture solution by centrifugal separation, the cells were washed with 0.05 M Tris-HCl buffer (pH 7.2) and further centrifuged to give washed cells.

The washed cells described above were added to 0.05 M Tris-HCl buffer (pH 7.2) containing 1 g/dl of 2',3'-dideoxyadenosine in a concentration of 5 g/dl followed by reacting at 30°C for 2 hours. The amount of 2',3'-dideoxyinosine produced at this stage is shown in the next Table.

Table

2',3'-Dideoxyinosine Produced (mg/dl)	Strain
785	Achromobacter candidans FERM-P 8778
52	Acinetobacter lwoffii ATCC-9036
412	Aeromonas salmonicida ATCC-14174
106	Agrobacterium tumefaciens FERM-P 2343

2',3'-Dideoxyinosine Produced (mg/dl)	Strain
603	Alcaligenes faecalis FERM-P 8030
36	Arthrobacter citreus ATCC-11624
317	Bacillus firmus ATCC-8247
931	Brevibacterium pusillum ATCC-19096
135	Cellulomonas flavigena ATCC-491
848	Citrobacter freundii ATCC-8090
742	Corynebacterium aquaticum ATCC-14665
816	Escherichia coli FERM-P 7404
198	Enterobacter cloacae ATCC-13047
495	Erwinia carotovora FERM-P 2766
603	Flavobacterium aquatile ATCC-8375
416	Hafnia alvei ATCC-9760
186	Klebsiella pneumoniae ATCC-8308
223	Kluyvera citrophila FERM-P 8193
109	Microbacterium imperiable ATCC-8365
795	Micrococcus luteus ATCC-400
86	Mycoplana dimorpha ATCC-4279
107	Nocardia restricta ATCC-14887
39	Planococcus citreus ATCC-15234
26	Protaminobacter alboflavus ATCC-8458
896	Proteus rettgeri FERM-P 8196
113	Pseudomonas oleovorans ATCC-8062
98	Rhizobium meliloti FERM-P 8197
109	Rhodococcus rhodochrous ATCC-12974
416	Salmonella typhimurim FERM-P 9470
727	Sarcina albida FERM-P 7048
213	Serratia grimesii ATCC-14460
98	Staphylococcus epidermidis ATCC-155
145	Streptomyces flavovirens IFO-3197
46	Vibrio metschnikovii ATCC-7708
465	Xanthomonas citri FERM-P 3396

This way 2',3'-dideoxyinosine may be produced from 2',3'-dideoxyadenosine in a short period of time, by contacting microorganisms supplied at low cost, products containing the same or treated products thereof, with a substrate.

References

Yokozeki K. et al.; US Patent No. 4,970,148; Nov. 13, 1990; Assigned to Ajinomoto Co., Inc., Tokyo, Japan

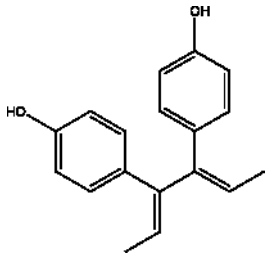
DIENESTROL

Therapeutic Function: Estrogen

Chemical Name: 4,4'-(1,2-Diethylidene-1,2-ethanediyl)bisphenol

Common Name: Dienoestrol

Structural Formula:



Chemical Abstracts Registry No.: 84-17-3

Trade Name	Manufacturer	Country	Year Introduced
Synestrol	Schering	US	1947
Cycladiene	Bruneau	France	1948
Agaldog	Vetoquinol	France	-
Bi-Star	Merit	US	-
Dinestrol	Reid-Provident	US	-
DV	Merrell Dow	US	-
Estan	Schering	US	-
Estraguard	Reid-Provident	US	-
Farmacyrol	Farmaryn	W. Germany	-
Follidene	Recordati	Italy	-
Hormofemin	Medo	UK	-
Lucidon	Westerfield	US	-
Oestrovis	Stotzer	Switz.	-
Para-Dien	Klimitschek	Austria	-
Reginol	Merz	W. Germany	-
Sexadien	A.F.I.	Norway	-

Raw Materials

4-Hydroxypropiophenone
Potassium hydroxide
Acetic anhydride
Benzoyl chloride
Sodium
Acetyl chloride

Manufacturing Process

Preparation of γ,δ-Bis-(4-Hydroxylphenyl)-Hexane-γ,δ-Diol: A sodium amalgam

is prepared containing 6 grams of sodium and 400 grams of mercury. The amalgam is covered with a solution of 20 grams of 4-hydroxypropiophenone in a mixture of 30 ml of 5 N sodium hydroxide solution and 220 ml of water and the mixture is heated to 28°-30°C and stirred gently. The reduction is accompanied by development of heat and the temperature of the solution rises to 34°-35°C, and then falls slowly. After 5 hours the alkaline solution is separated from the mercury and diluted with 3 or 4 times its volume of water, when, in order to form the benzoyl derivatives of the products, the solution is vigorously stirred, while it is being cooled, with 20 ml of benzoyl chloride, the solution being kept at a temperature of 15°-20°C. When the reaction is completed, the benzoyl derivatives are filtered off, washed with water and recrystallized from a mixture of benzene and alcohol, when a product with a melting point of 195°-215°C is obtained.

Preparation of Dienestrol: In order to obtain dienoestrol, 14.6 grams of dry 4,4'-dibenzoate are refluxed with a mixture of 40 ml of acetic anhydride and 40 ml acetylchloride by heating in an oil-bath at about 90°C for 6 hours after which the bath temperature is increased to 120°C and heating continued for a further 18 hours, after which time the evolution of hydrogen chloride practically ceases. The mixture is allowed to cool for several hours and the crystals which separate are filtered off and recrystallized from an alcohol-benzene mixture when the product melts at 210°-222°C. This product is converted into dienoestrol by adding 10.8 grams of it to 100 ml of 10% (w/v) alcoholic potassium hydroxide solution and then refluxing during 1 hour. After dilution with 200 ml of water and filtration from a small amount of insoluble material, dienoestrol is precipitated from the alkaline solution by treatment with carbon dioxide. It is filtered off, washed with water and recrystallized from dilute alcohol after which it melts at 233°-234°C according to US Patent 2,464,203.

References

Merck Index 3085
Kleeman and Engel p. 296
PDR pp. 1225, 1294
OCDS Vol. 1 p. 102 (1977)
I.N. p. 318
REM p. 988
Short, W.F. and Hobday, G.I; US Patent 2,464,203; March 15, 1949; assigned to Boots Pure Drug Company Limited, England
Adler, E.; US Patent 2,465,505; March 29,1949; assigned to Hoffmann-La Roche Inc.

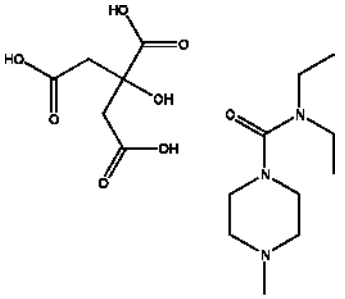
DIETHYLCARBAMAZINE CITRATE

Therapeutic Function: Anthelmintic

Chemical Name: N,N-Diethyl-4-methyl-1-piperazine-carboxamide citrate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 1642-54-2; 90-89-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Hetrazan	Lederle	US	1949
Banocide	Burroughs-Wellcome	-	-
Difil	Evsco	US	-
Filarcidin	Cidan	Spain	-
Filaribits	Norden	US	-
Franocide	Burroughs-Wellcome	-	-
Loxuran	EGYT	Hungary	-
Notezine	Specia	-	-

Raw Materials

1-Methylpiperazine
Diethyl carbamyl chloride
Sodium hydroxide
Sodium carbonate

Manufacturing Process

To 50 cc of water was added 18 grams of 1-methylpiperazine dihydrochloride and 8.34 grams of sodium hydroxide. When solution had been effected the beaker was cooled to 10°C and with stirring, 4.17 grams of sodium hydroxide dissolved in 15 cc of water and 14 grams of diethyl carbamyl chloride were added simultaneously. When all had been added, the solution was extracted 3 times with ether which was then dried and filtered. The ether solution was saturated with dry hydrogen chloride. A yellow gum appeared which on trituration gave a white, hygroscopic solid which was filtered and dried in a drying pistol. The N,N-diethyl-4-methyl-1-piperazine-carboxamide hydrochloride had a melting point of 150°-155°C.

If the compound itself is desired, the salt is dissolved in water and the solution saturated with a mild alkali such as potassium carbonate. The product is then extracted with chloroform, dried, and after removal of the chloroform, distilled.

References

Merck Index 3100
OCDS Vol. 1 p. 278 (1977)
I.N. p. 320
REM p. 1235
Kushner, S.and Brancone, L.; US Patent 2,467,893; April 19, 1949; assigned to American Cyanamid Company
Kushner, S. and Brancone, L.; US Patent 2,467,895; April 19,1949; assigned to American Cyanamid Company

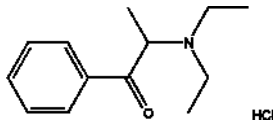
DIETHYLPROPION HYDROCHLORIDE

Therapeutic Function: Anorexic

Chemical Name: 2-(Diethylamino)-1-phenyl-1-propanone hydrochloride

Common Name: Amfepramone

Structural Formula:



Chemical Abstracts Registry No.: 134-80-5; 90-84-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Tenuate	Merrell National	US	1959
Tepanil	Riker	US	1959
Tenuate-Dospan	Merrell	France	1971
Adiposan	Phyteia	Switz.	1971
Anfamon	Ortscheit	W. Germany	-
Bonumin	Farmos	Finland	-
Brendalit	Dexter	Argentina	-
Delgamer	Merrell Dow	-	-
Derfon	Lafon	France	-
Dietec	Pharbec	Canada	-
Dietil-Retard	Trenker	Belgium	-
D.I.P.	Eri	Canada	-
Dobesin	Pharmacia	Sweden	-
Frekentine	Minerva-Chemie	Netherlands	-
Lineal-Rivo	Rivopharm	Switz.	-
Linea Valeas	Valeas	Italy	-

Trade Name	Manufacturer	Country	Year Introduced
Lipomin	Uriach	Spain	-
Liposlim	Pharma Farm. Spec.	Italy	-
Magrene	Ravasini	Italy	-
Menutil	Merrell Dow	-	-
Moderatan	Theranol	France	-
Nobesine-25	Nadeau	Canada	-
Nulobes	Disprovent	Argentina	-
Prefamone	Dexo	France	-
Regenon	Temmler	W. Germany	-
Regibon	Medic	Canada	-
Slim-Plus	Pharma-Plus	Switz.	-

Raw Materials

α-Bromopropiophenone
Diethylamine
Hydrogen chloride

Manufacturing Process

1,145 g of α-bromopropiophenone and 850 g of diethylamine are combined under stirring and heated on a water bath to boiling. The precipitate is filtered off under suction and washed with benzol. The filtrate is shaken up with aqueous hydrogen chloride, the aqueous solution made alkaline and etherified. The solution freed of the ether is fractionated. The boiling point (6 mm) is 140°C and the yield 800 g. The base is dissolved in acetic ester and precipitated with isopropanolic hydrogen chloride. After suction filtration and washing with ether the yield is found to be 750 g (80%)and the melting point 168°C.

References

Merck Index 3113
Kleernan and Engel p. 37
PDR pp. 991, 1453, 1606
DOT 9 (6) 213 (1973)
I.N. p. 66
REM p. 891
Schutte, J.; US Patent 3,001,910; September 26, 1961; assigned to Firma Ternmler-Werke (W. Germany)

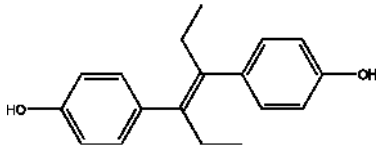
DIETHYLSTILBESTROL

Therapeutic Function: Estrogen

Chemical Name: 4,4'-(1,2-Diethyl-1,2-ethenediyl)bisphenol

Common Name: DES

Structural Formula:



Chemical Abstracts Registry No.: 56-53-1

Trade Name	Manufacturer	Country	Year Introduced
DES	Amfre-Grant	US	1946
Stilbetin	Squibb	US	1950
Microest	Massengill	US	1958
Vagestrol	Norwich Eaton	US	1969
Acnestrol	Dermik	US	-
Agostlben	Spofa	Czechoslovakia	-
Cyren A	Bayer	W. Germany	-
Desma	Tablicaps	US	-
Des-Plex	Amfre-Grant	US	-
Dicorvin	Amfre-Grant	US	-
Distilbene	Ucepha	France	-
Estilbin	Dumex	Denmark	-
Estrosyn	Cooper	US	-
Furacin-E	Eaton	US	-
Gerex	Consol. Midland	US	-
Makarol	Mallinckrodt Inc.	US	-
Mase-Bestrol	Mason	US	-
Menopax	Nicholas	UK	-
Micrest	Beecham	US	-
Oestrogen	Holzinger	Austria	-
Oestrol	Veterinaria	Switz.	-
Oestromon	Merck	W. Germany	-
Pelestrol	Franklin	US	-
Percutacrine	Besins-Iscovesco	France	-
Tylosterone	Lilly	US	-

Raw Materials

p-Hydroxypropiophenone
Sodium
Sodium hydroxide
Hydrogen chloride

Manufacturing Process

50 parts by weight of p-hydroxypropiophenone are dissolved in 200 parts by

weight of a 12.5% solution of caustic soda and shaken with 350 parts by weight of 3% sodium amalgam. The sodium salt of the pinacol thereby precipitating is reacted with glacial acetic acid, whereby the free pinacol is obtained (MP 205°C to 210°C, after purification 215°C to 217°C). The yield amounts to 95% of the theoretical. The pinacol is suspended in ether and gaseous hydrogen chloride introduced, whereby water separates and the pinacolin formed is dissolved in the ether, from which it is obtained by evaporation as a viscous oil (diacetateof MP 91°C). The yield is quantitative.

40 parts by weight of pinacolin are dissolved in ethyl alcohol and gradually treated with 80 parts by weight of sodium under reflux. The solution is decomposed with water and the pinacolin alcohol formed extracted from the neutralized solution with ether. The pinacolin alcohol is a viscous oil which is characterized by a dibenzoate of MP 172°C. The yield is 95% of the theoretical.

A solution of 30 parts by weight of pinacolin alcohol in ether is saturated with hydrogen chloride at room temperature and the ether solution then agitated with bicarbonate. After concentration by evaporation it leaves behind the crude diethylstilbestrol [α,β-(p,p'-dihydroxydiphenyl)-α,β-diethylethylene] which, when recrystallized from benzene, melts at 170°C to 171°C. The yield amounts to 75% of the calculated. The total yield of diethylstilbestrol, calculated on p-hydroxypropiophenone, is 68% of the theoretical.

References

Merck Index3115
Kleeman and Engel p. 298
PDR p. 1045
OCDS Vol. 1 p. 101 (1977)
I.N. p. 321
REM p. 988
Adler, E., Gie, G.J. and von Euler, H.; US Patent 2,421,401; June 3, 1947; assigned to Hoffmann-La Roche, Inc.

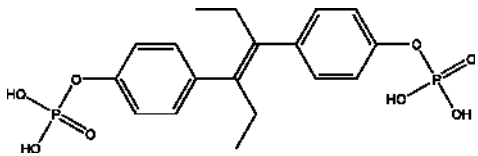
DIETHYLSTILBESTROL DIPHOSPHATE

Therapeutic Function: Estrogen, Antitumor

Chemical Name: 4,4'-(1,2-Diethyl-1,1-ethenediyl)bisphenol-bis(dihydrogen phosphate)

Common Name: Fosfestrol

Structural Formula:



Chemical Abstracts Registry No.: 522-40-7; 23519-26-8 (Tetrasodium salt)

Trade Name	Manufacturer	Country	Year Introduced
Stilphostrol	Dome	US	1955
ST 52	Lucien	France	1955
Cytonal	VEB Berlin Chemie	E. Germany	-
Honvan	Asta	W. Germany	-
Honvan	Funk	Spain	-
Honvan	W.B. Pharm.	UK	-
Honvan	Noristan	S. Africa	-
Honvan	Schering	Italy	-
Honvan	Asta-Kyorin	Japan	-
Stilbetin	Squibb	-	-
Stibol	A.C.O.	Sweden	-

Raw Materials

α,α'-Diethyl-4,4'-dihydroxystilbene
Phosphorus oxychloride
Sodium bicarbonate

Manufacturing Process

A solution of 1 part of α,α'-diethyl-4,4'-dihydroxystilbene in 5 parts of pyridine is added drop by drop to the strongly cooled solution of 2 parts of phosphorus-hydroxy chloride in 5 parts of pyridine. The mixture soon solidifies to a crystalline magma. It is allowed to stand in ice for ¼ hour and then for an hour at room temperature. The mass is then poured into an excess of saturated sodium bicarbonate solution. Unconsumed parent material is removed by extraction with ether. The aqueous solution is then mixed with 2 N hydrochloric acid, whereupon the primary phosphoric acid ester of α,α'-diethyl-4,4'-dihydroxystilbene of the formula is precipitated in the form of a voluminous white powder. By recrystallization or reprecipitation this ester may be further purified.

References

Merck Index 4136
Kleeman and Engel p. 433
PDR p. 1261
OCDS Vol. 1 p. 101 (1977)
I.N. p. 321
REM p. 989 Miescher, K.and Heer, J.; US Patent 2,234,311; March 11, 1941; assigned to Ciba Pharrnaceutical Products, Inc.

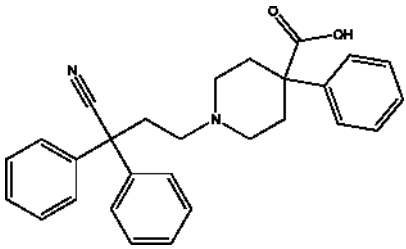
DIFENOXINE

Therapeutic Function: Antiperistaltic

Chemical Name: 1-(3-Cyano-3,3-diphenylpropyl)-4-phenyl-4-piperidinecarboxylic acid

Common Name: Difenoxilic acid

Structural Formula:



Chemical Abstracts Registry No.: 28782-42-5; 35607-36-4 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Lyspafena	Cilag Chemie	W. Germany	1980
Lyspafen	Protea	Australia	-

Raw Materials

t-Potassium butanolate
Ethyl-1-(3-cyano-3,3-diphenylpropyl)-4-phenylisonipecotate HCl
Acetic acid
Hydrogen chloride

Manufacturing Process

To a stirred solution of 5.52 parts of t-potassiurn butanolate in 60 parts of dimethylsulfoxide are added 1.7 parts of ethyl-1-(3-cyano-3,3-diphenylpropyl)-4-phenylisonipecotate hydrochloride and the whole is stirred on an oil bath (90°C) for 4 hours. The reaction mixture is cooled (30°C) and poured onto 180 parts of water with stirring. After two extractions with benzene, the aqueous phase is acidified with glacial acetic acid to pH 6.5 with stirring. The precipitated product is filtered off, washed with water, dried, dissolved in 50 parts of 0.4 N potassium hydroxide and precipitated again with glacial acetic acid. The crude free base is filtered off and dissolved in a mixture of 2-propanol and chloroform and gaseous hydrogen chloride is introduced into the solution. The whole is filtered and the filtrate is evaporated. The residue is mixed with benzene and the latter is evaporated again. The residue is recrystallized from 2-propanol, yielding 1-(3-cyano-3,3-diphenylpropyl)-4-phenylisonipecotic acid hydrochloride.

References

Merck Index 3122

Kleeman and Engel p. 300
OCDS Vol. 2 p. 331 (1980)
DOT 10 (6) 205 (1974)
I.N. p. 323
Soudyn, W. and van Wijngaarden, I.; US Patent 3,646,207; February 29, 1972; assigned to Janssen Pharmaceutica, N.V. (Belgium)

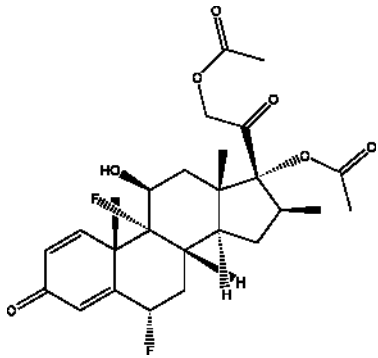
DIFLORASONE DIACETATE

Therapeutic Function: Antiinflammatory

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

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 2557-49-5; 33654-31-7 (Diacetate)

Trade Name	Manufacturer	Country	Year Introduced
Florone	Upjohn	US	1978
Florone	Upjohn	Switz.	1979
Maxiflor	Herbert	US	1980
Florone	Upjohn	W. Germany	1981
Florone	Basotherm	W. Germany	1982
Flutone	Rorer	US	-

Raw Materials

6α-Fluoro-9α-bromo-11β,17α,21-trihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione-21-acetate
Potassium acetate
Hydrogen fluoride
Orthoacetic acid trimethyl ester

Manufacturing Process

6α-Fluoro-9β-epoxy-17α,21-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione-21-acetate:To a solution of 6.78 g of 6α-fluoro-9α-bromo-11β,17α,21-trihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione-21-acetate in 175 ml of acetone was added 6.78 g of potassium acetate and the resulting suspension was heated under reflux for a period of 17 hours. The mixture was then concentrated to approximately 60 ml volume at reduced pressure on the steam bath, diluted with water and extracted with methylene chloride. The methylene chloride extracts were combined, washed with water, dried over anhydrous sodium sulfate and evaporated. The residue was redissolved in methylene chloride and chromatographed over 500 g of Florisil anhydrous magnesium silicate. The column was eluted with 1 liter portions of hexanes (Skellysolve B) containing increasing proportions of acetone. There was so eluted 6α-fluoro-9β,11β-epoxy-16α-methyl-17α,21-dihydroxy-1,4-pregnadiene-3,20-dione-21-acetate which was freed of solvent by evaporation of the eluates.

6α,9α-Difluoro-11β,17α,21-trihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione-2-1-acetate: To approximately 1.3 g of hydrogen fluoride contained in a polyethylene bottle and maintained at -60C was added 2.3 ml of tetrahydrofuran and then a solution of 500 mg (0,0012 mol) of 6α-fluoro-9β,11β-epoxy-16α-methyl-17α,21-dihydroxy-1,4-pregnadiene-3,20-dione-21-acetate in two ml of methylene chloride. The steroid solution was rinsed in with an additional 1 ml of methylene chloride. The light red colored solution was then kept at approximately -30°C for 1 hour and at -10°C for 2 hours. At the end of this period it was mixed cautiously with an excess of cold sodium bicarbonate solution and the organic material extracted with the aid of additional methylene chloride.

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

6α,9α-Difluoro-11β,17α,21-trihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione: 3.25 g of 6α,9α-difluoro-11β,17α,21-trihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione-21-acetate was dissolved in 325 ml of methanol, previously purged of air-oxygen by passing nitrogen through it for 10 minutes and thereto was added a solution of 1.63 g of potassium bicarbonate in 30 ml of water, similarly purged of oxygen. The mixture was allowed to stand at room temperature for a period of 5 hours in a nitrogen atmosphere, thereupon neutralized with 2.14 ml of acetic acid in 40 ml of water. The mixture was concentrated to approximately one-third volume at reduced pressure on a 60°C water bath. Thereupon 250 ml of water was added and the mixture chilled. The crystalline product was collected on a filter, washed with water and dried to give 6α,9α-difluoro-11β,17α,21-trihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione.

The diflorasone is reacted with orthoacetic acid trimethyl ester in the presence of toluenesulfonic acid to give diflorasone diacetate.

References

Merck Index 3124
DFU 2 (4) 238 (1977)
Kleeman and Engel p. 301
PDR pp. 832, 932
DOT 15 (4) 445 (1979)
I.N. p. 324
REM p. 972
Lincoln, F.H., Schneider, W.P. and Spero, G.B.; US Patent 3,557,158; January 19,1971; assigned to The Upjohn Company
Ayer, D.E., Schiagel, C.A. and Flynn,G.L.; US Patent 3,980,778; September 14, 1976; assigned to The Upjohn Co.

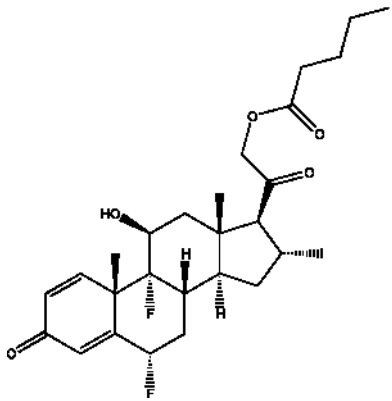
DIFLUCORTOLONE VALERATE

Therapeutic Function: Antiinflammatory

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

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 59198-70-8; 2607-06-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Nerisone	Schering	UK	1976
Temetex	Roche	UK	1976
Temetex	Roche	W. Germany	1977
Nerisone	Schering	France	1979
Nerisona	Schering	Italy	1979

Trade Name	Manufacturer	Country	Year Introduced
Temetex	Roche	Italy	1980
Nerisona	Schering	Japan	1981
Texmeten	Roche	Japan	1981
Travocort	Schering	W. Germany	-

Raw Materials

16α-Methyl-6α,9α-fluoro-δ(4)-pregnene-11α,21-diol-3,20-dione-21-acetate
Bacterium Bacillus lentus
Valeric acid chloride

Manufacturing Process

16α-Methyl-6α,9α-difluoro-δ4-pregnene-11α,21-diol-3,20-dione-21-acetate (MP = 229°/232°-234°C (with decomposition) is dehydrogenated in 1.2-position by means of Bacillus lentus, Mutant MB 284, whereby the 21-acetate group is simultaneously saponified. (It is possible under the same conditions to start with the free 21-hydroxyl compound.)

For this purpose a fermenter made of stainless steel having a 50 liter capacity is charged with 30 liters of a nutrient solution of 0.1% yeast extract, 0.5% cornsteep and 0.2% glucose, heated for one-half hour at 120°C for sterilization purposes, and after cooling, inoculated with a bacterial suspension of Bacillus lentus MB 284.

After 24 hours of growth at 28°C under stirring (220 revolutions per minute) and aeration (1.65 m3/hr), 1.8 liters of the obtained culture is removed under sterile conditions and transferred with 28 liters of the same sterilized nutrient medium into a fermenter of the same size.

Simultaneously, 6 g of 16α-methyl-6α,9α-difluoro-δ4-pregnene-11β,21-diol-3,20-dione-21-acetate in 200 cc of dimethylformamide are added and the fermentation is continued for 50 hours under the same conditions.

The course of the fermentation is tested by removal of samples which are extracted with methyl isobutyl ketone. The extracts are analyzed by thin layer chromatography using a system of benzene/ethyl acetate (4:1).

After further working up there is obtained an oily crystalline residue which is subjected to chromatography on silica gel. The 16α-methyl-6α,9α-difluoro-δ1,4-pregnadien-11β,21-diol-3,20-dione is eluated with ethyl acetate-chloroform (1:2), it is recrystallized from ethyl acetate/ether and then formed to melt at 240°/242°-244°C. The yield is 60% of the theoretical. The product is reacted with valeric acid chloride to give the valerate ester.

References

Merck Index 3126
Kleeman and Engel p. 302
OCDS Vol. 2 p. 192 (1980)

DOT 12 (7) 259 (1976)
I.N. p. 324
Kieslich, K., Kerb, U. and Raspe, G.; US Patent 3,426,128; February 4, 1969; assigned to Schering A.G. (West Germany)

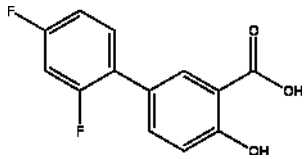
DIFLUNISAL

Therapeutic Function: Analgesic, Antiinflammatory

Chemical Name: 2',4'-Difluoro-4-hydroxy-[1,1'-biphenyl]-3-carboxylic acid

Common Name: Difluorophenyl salicylic acid

Structural Formula:



Chemical Abstracts Registry No.: 22494-42-4

Trade Name	Manufacturer	Country	Year Introduced
Dolobid	Morson	UK	1978
Unisal	Chibret	Switz.	1978
Dolobid	MSD	Italy	1979
Dolobis	MDS-Chibret	France	1981
Fluniget	Sharp and Dohme	W. Germany	1981
Dolobid	MSD	Canada	1982
Adomal	Malesci	Italy	1982
Dolobid	MSD	US	1982
Citidol	C.T.	Italy	-
Diflonid	Dumex	Denmark	-
Diflunil	I.C.I.	-	-
Dugodol	Alkaloid	Yugoslavia	-
Flovacil	Andromaco	Argentina	-
Flustar	Firma	Italy	-
Reuflos	Scharper	Italy	-

Raw Materials

4-(2',4'-Difluorophenyl)phenol
Carbon dioxide

Manufacturing Process

A mixture of 10 g of 4-(2',4'-difluorophenyl)-phenol and 27.2 g of potassium carbonate is exposed to carbon dioxide at 1,300 psi and 175°C. The dark mass obtained from this carbonation is then dissolved in 300 ml of water and 200 ml of methylene chloride and the two layers separated. The water layer is then extracted with 100 ml of methylene chloride and then acidified with 2.5 N hydrochloric acid. This mixture is then filtered and the cake dried in vacuo to yield 5.32 g of the crude product. The crude product is then recrystallized from benzene-methanol. An additional crystallization of this semipure material from benzene-methanol yields analytically pure 2-hydroxy-5-(2',4'-difluorophenyl)-benzoic acid (MP 210-211°C).

References

Merck Index 3127
Kleeman and Engel p. 303
PDR p. 1171
OCDS Vol. 2 p. 85 (1980)
DOT 14 (7) 269 (1978)
I.N.p. 324
REM p.1116
Ruyle, W.V., Jarett, L.H. and Matzuk, A.R.; US Patent 3,714,226; January 30, 1973; assigned to Merck and Co., Inc.

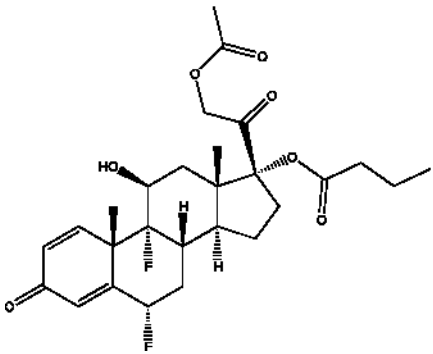
DIFLUPREDNATE

Therapeutic Function: Antiinflammatory

Chemical Name: 21-(Acetyloxy)-6,9-difluoro-11-hydroxy-17-(1-oxobutoxy) pregna-1,4-diene-3,20-dione

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 23674-86-4

Trade Name	Manufacturer	Country	Year Introduced
Epitopic	Clin Midy	France	1978

Raw Materials

6α,9α-Difluoroprednisolone
Oxalic acid
Methyl orthobutyrate
Acetic anhydride

Manufacturing Process

Orthoesterification: A mixture of 1 g of 6α,9α-difluoroprednisolone, 10 mg of p-toluenesulfonic acid, 5 cc of dimethylformamide and 3 cc of methyl orthobutyrate is heated for 15 hours on an oil bath at 105°C while a slow stream of nitrogen is passed through the mixture so that the methanol produced as a by-product of the reaction, is distilled off. After addition of several drops of pyridine to neutralize the acid catalyst, the reaction mixture is evaporated under vacuum and there is obtained a solid residue which is taken up with methanol, and filtered. The product is recrystallized from a methylene chloride-methanol mixture to yield 682 mg of 6α,9α-difluoroprednisolone 17α,21-methylorthobutyrate, also identified as 17α,21-(1'-methoxy)-n-butylidenedioxy-6α,9α-difluoro-$\delta^{1,4}$-pregnadiene-11β-ol-3,20-dione, MP 194°C-198°C.

Upon chromatography of the mother liquor on a column of alumina another 338 mg of a crystalline mixture of the epimeric orthobutyrates are isolated.

Hydrolysis: A suspension of 1 g of the 6α,9α-difluoroprednisolone 17α,21-methylorthobutyrate in 10 cc of methanol is treated with 2 cc of a 2 N aqueous solution of oxalic acid and heated on a water bath at 40°-50°C for about 5-10 minutes and, afterwards, the mixture is concentrated under vacuum. The residue is then shaken with water, the insoluble product is filtered off and then dried. The solid material is recrystallized from acetone-ether and 6α,9α-difluoroprednisolone 17-butyrate is obtained, MP 193°-196°C.

Esterification: A solution of 500 mg of 6α,9α-difluoroprednisolone-17-butyrate in 2.5 cc of pyridine is treated with 1.25 cc of acetic anhydride and the reaction mixture permitted to stand overnight at 0°C. The reaction mixture is then poured into ice water and the crystalline precipitate formed is filtered off and recrystallized from a methylene chloride-ether-petroleum ether mixture to yield 494 mg of 6α,9α-difluoroprednisolone 17-butyrate, 21-acetate; MP 191°-194°C.

References

Merck Index 3131
Kleeman and Engel p. 303
OCDS Vol. 2 p. 191 (1980)
DOT 15 (1) 25 (1979)
I.N. p. 325
Ercoli, A. and Gardi, R.; US Patent 3,780,177; December 18, 1973; assigned to Warner-Lambert Co.

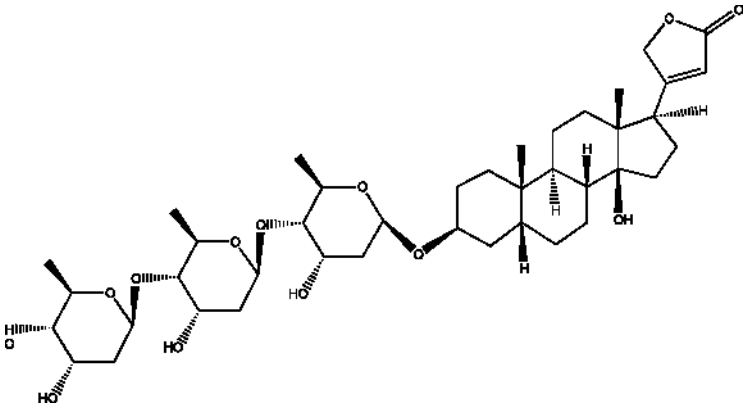
DIGITOXIN

Therapeutic Function: Cardiotonic, Topical venotonic

Chemical Name: Card-20(22)-enolide, 3-((O-2,6-dideoxy-β-D-ribohexopyranosyl-(1-4)-O-2,6-dideoxy-β-D-ribo-hexopyranosyl-(1-4)-2,6-dideoxy-β-D-ribo-hexopyranosyl)oxy)-14-hydroxy-, (3β,5β)-

Common Name: Digitaline cristallisee; Digitoksin; Digitossina; Digitoxin; Digitoxoside

Structural Formula:



Chemical Abstracts Registry No.: 71-63-6

Trade Name	Manufacturer	Country	Year Introduced
Crystodigin	Lilly	-	-
Digitoxin	Boehringer	-	-
Digaloid	Hadra	-	-
Digicor-Neu	Hennig	-	-
Digitoxin	Abbott	-	-
Dixin	Knoll	-	-

Raw Materials

Digitalis purpurea leaves	Lead acetate
Hydrogen sulfide	Amyl ether

Manufacturing Process

1000 g of Digitalis purpurea leaves were moistened thoroughly with a menstruum consisting of 60% ethyl alcohol and 40% water and were packed in a percolator with enough of the menstruum to leave a stratum above the drug. After maceration overnight, the drug was percolated with about 7 liters

of the 60%-alcohol menstruum and about 5 liters of percolate or extract were collected. 400 g of solid lead acetate were added to the percolate and the mixture was stirred until all the lead acetate had dissolved. After standing for at least one hour, the copious light green precipitate was centrifuged off and washed successively with 1000 ml and 500 ml portions of 60% alcohol. The washings were combined with the filtrate from the centrifuge and most of the excess lead acetate removed by treatment with a saturated solution of sodium carbonate monohydrate. The resulting lead carbonate was filtered off, washed with two 200 ml portions of 60% ethyl alcohol, and the washings combined with the filtrate. Hydrogen sulfide was then passed through the combined liquids until no more lead sulfide precipitated. The filtrate and washings resulting from filtering off the lead sulfide were concentrated in vacuo at or below 40°C to a volume of 2000 ml and saturated with a salt, such as sodium chloride, to facilitate subsequent extraction with a water-immiscible organic solvent. The mixture was extracted five times with 600 ml of a solvent consisting of two volumes of chloroform and three volumes of amyl ether. The chloroform-amyl ether solution is extracted with about four 400 ml portions of a 10% solution of sodium carbonate monohydrate to remove any gitalin that may have carried through in the process and vegetative extractive material. After drying over anhydrous sodium sulfate and filtering, the chloroform-amyl ether solution was concentrated in vacuo at 75°-85°C to a volume of about 25 ml. After cooling to room temperature, the concentrate was mixed with about four volumes of petroleum ether and allowed to stand for about one hour at room temperature. The dark colored, amorphous precipitate was filtered and washed with petroleum ether to ensure that all fat had been removed. The precipitate was dissolved in 100 ml of dilute alcohol (1:1) and the slight precipitate remaining after thorough agitation was filtered off. The filtrate was made slightly alkaline with 10% ammonia water and 10 g of solid lead acetate were dissolved therein with agitation. The light brown precipitate, which formed, was centrifuged off and washed with two 50 ml portions of dilute alcohol. Excess lead acetate was removed by passage of hydrogen sulfide through the solution until no more lead sulfide precipitated. The filtrate and washings resulting from removal of the lead sulfide was concentrated below 40°C. After making slightly alkaline with ammonia water, the concentrate was extracted with three 50 ml portions of chloroform. The chloroform extract of digitoxin was dried over anhydrous sodium sulfate. After filtering and washing the filter with dry chloroform, the chloroform extract was heated on a water bath to remove the chloroform and the residue was dissolved in 20ml of hot alcohol at about 60°C., and diluted with hot distilled water at 60°C to an alcohol concentration of 30%. Upon standing overnight, the digitoxin settled out as a yellowish orange, mostly amorphous solid together with some needle and rosette crystals.

The digitoxin was filtered off, and dried in a vacuum desiccator over calcium chloride and then was dissolved In 10 cc. of dry chloroform after which 15 ml of dry amyl ether was added, followed by 100 ml of petroleum ether. After standing one hour, the precipitate was filtered off, washed with petroleum ether, and dried in a vacuum desiccator until all traces of amyl ether were removed. One 1ml of alcohol for each 25 milligrams of material was added to the dried precipitate and the mixture was heated on a water-bath at 60°C until the precipitate had completely dissolved, after which hot distilled water at 60°C was added to produce an alcohol concentration of 40%. Upon standing overnight at room temperature the digitoxin came down as almost completely white crystals. Upon recrystallizing a second time from 40% alcohol, completely white crystals of digitoxin were obtained. On the basis of

the digitalis cat assay, the digitoxin was completely pure and is a prompt and powerful heart tonic in doses of 25 mg to 1 mg. The crystalline digitoxin is also substantially stable and may be relied upon by the physician to furnish a uniform degree of activity of the same kind insofar as the digitoxin is concerned.

References

Rosen H. et al.; US Patent No. 2,449,673; Sept. 21, 1948; Assigned to Wyeth Incorporated, Philadelphia, Pa., a corporation of Delaware

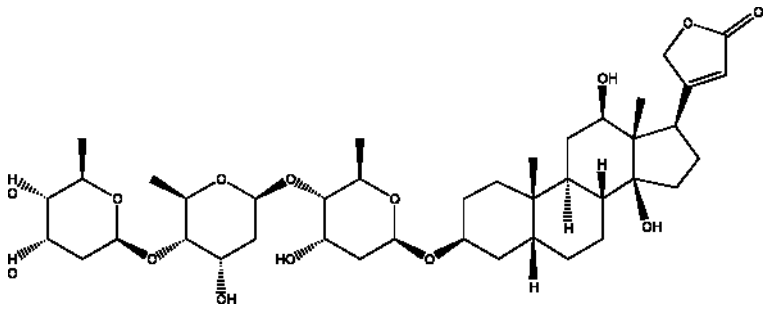
DIGOXIN

Therapeutic Function: Cardiotonic

Chemical Name: Card-20(22)-enolide, 3-((O-2,6-dideoxy-β-D-ribo-hexopyranosyl-(1-4)-O-2,6-dideoxy-β-D-ribo-hexopyranosyl-(1-4)-2,6-dideoxy-β-D-ribo-hexopyranosyl)oxy)-12,14-dihydroxy-, (3β,5β,12β)-

Common Name: Digossina; Digosin; Hydroxydigitoxin; Oxydigitoxin

Structural Formula:



Chemical Abstracts Registry No.: 20830-75-5

Trade Name	Manufacturer	Country	Year Introduced
Digoxin	Alexandria Co.	-	-
Digoxin	Medimpex	-	-
Digoxin	Glaxo Smithkline	-	-
Lanoxin	Glaxo Wellcome Co.	-	-
Lanoxin	Glaxo Smithkline	-	-
Lanoxin Digoxin	Glaxo Wellcome Co.	-	-
Lanoxin P.G Elix	Glaxo Wellcome Co.	-	-
Lanoxin PG	Glaxo Wellcome Co.	-	-
Cardioxin	Novartis	-	-

Trade Name	Manufacturer	Country	Year Introduced
Digitran-250	Macleods Pharmaceuticals Pvt. Ltd.	-	-
Digox	Zydus Cadila	-	-
Dixin	Samarth Pharma Pvt. Ltd.	-	-
Sangoxin	Sanofi Synthelabo (India) Ltd.	-	-

Raw Materials

Leaves of Digitalis lanata
Methyl ethyl ketone

Manufacturing Process

It has long been known that digitalis leaves owe their physiological activity to the presence in them of certain glucosidal constituents. A method of preparation of a well-defined crystalline glucoside is described. The new glucoside is separated in the following manner. The total glucosides of the leaf of Digitalis lanata prepared by the usual methods (e.g. that of Keller and Fromme, Lehrbuch der Pharm. Chem., Schmidt) are stirred with acetone or methyl ethyl ketone in the cold using approximately two parts of acetone or methyl ethyl ketone to one part of the glucosidal mixture. After standing the sparingly soluble glucosides (A) are separated. The filtrate is fractionally precipitated with water until no more solid separates on further addition of water. The solid (B) is separated and the filtrate is saturated with salt when a further precipitate (C) is formed. This salt precipitate is dried and extracted in the cold with methyl or ethyl alcohol and the solution diluted with water. On standing crystals of the new glucoside separate. The glucoside is freed from more soluble glucosides by boiling with small quantities of chloroform, acetone or methylethyl ketone in which it is sparingly soluble and then crystallized by concentrating a solution in hot 80% methyl or ethyl alcohol. The glucoside can also be crystallized by the addition of water or ether to a solution of the substance in pyridine. Further quantities of the glucoside may be obtained by extracting the aqueous filtrate from salt precipitate (C) with cold chloroform. The chloroform extract after evaporation is stirred with acetone or methyl ethyl ketone and the sparingly soluble portion is further purified by boiling with small quantities of chloroform and the sparingly soluble portion crystallized as above described. The glucoside is also present in precipitate, which separates from the acetone or methyl ethyl ketone and in the fraction (B) precipitated by water from the acetone or methyl ethyl ketone solution. It may be separated from these solutions by fractional crystallization from hot dilute alcohol, followed by boiling the less soluble fractions with acetone, methyl ethyl ketone, or chloroform and crystallization of the sparingly soluble portions above described. The new glucoside digoxin crystallizes in stout plates; MP: at about 265°C. (decomp.); $\alpha_D^{25} = +17.9°$.

References

Smith S.; G.B. Patent No. 337,091; Aug. 8, 1929; Assigned to Wellcome Foundation Limited (a British Company) of 67 Holborn Viaduct, London, E.C.1, England

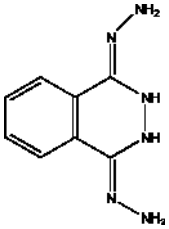
DIHYDRALAZINE

Therapeutic Function: Antihypertensive

Chemical Name: Phthalazine, 1,4-dihydrazino-

Common Name: Dihydralazine; Dihydrallazine

Structural Formula:



Chemical Abstracts Registry No.: 484-23-1

Trade Name	Manufacturer	Country	Year Introduced
Nepresol	Novartis	-	-
Dihydralazine	Yick-Vic Chemicals and Pharmaceuticals (HK) Ltd.	-	-
Hipopresol	Terapia S.A.	-	-
Ileton	Pliva	-	-

Raw Materials

Hydrazine hydrate
Phthalic acid dinitrile

Manufacturing Process

115 parts of hydrazine hydrate in 80 parts 50% acetic acid were added to 128 parts of phthalic acid dinitrile in 250 parts dioxane. The mixture was heated at the temperature 95°C for 3 hours with stirring. After 20 minutes the crystallization and discharging of NH_3 began. The orange needles were filtered off after cooling. The product was washed with dioxane and ethanol and recrystallized from 3000 parts of water to yield 110 parts colorless needles of 1,4-dihydrazino-phthalazine; MP: 191°-193°C (decomp.). The crystals were getting a little orange color by standing because of a reaction with an air oxygen.

References

Zerweck W. et al.; D.B. Patent No. 845,200; July 28, 1951; Assigned to Cassella Farbwerke Mainkur, Francfurt/M.-Fechenheim.

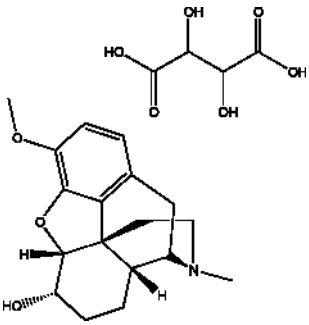
DIHYDROCODEINE TARTRATE

Therapeutic Function: Antitussive, Narcotic analgesic

Chemical Name: Morphinan-6-ol, 4,5-epoxy-3-methoxy-17-methyl-, (5α,6α)-, tartrate (1:1)

Common Name: Dihydrocodeine tartrate; Drocode; Hydrocodein tartrate

Structural Formula:



Chemical Abstracts Registry No.: 5965-13-9; 125-28-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Bicodein	Uquifa	-	-
Dolcontin	Remek	-	-
Hydol	Napp	-	-

Raw Materials

Codein
Platinum
Hydrogen
Tartaric acid

Manufacturing Process

The codein was reduced by hydrogen in the presence catalyst Pt (or Pd, or Ni) and 7,8-dihydrocodein was obtained.

To the 7,8-dihydrocodein tartaric acid was added and mixed, in the result 7,8-dihydrocodein bitartrate was obtained.

References

Kleemann A., Engel J.; Pharmazeutische Wirkstoffe, GeorgThieme Verlag Stuttgart. New York, 1982

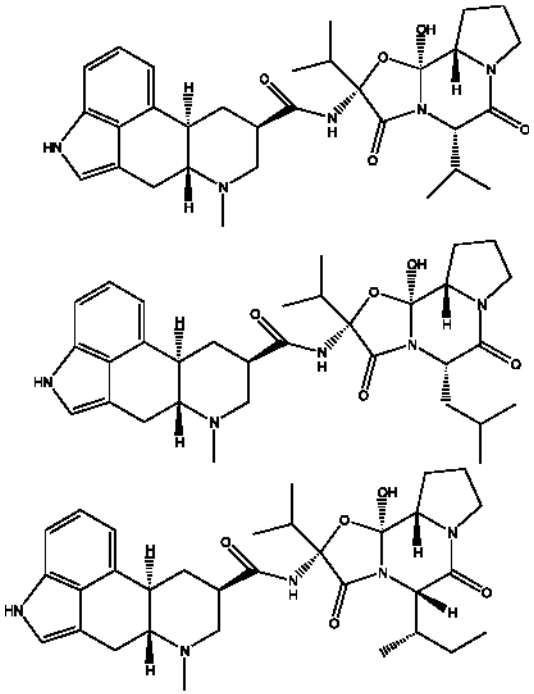
DIHYDROERGOTOXINE

Therapeutic Function: Vasodilator

Chemical Name: Ergotoxine, dihydro-

Common Name: Dihydroergotoxine; Dihydrogenated ergot alkaloids

Structural Formula:



Chemical Abstracts Registry No.: 11032-41-0

Trade Name	Manufacturer	Country	Year Introduced
Redergin	Lek	-	-
DH-Ergotoxin	Galena	-	-
Hydergine	Novartis	-	-
Huperloid	Rafarm AE	-	-
Resinat	Proel	-	-
Hidrosan	COUP OE	-	-
Diertina	Pharmanel A.E.	-	-

Raw Materials

Ergotoxine
Palladium on barium sulfate

Manufacturing Process

Dihydrotoxine is a mixture of three hydrogenated alkaloides of ergot spur. (Claviceps purpurea). 10 g ergotoxine (the mixture of ergocornine, ergocristine, ergocryptine 1:1:1) in 200 ml dioxane and 20 g $Pd/BaSO_4$ were stirred at a H_2 pressure 10 atmospheres at 80°C for 5 hours. The catalyst was filtered off, a filtrate was distilled to dryness in vacuum. The residue was in chloroform dissolved and shook with aluminum oxide. The Al_2O_3 was filtered off, the filtrate was crystallized after adding of hot benzene and cooling. Yield 6-8 g dihydroergotoxine. It crystallized with 1 mol of benzene. MP: 185°C.

References

Stoll A. et al.; D.B. Patent No. 883,153; July 8, 1949; Assigned to Sandoz A.G., Basel (Schweiz).

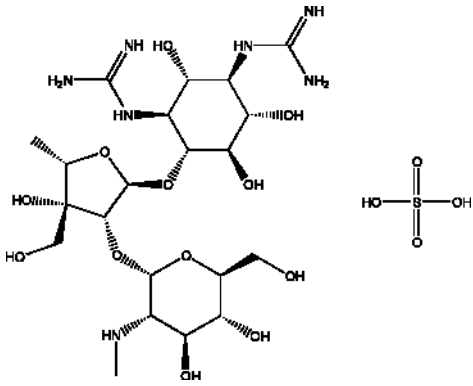
DIHYDROSTREPTOMYCIN SULFATE

Therapeutic Function: Antibiotic

Chemical Name: O-2-Deoxy-2-(methylamino)-α-L-glucopyranosyl-(1-->2)-O-5-deoxy-3-C-(hydroxymethyl)-α-L-lyxofuranosyl-(1-->4)-N,N'-bis(aminoiminomethyl)-D-streptamine sulfate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 5490-27-7; 128-46-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Dihydrostrepto	MSD	US	1948
Abiocine	Lepetit	France	-
Didromycin	Specia	France	-
Didrothenat	Gruenenthal	W. Germany	-
Diestreptopab	Martin Santos	Spain	-
Dihydro-Cidan Sulfato	Cidan	Spain	-
Dihydromycine	Specia	France	-
Dihydrostreptofor	Kwizda	Austria	-
Dihydrostreptomycin-Rafa	Rafa	Israel	-
Entera-Strept	Heyl	W. Germany	-
Estreptoluy	Miluy	Spain	-
Guanimycin	Allen and Hanburys	UK	-
Sanestrepto	Santos	Spain	-
Solvo-Strept	Heyl	W. Germany	-
Streptoral	Taro	Israel	-
Vibriomycin	Evans Medical	Australia	-

Raw Materials

Streptomycin sulfate
Hydrogen

Manufacturing Process

Dihydrostreptomycin sulfate may be prepared from streptomycin sulfate by catalytic hydrogenation (Merck, Pfizer, Cyanamid), electrolytic reduction (Schenley, Olin Mathieson), or by sodium borohydride reduction (Bristol), or by isolation from a fermentation process (Takeda).

References

Merck Index 3161
Kleeman and Engel p. 309
I.N. p. 328
Peck, R.L.; US Patent 2,498,574; February 21, 1950; assigned to Merck and Co., Inc.
Carboni, R.A. and Regna, P.P.; US Patent 2,522,858; September 19, 1950; assigned to Chas. Pfizer and Co., Inc.
Levy, G.B.; US Patent 2,663,685; December 22, 1953; assigned to Schenley Industries, Inc.
Dolliver, M.A. and Semenoff, S.; US Patent 2,717,236; September 6, 1955; assigned to Olin Mathieson Chemical Corp.
Sokol, H. and Popino, R.P.; US Patent 2,784,181; March 5, 1957; assigned to American Cyanamid Co.
Kaplan, M.A.; US Patent 2,790,792; April 30, 1957; assigned to Bristol Laboratories, Inc.

Tatsuoka, S., Kusaka, T., Miyake, A., Inoue, M., Shiraishi, Y., Iwasaki, H. and Imanishi, M.; US Patent 2,950,277; August 23, 1960; assigned to Takeda Pharmaceutical Industries, Ltd.

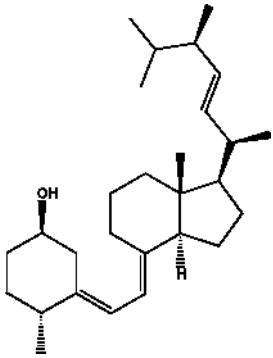
DIHYDROTACHYSTEROL

Therapeutic Function: Blood calcium regulator

Chemical Name: 9,10-Secoergosta-5,7,22-trien-3β-ol

Common Name: Dichystrolum

Structural Formula:



Chemical Abstracts Registry No.: 67-96-9

Trade Name	Manufacturer	Country	Year Introduced
Hytakerol	Winthrop	US	1950
Calcamine	Sandoz	France	1949
D.H.T.	Roxane	US	1983
A.T. 10	Bayer	W. Germany	-
Atecen	Merck	W. Germany	-
Dygratyl	Ferrosan	Denmark	-
Dihydral	Duphar	Belgium	-
Tachyrol	Duphar	Belgium	-
Tachystin	Ankerwerk	E. Germany	-

Raw Materials

Tachysterol
Hydrogen

Manufacturing Process

The process of isolating chemically uniform crystalline dihydrotachysterol comprises subjecting the solution of the crude hydrogenation product of tachysterol in benzine to chromatographic adsorption by means of active aluminum oxide while collecting the components having a minor tendency of being adsorbed, subjecting the said components to a repeated chromatographic adsorption and converting the components having a minor tendency of being adsorbed into its ester by treatment with acetic anhydride in pyridine solution, isolating the ester formed from the reaction mixture, subjecting its solution in benzine to chromatographic adsorption while collecting the components having a minor tendency of being adsorbed, recrystallizing these components, saponifying the crystalline ester and recrystallizing the dihydrotachysterol obtained.

References

Merck Index 3163
Kleeman and Engel p. 309
PDR p. 1570
I.N.p. 329
REM p. 978
von Werder, F.; US Patent 2,228,491; January 14, 1941; assigned to Winthrop Chemical Company, Inc.

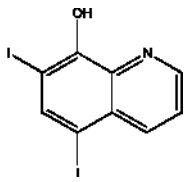
DIIODOHYDROXYQUINOLINE

Therapeutic Function: Antibacterial

Chemical Name: 8-Quinolinol, 5,7-diiodo-

Common Name: Diiodohydroxyquin; Diiodohydroxyquinoleine; Diiodohydroxyquinoline; Diiodoossichinolina; Diiodoxyquinoleine; Dijodoxichinolinum; Iodoquinol

Structural Formula:



Chemical Abstracts Registry No.: 83-73-8

Trade Name	Manufacturer	Country	Year Introduced
Diiodohydroxyquinoline	Adco Co.	-	-
Floraquin	Pfizer Australia Pty Ltd.	-	-

Trade Name	Manufacturer	Country	Year Introduced
Diiodohydroxyquinoline	Fybros Pharmaceuticals Limited	-	-
Diiodohydroxyquinoline	Bristhar Laboratorios, C.A.	-	-
Ioquin	Abbott	-	-
Direxiode	Delalande	-	-

Raw Materials

8-Oxychinoline
Potassium iodide
Potassium iodate
Salicylic acid

Manufacturing Process

5,7-Diiodo-8-quinolinol widely used as an intestinal antiseptic, especially as an antiamebic agent. It is also used topically in other infections and may cause CNS and eye damage. It is known by very many similar trade names worldwide.

0.01 mol 8-oxychinoline and 0.01 mol salicylic acid were dissolved in 500 ml of water and then 0.05 mol potassium iodide was added. The mixture was heated to temperature 90°-100°C. After that 0.01 mol of KIO_3 by little tiles was added. The next tile was added after a disappearence of discharging iodine. Then 10 ml 2 N HCl was added. The solid product was fallen, filtered off, washed with hot water and in 0.25 N NaOH dissolved. The solution was filtered and the clear filtrate precipitated with a very little excess of HCl. The product 5,7-diiodo-8-quinolinol was filtered, washed with hot water and dried. MP: 200°-250°C (with decomposition).

References

Passek F.; D.P. Patent No. 411,050; March, 24, 1925

DIISOPROMINE HYDROCHLORIDE

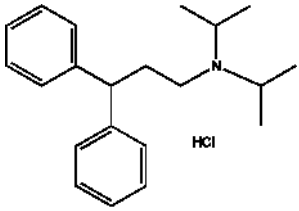
Therapeutic Function: Spasmolytic, Choleretic

Chemical Name: N,N-Diisopropyl-3,3-diphenylpropylamine hydrochloride

Common Name: Diisopromine hydrochloride; Disoprominii chloridum

Chemical Abstracts Registry No.: 24358-65-4; 5966-41-6 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Agofell	Janssen-Cilag	-	-
Bilagol	Janssen	-	-
Bilagol	Schazoo	-	-
Norbilin	Phoenix	-	-

Raw Materials

4-Diisopropylamino-2,2-diphenyl-butyronitrile
Sodium amide

Manufacturing Process

A vigorously stirred suspension of 0.2 to 1 mole of sodium amide in 200 ml of xylene, in which 0.1 moles of 4-diisopropylamino-2,2-diphenyl-butyronitrile were dissolved, was boiled for about twelve hours. After this the excess of sodium amide was decomposed with water and the xylene layer was separated, washed with water and extracted with dilute hydrochloric acid. This acidic extract was made strongly alkaline with a concentrated aqueous sodium hydroxide solution and the separated base was extracted with ether. After drying, the ether evaporated and the 1,1-diphenyl-3-diisopropylamino-propane was distilled in vacuum. The oil obtained can be dissolved in ether and after introduction of hydrochloric acid gas the hydrochloric acid addition salt precipitates. It shows a melting point of 171°C.

References

Janssen C.; G.B. Patent No. 808,158; Jan. 28, 1958

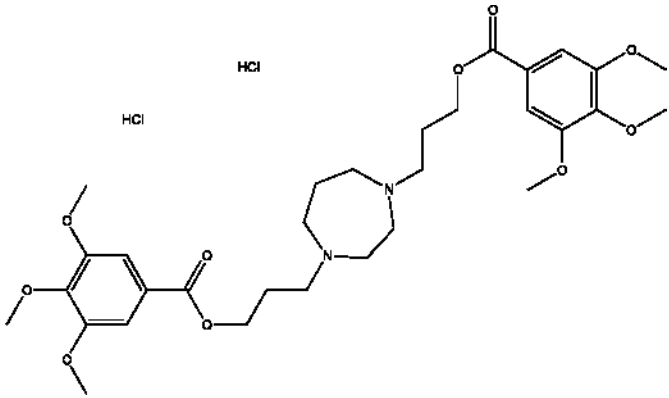
DILAZEP HYDROCHLORIDE

Therapeutic Function: Coronary vasodilator

Chemical Name: 3,4,5-Trimethoxybenzoic acid diester with tetrahydro-1H-1,4-diazepine-1,4(5H)-dipropanol dihydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 20153-98-4; 35898-87-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Cormelian	Asta	W. Germany	1972
Cormelian	Schering	Italy	1976
Comelian	Kowa	Japan	1979

Raw Materials

Bis(3-Hydroxypropyl)ethylene diamine
1,3-Chlorobromopropane
Triethylamine
3,4,5-Trimethoxybenzoic acid chloride

Manufacturing Process

528.8 grams of bis-(3-hydroxypropyl)-ethylene diamine [K. Schlgl and R. Schlgl, Monatschefte der Chemie 95 (1964) page 935] are dissolved in a mixture of 1,500 cc of anhydrous ethyl alcohol and 1,250 grams of triethylamine. 520 grams of 1,3-chlorobromopropane are added thereto dropwise over a period of about 3 hours while stirring and heating the reaction mixture in an oil bath of 50°C. After completion of the addition, the oil bath is heated to 60°C for 20 minutes while stirring of the reaction mixture is continued. With increasing reaction time, triethylamine hydrochloride is precipitated. After completion of the reaction, the mixture is allowed to cool to room temperature.

Triethylamine hydrochloride is separated by filtration and the filter cake is washed with 100 cc of anhydrous ethyl alcohol. The alcohol and the excess of triethylamine is distilled off in a vacuum of a water pump. The residue represents a light-yellowish brown viscous oil which is extracted 3 times with 500 cc of anhydrous benzene each time with stirring at 40° to 60°C. The benzene is distilled off on a water bath at 60°C. Thus, an oil is obtained which solidifies to a hard mass after some hours. This mass is crushed and dried

over P_2O_5 in an exsiccator. The compound represents N,N'-bis-(3-hydroxypropyl)homopiperazine. Yield: 128.5 grams. FP: 46°-47°C; $BP_{0.02mm}$: 141°-142°C.

21.6 grams of N,N'-bis-(3-hydroxypropyl)homopiperazine obtained as described and 63.8 grams of 3,4,5-trimethoxy benzoic acid chloride are dissolved in 600 parts by volume of anhydrous chloroform. The solution is heated to boiling for 5 hours. Thereafter, chloroform is distilled off in a vacuum. The residue is dissolved in water and the aqueous solution is washed with ether. Thereafter, the aqueous phase is rendered alkaline by the addition of soda lye and the separated oil base is extracted with ether. The ethereal solution is dried over Na_2SO_4. Ether is separated in a vacuum and the highly viscous residue is dissolved in 150 parts by volume of ethyl alcohol. The calculated equivalent amount of ethereal HCl is added thereto.

The soon crystallizing dihydrochloride is separated by filtration, dried and recrystallized from 120 parts by volume of ethanol. Thus, after drying for 3 days over P_2O_5, 40-50 grams (66-70% of the theoretical) of N,N'-bis-[(3,4,5-trimethoxy benzoloxy)propyl] homopiperazine dihydrochloride containing 1 mol of water of crystallization is obtained. This product has a melting point at 194°-198°C.

References

Merck Index 3187
Kleeman and Engel p. 312
DOT 8 (7) 255 (1972)
I.N. p. 332
Arnold, H., Pahls, K., Rebling, R., Brock, N. and Lenke, H.-D.; US Patent 3,532,685; October 6, 1970; assigned to Asta-Werke AG, Chemische Fabrik, Germany

DILTIAZEM HYDROCHLORIDE

Therapeutic Function: Coronary vasodilator

Chemical Name: cis-(+)-3-(Acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one hydrochloride

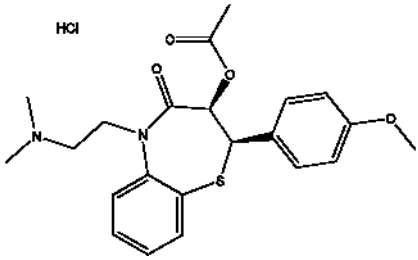
Common Name: -

Chemical Abstracts Registry No.: 33286-22-5; 42399-41-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Herbesser	TANABE SEIYAKU	Japan	1974
Tildiem	Dausse	France	1980
Dilzem	Goedecke	W. Germany	1981
Cardizem	Marion	US	1982

Trade Name	Manufacturer	Country	Year Introduced
Cardizem	Nordic	Canada	1983
Tilazem	Parke Davis	-	-

Structural Formula:



Raw Materials

β-Diethylaminoethyl chloride
2-Aminothiophenol
Acetic anhydride
Hydrogen chloride
Sodium ethoxide
4-Methoxybenzaldehyde
Sodium bicarbonate
Ethyl chloroacetate

Manufacturing Process

β-Diethylaminoethyl chloride is condensed with 2-(4-methoxyphenyl)-3-hydroxy-2,3-dihydro-1,5-benzothiazepin-4(5H)-one in a first step. Then a mixture of 1.5 grams of 2-(4-methoxyphenyl)-3-hydroxy-5-(β-dimethylaminoethyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one and 20 ml of acetic anhydride was heated on a water bath for 5 hours. The reaction mixture was evaporated under reduced pressure to remove acetic anhydride and the concentrated product was poured into ice water. The resulting mixture was made alkaline with sodium bicarbonate and extracted with chloroform. The chloroform layer was dried and evaporated to remove the solvent. The residue was dissolved in acetone, and an ethanol solution containing hydrogen chloride was added thereto producing 1.53 grams of 2-(4-methoxyphenyl)3-acetoxy-5-(β-dimethylaminoethyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one hydrochloride having a melting point from 187° to 188°C.

The starting material is made by reacting 4-methoxybenzaldehyde with ethyl chloroacetate; that product with sodium ethoxide; and that product with 2-aminothiophenol.

References

Merck index 3189
Kleeman and Engel p. 312
PDR p. 1074
OCDS Vol. 3 p. 198 (1984)
DOT 10 (4) 127 (1974)
I.N. p. 333

REM p. 862
Kugita, H., Inoue, H., Ikezeki, M. and Takeo, S.; US Patent 3,562,257; February 9, 1971; assigned to Tanabe Seiyaku Co., Ltd., Japan

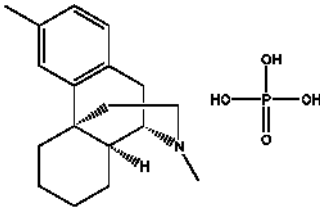
DIMEMORFAN PHOSPHATE

Therapeutic Function: Antitussive

Chemical Name: Morphinan, 3,17-dimethyl-, (9α,13α,14α)-, phosphate

Common Name: Dimemorfan phosphate

Structural Formula:



Chemical Abstracts Registry No.: 36309-01-0 (Base); 36304-84-4

Trade Name	Manufacturer	Country	Year Introduced
Astomin	Yamanouchi Pharmaceutical Co., Ltd.	-	-
Dimemorfan phosphate	Standard Chem. and Pharm. Co., Ltd.	-	-
Dastosin	Yamanouchi Europe	-	-
Tusben	Benedetti SpA	-	-

Raw Materials

Magnesium
p-Methylbenzyl chloride
2-Methyl-5,6,7,8-tetrahydroisoquinoline bromide
Sodium borohydride

Manufacturing Process

Preparation of 1-p-methylbenzyl-1,2,5,6,7,8-hexahydroisoquinoline:

a) To a suspension of 2.24 g of a metallic magnesium in 36 ml of an 1:1 mixture of tetrahydrofuran and ether was added dropwise a solution of 13.5 g

of p-methylbenzyl chloride in 36 ml of an 1:1 mixture of tetrahydrofuran and ether over a period of about 30 min and then the resultant mixture was refluxed under heating for 30 min. The solution thus obtained was added dropwise to a suspension of 17.5 g of 2-methyl-5,6,7,8-tetrahydroisoquinoline bromide in 90 ml of an 1:1 mixture of tetrahydrofuran and ether cooled to 0-5°C over a period of about 25 min. After stirring the mixture for 2 hours at temperatures of from 0-5°C, 100 ml of cooled ether and 1.7 N ammonia were added to the reaction product liquid and after shaking sufficiently the system, the ether layer thus formed was recovered. The product in the aqueous layer was further extracted with 50 ml of ether. The ether extract was combined with the ether layer recovered above and then the product in the mixture was extracted 4-times with 30 ml each of 1 N hydrochloric acid cooled. To the hydrochloric acid extract was added 100 ml of cooled 1.7 N ammonia, and the oily material formed was extracted thrice with 80 ml each of ether. After drying the ether extract over anhydrous potassium carbonate, ether was distilled away to provide 15.4 g of oily 1-p-methylbenzyl-1,2,5,6,7,8-hexahydroisoquinoline.

b) In a mixture of 300 ml of methanol and 30 ml of water were dissolved 15.4 g of oily 1-p-methylbenzyl-2-methyl-1,2,5,6,7,8-hexahydroisoquinoline and while stirring the mixture, 2 g of sodium borohydride was added little by little to the mixture at room temperature over a period of about 15 min. After stirring the light yellow solution obtained overnight at room temperature, the solvent was distilled away under a reduced pressure. The residue was mixed with 50 ml of water and 150 ml of ether and after sufficiently shaking the mixture, the ether layer formed was separated. The aqueous layer thus separated was adjusted to basicity by the addition of a small amount of 1.7 N ammonia and then the product in the layer was extracted with 100 ml of ether. The ether layer separated above was combined with the ether extract and after washing the mixture with 1.7 N ammonia and water, the mixture was dried over anhydrous potassium carbonate and then ether was distilled away to provide 13.8 g of an orange oily material. By subjecting the product to a distillation under a reduced pressure, oily D-1-p-methylbenzyl-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline was obtained. Boiling point 133-136°C/0.35 mm Hg.

Preparation of D-3-methyl-N-methylmorphinane:

To 130 ml of 85% phosphoric acid was added 26.5 g of D-1-p-methylbenzyl-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline and the mixture was heated to 130-140°C for 72 hours. After the reaction was over, the reaction product liquid was dispersed in ice-water and the solution was made strongly alkaline by the addition of about 300 ml of concentrated aqueous ammonia, whereby an oily material and a crystal were formed. The aqueous solution was mixed with 500 ml of water and 500 ml of ether followed by sufficient shaking; thereafter, the aqueous layer and the ether layer were separated. The aqueous layer was extracted with 500 ml of ether and the extract was combined with the ether layer separated above. Black resinous material floating in the mixture was filtered away. After washing with water the ether solution thus obtained and drying over anhydrous potassium carbonate, 14 g of a black-orange oily material was obtained. When the oily material was immediately distilled under a reduced pressure, 11 g of a faint yellow transparent oily material showing a boiling point of 130-136°C/ 0.3 mm Hg was obtained. The product was crystallized immediately after distillation. The

crystals were recrystallized from 12 ml of acetone, recovered by filtration, and washed with 7 ml of acetone to provide 7.3 g of the white prism crystal of D-3-methyl-N-methylmorphinane. Furthermore, from the filtrate in the recrystallization were recovered the same crystals. Melting point 90-93°C, $[\alpha]_D^{22}$ = +51.5° (c=1, methanol).

References

Merck Index, Monograph number: 3251, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Murakami M. et al.; US Patent No. 3,786,054; Jan. 15, 1974; Assigned to Yamanouchi Pharmaceutical Co., Ltd.

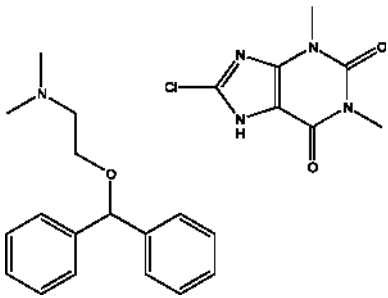
DIMENHYDRINATE

Therapeutic Function: Antinauseant

Chemical Name: 8-Chloro-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione compound with 2-(diphenylmethoxy)-N,N'-dimethylethanamine (1:1)

Common Name: Chloranautine; O-Benzhydryldimethylaminoethanol 8-chlorotheophyllinate

Structural Formula:



Chemical Abstracts Registry No.: 523-87-5

Trade Name	Manufacturer	Country	Year Introduced
Dramamine	Searle	US	1949
Dramamine	Searle	France	1957
Dramocen	Central	US	1977
Dimate	Totag	US	1980
Dramaban	Mallard	US	1983
Amalmare	Saita	Italy	-
Amosyt	Leo	Sweden	-
Andrumin	Ethnor	Australia	-

Trade Name	Manufacturer	Country	Year Introduced
Antemin	Streuli	Switz.	-
Anti-Em	Adeka	Turkey	-
Antivomit	Farmos	Finland	-
Aviomarine	Polfa	Poland	-
Betadorm A	Woelm Pharma	W. Germany	-
Bontourist	Katwijk	Netherlands	-
Calm-X	Republic	US	-
Dimenest	Fellows-Testagar	US	-
Dipendrate	Kenyon	US	-
Dramarr	Quimia	Spain	-
Dramavir	Vir	Spain	-
Drarnavol	Barlow Cote	Canada	-
Dromyl	A.F.Z.	Norway	-
Dymenol	Dymond	Canada	-
Emedyl	Montavit	Austria	-
Epha	Woelm	W. Germany	-
Gravol	Horner	Canada	-
Gravol	Carter Wallace	UK	-
Hydrate	Hyrex	US	-
Lomarin	Geymonat	Italy	-
Mareosan	Bescansa	Spain	-
Marolin	Andreu	Spain	-
Motion Aid	Vangard	US	-
Nauseal	Eri	Canada	-
Nauseatol	Sabex	Canada	-
Neptusan	Benzon	Denmark	-
Novomina	Robisch	W. Germany	-
Novodimenate	Novopharm	Canada	-
Paranausine	Couvreur	Belgium	-
Pastillas Azules	Liano	Spain	-
Reidamine	Reid-Provident	US	-
Removine	Kerkhoff-Unicura	Netherlands	-
Solbrine	Solac	France	-
Stada-Reisedragees	Stada	W. Germany	-
Travamin	Teva	Israel	-
Travamine	I.C.N.	Canada	-
Travel-Gum	Chemofux	Austria	-
Travin	Rondex	US	-
Trawell	Chemofux	Austria	-
Troversin	Santuron	W. Germany	-
Valontan	Recordati	Italy	-
Vertirosan	Sigmapharm	Austria	-
Vomex	Endopharm	W. Germany	-
Voyal	Kwizda	Austria	-
Xamamina	Zambeletti	Italy	-

Raw Materials

8-Chlorotheophylline
β-Dimethylaminoethylbenzhydryl ether

Manufacturing Process

58.8 grams of 8-chlorotheophylline and 70 grams of β-dimethylaminoethyl benzohydryl ether are dissolved in 150 cc of hot methanol. Then 5 grams of activated charcoal are added and the mixture is boiled for an hour. It is filtered hot and the filtrate cooled. The crystalline precipitate of β-dimethylaminoethyl benzohydryl ether 8-chlorotheophyllinate is collected on a filter, washed with ether and dried. It melts at 96-99°C. It is dissolved in boiling ethyl acetate, filtered hot to remove any insoluble material, and then chilled. The salt so obtained melts at 102.5°-104°C after filtration, washing with ether and drying.

References

Merck Index 3195
Kleeman and Engel p. 314
PDR pp. 1669,1989
I.N. p. 334
REM p. 808
Cusic, J.W.; US Patent 2,499,058; February 28, 1950; assigned to G.D. Searle and Co.
Cusic, J.W.; US Patent 2,534,813; December 19, 1950; assigned to G.D. Searle and Co.

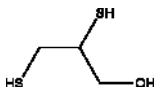
DIMERCAPROL

Therapeutic Function: Antidote (heavy metal)

Chemical Name: 2,3-Dimercapto-1-propanol

Common Name: 1,2-Dithioglycerol

Structural Formula:



Chemical Abstracts Registry No.: 59-52-9

Trade Name	Manufacturer	Country	Year Introduced
Bal	Hynson/Westcott	US	1944
Bal	Delalande	France	1950

Trade Name	Manufacturer	Country	Year Introduced
Antoxol	Ferrosan	Denmark	-
Sulfactin	Homburg	W. Germany	-

Raw Materials

Glycerol 1,2-dibromohydrin
Sodium sulfide
Hydrogen

Manufacturing Process

1,2-Dithioglycerol is prepared in the following manner: 1,537 parts of sodium monosulfide nonahydrate and 411 parts of powdered sulfur are dissolved with stirring in 1,345 parts of water. Magnesium hydroxide is precipitated in the stirred sodium trisulfide solution by adding successively 97 parts of sodium hydroxide dissolved in 180 parts of water and then slowly 246 parts of magnesium chloride hexahydrate dissolved in 180 parts of water. The magnesium hydroxide serves as a dispersing agent to maintain the resulting sulfide polymer in finely divided condition. The mixture is heated and stirred at 50°C while 1,329 parts of glycerol 1,2-dibromohydrin is added continuously during a period of 1.5 hours. The reaction is exothermic and external cooling is employed to maintain the temperature within the range of 50°-55°C. After the addition of the dibromohydrin is complete, the mixture is stirred and heated at 75°C for 6 hours.

The finely divided yellow sulfide polymer formed is then allowed to settle and the reaction liquor is separated by decantation. The product is washed by decantation five times with water and finally filtered by suction. The moist cake of polymer is then air dried. The yield is 988 parts including approximately 75 parts of magnesium hydroxide.

Thirty-two hundred fifty parts of the hydroxypropylene trisulfide containing magnesium hydroxide is charged into a steel autoclave equipped with a mechanical agitator. There is also charged into the autoclave 2,550 parts of dry dioxane and 350 parts of cobalt trisulfide catalyst pasted with 700 parts of dioxane. Hydrogen is charged into the autoclave to a pressure of 1,000 lb/in^2 and the autoclave is heated to a temperature of 125°C during 1.5 hours, agitation being employed during this operation. When the temperature reaches about 110°C the pressure commences to drop and is kept between the limits of 1,000 and 1,300 lb/in^2 by the addition of hydrogen. When the temperature reaches 125°C the pressure is raised to 1,700 lb/in^2 with hydrogen. The rate of hydrogenation increases as the temperature rises and the process is about complete when a temperature of 125°C is reached.

After the hydrogen absorption ceases, the autoclave is cooled, vented, and the reaction mixture is filtered to separate the catalyst. The filtrate is then heated on a steam bath at 60-80 mm pressure to remove the dioxane. The less volatile residue consists of 1,933 parts of crude dithioglycerol, a viscous oil.

1,2-Dithioglycerol is isolated from the oil by distillation from an oil heated pot through a short still. The distillation is carried out at a pressure of less than 1

mm and at a bath temperature of 120°-175°C, the dithioglycerol distilling over at a head temperature of 60°-65°C/0.2 mm or 75°-80°C/0.8 mm. Starting from 550 parts of crude dithioglycerol, 340 parts of distillate is obtained which contains 53% of mercapto sulfur and is nearly pure 1,2-dithioglycerol. The overall yield of dithioglycerol from the glycerol dibromohydrin is 48% of theoretical.

References

Merck Index 3198
Kleeman and Engel p. 315
PDR p. 948
I.N. p. 335
REM p. 1224
Peppel, W.J. and Signaigo, F.K.; US Patent 2,402,665; June 25, 1946; assigned to E.I. du Pont de Nemours and Company

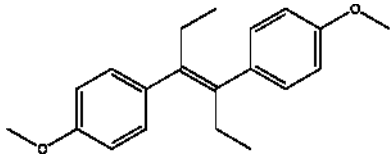
DIMESTROL

Therapeutic Function: Estrogen

Chemical Name: (E)-4,4'-(1,2-Diethylethylene)dianisole

Common Name: Diaethylstilboestroldimethylaether; Dianisylhexene; Diethylstilbestrol dimethyl ether; Dimethoxydiethylstilbene Stilboestroldimethylaether

Structural Formula:



Chemical Abstracts Registry No.: 130-79-0

Trade Name	Manufacturer	Country	Year Introduced
Dimestrol	Yick-Vic Chemicals and Pharmaceuticals (HK) Ltd.	-	-
Dimestrol	Shanghai Lansheng Corporation	-	-

Raw Materials

1-(1-Chlorobutyl)-4-methoxybenzene
1-(Methoxyphenyl)-propan-1-one
Potassium hydroxide
Magnesium
Iodine

Manufacturing Process

20 g of 1-(1-chlorobutyl)-4-methoxybenzene is dissolved in 50 ml of ether which had been dried over sodium. Separately, 2.8 g of magnesium turnings are covered with 20 ml of ether. 0.2 g of iodine, as a catalyst, is added and the solution of 1-(1-chlorobutyl)-4-methoxybenzene is added at such a rate as to keep the ether refluxing gently. If there action dopes not start immediately after the addition of a few drops of the halide, the solution may be heated cautiously in order to start the reaction. The mixture is then refluxed for another 0.5 hour and then allowed to cool down. During the whole reaction a current of hydrogen or nitrogen is passed through the apparatus. The resulting grignard reagent is filtered, cooled to -10°C and added slowly to a solution of 18 g of 1-(methoxyphenyl)-propan-1-one in 20 ml benzene to which 0.2 g of $MnCl_2$. The grignard reagent is added so slowly that the temperature is kept below 0°C. After 2 hours, the temperature is raised to room temperature and the solvent distilled off in vacuo. The residue is heated to 170°C at a pressure of 0.4 mm Hg. MgCl(OH) is split off and the product distils over. This compound is dealkylated by heating it for 20 hours with a solution of KOH in glycerin at 190°C in an atmosphere of nitrogen to obtain α,α-diethyl-4,4'-dimethoxystilbene.

References

Merck Index, Monograph number: 3257, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
GB Patent No. 584,253; Dec. 26, 1941; Assigned to Burton T. Bush, INC., USA, New Jersey

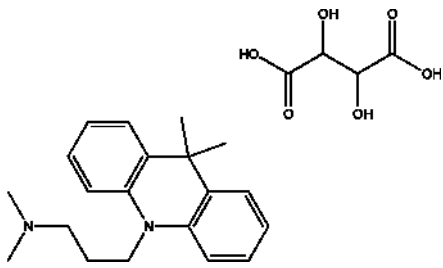
DIMETACRINE TARTRATE

Therapeutic Function: Antidepressant

Chemical Name: N,N,9,9-Tetramethyl-10(9H)acridinepropanamine tartrate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 4757-55-5; 3759-07-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Isotonil	Siegfried	W. Germany	1967
Isotonil	Nippon Chemiphar	Japan	1976
Isotonil	Triosol	Belgium	-
Linostil	Siegfried	Switz.	-

Raw Materials

5,5-Dimethylacridan
Sodium amide
1-Chloro-3-dimethylaminopropane
Tartaric acid, D-

Manufacturing Process

A mixture of 10.0 g of 5.5-dimethylacridan, 2.0 g of pulverized sodium amide and 6.5 g of 1-chloro-3-dimethylaminopropane in 50 ml of xylene is heated at reflux with stirring for one hour. To the cooled reaction mixture is added one volume of water. The organic layer is separated and extracted several times with diluted lactic acid. The acidic extracts are combined, washed with ether and neutralized by alkali. The crude 10-(3'-dimethylaminopropyl)-5,5-dimethylacridan is isolated by ether extraction and purified by distillation in a high vacuum. The yield is 6.4 g BP 170°-180°C/0.005mm. n_D^{29} = 1.5990.

43 g of the base I are dissolved in 229 ml of 1 N aqueous d-tartaric acid and the clear solution so obtained is evaporated to dryness under reduced pressure. The residue is dissolved in 150 ml of 90% ethanol which solution after cooling gives the tartaric acid salt of I in white needles. The salt contains 1 mol of tartaric acid per 1 mol of the base. MP 155°-156°C. Easily soluble in cold water.

References

Merck Index 3201
Kleeman and Engel p. 316
OCDS Vol. 1 p. 397 (1977)
DOT 4 (4) 150 (1968)
I.N. p. 335
British Patent 933,875; August 14, 1963; assigned to Kefalas S/A Haring, M., Molnar, I. and Wagner-Jauregg, T.; US Patent 3,284,454; November 8, 1966; assigned to Siegfried AG (Switzerland)

DIMETHICONE

Therapeutic Function: Antiflatulent

Chemical Name: Poly(oxy(dimethylsilylene)), alpha-(trimethylsilyl)-omega-methyl-

Common Name: Simethicone

Structural Formula: Dimethylpolysiloxane

Chemical Abstracts Registry No.: 8050-81-5

Trade Name	Manufacturer	Country	Year Introduced
Silicote	Amer. Crit. Care	US	1953
Aeropax	Green Cross	Japan	-
Bicolun	Warner	W. Germany	-
Ceolat	Kali-Chemie	W. Germany	-
Endo-Paractol	Homburg	W. Germany	-
Ganatone	Hokuriku	Japan	-
Gasace	Kanto	Japan	-
Gascon	Kissei Pharmaceutical Co., Ltd.	Japan	-
Gasless	Hishiyama	Japan	-
Gaspanon	Kotani	Japan	-
Gasteel	Fuso	Japan	-
Gaszeron	Nichiiko	Japan	-
Gersmin	Kowa	Japan	-
Harop	Toyo	Japan	-
Kestomatine	Lircal	Italy	-
Lefax	Ascher	W. Germany	-
Margarte	Mohan	Japan	-
Mylicon	Parke Davis	Italy	-
Mylicon	Stuart	US	-
Pleiazim	Guidotti	Italy	-
Polisilon	Midy	Italy	-
Polysilo	Toa	Japan	-
Silian	Lafare	Italy	-
Silies	Nippon Shoji	Japan	-
Silicogamma	I.B.P.	Italy	-
Sili-Met-San S	Nippon Shoji	Japan	-
Spalilin	Maruishi	Japan	-
Trimex	Winthrop	Italy	-
Unicare	United	US	-

Raw Materials

Dimethyl diethoxy silane
Trimethyl ethoxy silane
Sodium hydroxide

Manufacturing Process

In a 5 liter three-necked flask, fitted with a reflux condenser, agitator and thermometer, were placed 1,393 g (9.41 mold) of redistilled $(CH_3)_2Si(OEt)_2$ and 1,110 g (9.41 mols) of $(CH_3)_3SiOEt$. To this solution was added 254 g

(14.11 mols) of water containing 7.5 g of NaOH (approximately 1 NaOH per 100 silicon atoms). This insured the formation of only straight chain polymers. The mixture was heated to 40°C and the temperature continued to rise for nearly an hour. After adding 50 cc (20% excess) more water, the mixture was refluxed for two hours and then allowed to stand overnight.

Alcohol was then distilled off, until the temperature reached 100°C. 1,706.6 g of distillate was collected. (Theory 1,430 g.) This alcohol was poured into four times its volume of water and an insoluble oil separated (457 g). The insoluble fraction was added back to the copolymer residue from the distillation and 555 cc of 20% hydrochloric acid was added. The acid mixture was refluxed for two hours, and the silicon oils were carefully washed with distilled water until neutral. The yield was 1,420 g. (Theory 1,409 g.)

References

Merck Index 8374
Kleeman and Engel p. 317
PDR p. 1826
Rem p. 774
Hyde, J.F.; US Patent 2,441,098; May 4, 1948; assigned to Corning Glass Works

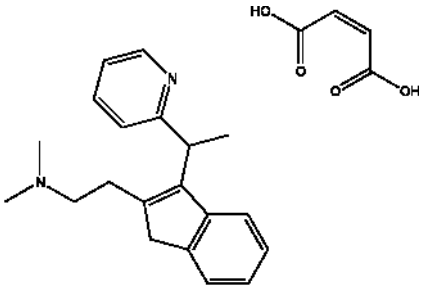
DIMETHINDENE MALEATE

Therapeutic Function: Antihistaminic

Chemical Name: N,N-Dimethyl-3-[1-(2-pyridinyl)ethyl]-1H-indene-2-ethanamine maleate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 3614-69-5; 5636-83-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Fenistil	Zyma	W. Germany	1961

Trade Name	Manufacturer	Country	Year Introduced
Forhistal	Ciba	US	1961
Fenostil	Zyma	UK	1963
Triten	Marion	US	1971
Foristal	Ciba Geigy	Japan	-

Raw Materials

2-Ethylpyridine
2-(2-Dimethylaminoethyl)-indan-1-one
Phenyl lithium
Maleic acid

Manufacturing Process

26 grams of 2-ethylpyridine is added dropwise with cooling to 20°C and in an atmosphere of nitrogen to a stirred solution of 650 ml of an 0.37 molar solution of phenyl lithium in benzene. After two hours a solution of 10 grams of 2-(2-dimethylaminoethyl)-indan-1-one in 50 ml of dry ether is added over a period of five minutes while stirring and cooling to room temperature. After standing for 24 hours the organo-lithium compounds are decomposed by the addition of 50 ml of water with external cooling. After separating the water phase from the organic solution, the latter is washed several times with 50 ml of water, and then extracted with a mixture of 40 ml of concentrated hydrochloric acid and 100 ml of water.

The acidic solution, containing the 2-(2-dimethylaminoethyl)-1-[1-(2-pyridyl)-ethyl]-indan-1-ol is heated on the steam bath for thirty minutes to effect dehydration to the desired indene derivative. The solution is cooled, made strongly basic with an aqueous solution of ammonia and then extracted with ether. The ether phase is dried over sodium sulfate, filtered, evaporated and the residue distilled.

At 15 mm pressure the excess of 2-ethylpyridine is removed, at 120°C/0.5 mm some unreacted 2-(2-dimethylaminoethyl)-indene distills and at 165°-175°C/0.5 mm the 2-(2-dimethylaminoethyl)-3-[1-(2-pyridyl)-ethyl]-indene is collected. It may be converted to an aqueous solution of the dihydrochloride by dissolving it in the appropriate amount of dilute hydrochloric acid.

To a solution of 1.0 gram of 2-(2-dimethylaminoethyl)-3[1-(2-pyridyl)-ethyl]-indene in 10 ml of ethanol is added while stirring and heating 0.4 gram of maleic acid. On cooling the 2-(2-dimethylaminoethyl)-3-[1-(2-pyridyl)-ethyl]-indene maleate crystallizes, is filtered off, washed with a small amount of ethanol and recrystallized from ethanol, MP 158°C.

References

Merck Index 3205
Kleeman and Engel p. 320
REM p. 1127
Huebner, C.F.; US Patent 2,970,149; January 31, 1961; assigned to Ciba Pharmaceutical Products, Inc.

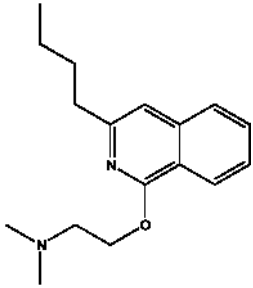
DIMETHISOQUIN

Therapeutic Function: Local anesthetic

Chemical Name: 2-[(3-Butyl-1-isoquinolinyl)oxy]-N,N-dimethylethanamine

Common Name: Quinisocaine

Structural Formula:



Chemical Abstracts Registry No.: 86-80-6; 2773-92-4 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Quotane	SKF	US	1951
Quotane	Roger Bellon	France	1981
Isochinol	Chemipharma	W. Germany	-
Pruralgin	Pharmacia	Sweden	-
Pruralgin	Pharmacia	Italy	-

Raw Materials

β-Dimethylaminoethanol
Sodium
3-Butyl-1-chloroisoquinoline

Manufacturing Process

A mixture of 10.0 grams of β-dimethylaminoethanol and 1.9 grams of sodium in 90 cc of dry xylene was heated at 95°C for 5 hours. To the resulting solution was added at 30°C, 18 grams of 3-butyl-1-chloroisoquinoline. The solution, which turned very dark, was heated at 100°-125°C for 3.5 hours. The mixture was extracted with two 100 cc portions of 2N hydrochloric acid solution. The acid solution was made strongly alkaline with 40% potassium hydroxide solution and the oil which separated was taken into ether. The ether solution was washed with two 100 cc portions of water saturated with sodium chloride, and then dried over anhydrous sodium sulfate for 3 hours. The sodium sulfate was removed by filtration and the ether by distillation. Distillation of the residual oil gave a colorless liquid, BP 155°-157°C/3mm.

References

Merck Index 3208
Kleeman and Engel p. 799
OCDS Vol. 1 p. 18 (1977)
I.N. p. 835
REM p. 1055
Ullyot, G.E.; US Patent 2,612,503; September 30, 1952; assigned to Smith, Kline and French Laboratories

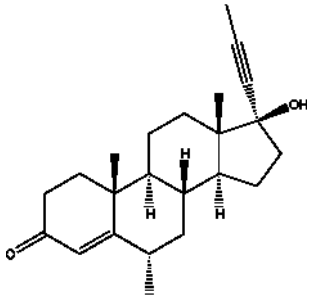
DIMETHISTERONE

Therapeutic Function: Progestin

Chemical Name: 17β-Hydroxy-6α-methyl-17-(1-propynyl)androst-4-en-3-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 79-64-1

Trade Name	Manufacturer	Country	Year Introduced
Oracon	Mead Johnson	US	1965
Secrosteron	Allen and Hanburys	UK	-
Secrosteron	Santen-Yamanouchi	Japan	-

Raw Materials

3,3-Ethylenedioxy-6α-methylandrost-4-ene-3,17-dione
Propyl Magnesium Bromide
Acetic acid

Manufacturing Process

A solution of a Grignard reagent, employing 1-propyne (8 grams) was prepared. To this reagent there was added the 3,3 ethylenedioxy derivative (4 grams) of 6-α-methylandrost-4-ene-3,17-dione in tetrahydrofuran (100 ml), and the mixture heated under reflux for 3 hours. After decomposition of the complex with aqueous ammonium chloride, the product was isolated with ether and treated with 90% acetic acid (50 ml) for 30 minutes at 100°C. The product obtained by pouring the mixture into water and extracting with ether was crystallized from aqueous methanol. 17β-Hydroxy-6α-methyl-17α-(prop-1-ynyl)androst-4-en-3-one formed plates MP 99° to 102°C.

References

Merck Index 3209
Kleeman and Engel p. 318
OCDS Vol. 1 pp. 176,187 (1977)
DOT 4 (1) 7 (1968)
I.N. p. 336
Ellis, B., Petrow, V., Stansfield, M. and Stuart-Webb, I.A.; US Patent 2,927,119; Mar. 1, 1960; assigned to The British Drug Houses Limited, England
Barton, S.P., Burn, D., Cooley, G., Ellis, B., Petrow, V. and Stuart-Webb, I.A.; US Patent 2,939,819; June 7, 1960; assigned to The British Drug Houses Limited, England

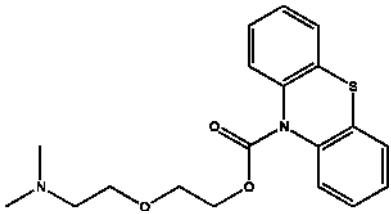
DIMETHOXANATE

Therapeutic Function: Antitussive

Chemical Name: 10H-Phenothiazine-10-carboxylic acid 2-[2-(dimethylamino) ethoxy]ethyl ester

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 477-93-0; 518-63-8 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Cothera	Ayerst	US	1957

Trade Name	Manufacturer	Country	Year Introduced
Cotrane	Midypharm	France	1960
Cothera	Ayerst	Italy	1961
Atuss	Arcana	Austria	-
Perlatos	Farm. Milanese	Italy	-
Tossizid	Beolet	Italy	-

Raw Materials

Phenothiazine-10-carboxylic acid chloride
Dimethylaminoethoxyethanol
Hydrogen chloride

Manufacturing Process

5.23 g of phenothiazine-10-carboxylic acid chloride were suspended in 8 g of dimethylaminoethoxyethanol and heated, with stirring, under anhydrous conditions, first for 1 hour at a temperature of 50°-105°C, then for another hour at 108°-110°C. All the suspended acid chloride had dissolved after the final heating, and the solution was then allowed to cool slowly to 75°C over a period of one hour. Infrared examination of a sample showed that the esterification reaction was essentially complete after the second hour.

The reaction mixture was then poured on 1 liter of crushed ice, and the oily precipitate washed repeatedly by decantation with ice water. It was then taken up in 75 ml of benzene, and again washed repeatedly with water until a pH of 8.2 in the washings indicated that substantially all of the excess β-dimethylaminoethoxyethanol had been removed. The benzene solution was then dried with anhydrous sodium sulfate, filtered, and the benzene evaporated in a current of dry nitrogen gas. The residual dark oil constituted the desired basic ester. β-Dimethylaminoethoxyethyl phenothiazine-10-carboxylate.

The basic ester may be dissolved in anhydrous ether and then precipitated by adding a slight excess of a solution of dry hydrogen chloride in ether and the hydrochloride salt may be isolated as an amorphous, glasslike product, which could be crystallized from anhydrous acetone or from methanol-ether. In this manner there was obtained as a stable, crystalline, colorless substance β-dimethylaminoethoxyethyl phenothiazine-10-carboxylate hydrochloride, one sample of which melted at 161°-163°C with decomposition.

References

Merck Index 3213
Kleeman and Engel p. 319
OCDS Vol. 1 p. 390 (1977)
I.N. p. 336
von Seemann, C.: US Patent 2,778,824; January 22,1957; assigned to American Home Products Corp.

DIMETHYL SULFOXIDE

Therapeutic Function: Topical antiinflammatory

Chemical Name: Sulfinylbis[methane]

Common Name: Methyl sulfoxide

Structural Formula:

Chemical Abstracts Registry No.: 67-68-5

Trade Name	Manufacturer	Country	Year Introduced
Rimso	Research Industries	US	1978
Damul	Pharm. Werk Meuselbach	E. Germany	-
Deltan	Serum Impfinst.	Switz.	-
Demasorb	Squibb	-	-
Demesco	MSD	-	-
Demsodrox	Nezel	Spain	-
Dermialgida	Andromaco	Spain	-
Dipirartril	Pons	Spain	-
Dromisol	MSD	-	-
Hyadur	Gruenenthal	-	-
Infiltrina	Heyden	W. Germany	-
Intran	Kwizda	Austria	-
Kemsol	Horner	Canada	-
Somipront	Mack	W. Germany	-

Raw Materials

Dimethyl sulfide
Oxygen
Nitrogen dioxide

Manufacturing Process

A current of oxygen at the rate of 370 ml/min was bubbled through a 30-cm layer of dimethyl sulfide maintained at 26.5°C, thereby producing a gaseous mixture containing the stoichiometric amount of oxygen required for the oxidation of the sulfide to sulfoxide. Nitric oxide at the rate of 30 ml/min was added to the gaseous mixture as it passed into the first of a series of four reaction chambers, each consisting of a glass tube 4.3 cm in diameter and 100 cm in length. The reaction started immediately, the temperature of the

reaction mixture reached a maximum of about 75°C in the first two tubes where most of the reaction occurred, and the reaction slowed down in the last two tubes. The crude, yellow product, which dropped from the tubes, contained about 10% dimethyl sulfide, about 2% dissolved nitrogen dioxide, about 2% methane sulfonic acid, and some water. The crude product was refluxed at 100°C for 30 minutes and the escaping gas was passed into the first reaction chamber. The dimethyl sulfide was removed by then heating the product to 150°C, the methane sulfonic acid was neutralized by adding slaked lime, and the dimethyl sulfoxide was distilled in vacuum. The yield of pure dimethyl sulfoxide (BP 63°C at 6 mm Hg) was 85% of the theoretical yield from the evaporated dimethyl sulfide.

References

Merck Index 3255
PDR p. 1450
DOT 1 (3) 94 (1965)
I.N. p. 340
REM p. 1121
Smedslund, T.H.; US Patent 2,581,050; January 1, 1952; assigned to A.B. Centrallaboratorium Helsinki
Coma, J.G. and Gerttula, V.G.; US Patent 3,045,051; July 17, 1962; assigned to Crown Zellerbach Corp.

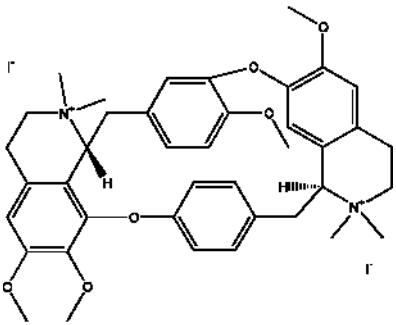
DIMETHYL TUBOCURARINE IODIDE

Therapeutic Function: Muscle relaxant

Chemical Name: 6,6',7',12'-Tetramethoxy-2,2,2',2'-tetramethyltubocuraranium diiodide

Common Name: Metocurine iodide

Structural Formula:



Chemical Abstracts Registry No.: 7601-55-0

Trade Name	Manufacturer	Country	Year Introduced
Metubine Iodide	Lilly	US	1949
Mecostrin	Squibb	US	-
Methyl Curarin	Ethicon	W. Germany	-

Raw Materials

Curare
Methyl iodide

Manufacturing Process

50 grams of crude, tarry curare as received in commerce and containing about 20% of d-tubocurarine are suspended in 400 cc of 0.5 N methanolic potassium hydroxide, and the mixture is boiled for ten minutes. The dark brown insoluble material is filtered off and the filtrate is treated with 50 cc of methyl iodide and refluxed gently for about 8 hours. An additional amount of 25 cc of methyl iodide is added to the reaction mixture and the refluxing is continued for 8 hours.

The reaction mixture is evaporated to a small volume, whereupon the d-tubocurarine dimethyl ether iodide precipitates. The precipitate is filtered off and dissolved in boiling water. The hot solution is treated with a small amount of decolorizing carbon, the carbon filtered off and the filtrate cooled to about 0°C. The dimethyl ether of d-tubocurarine iodide crystallizes in white crystals which melt at about 267°-270°C with decomposition.

References

Merck Index 6020
Kleeman and Engel p. 319
I.N. p. 340
REM p. 923
Bray, M.D.; US Patent 2,581,903; January 8, 1952; assigned to Eli Lilly and Company

DINOPROST TROMETHAMINE

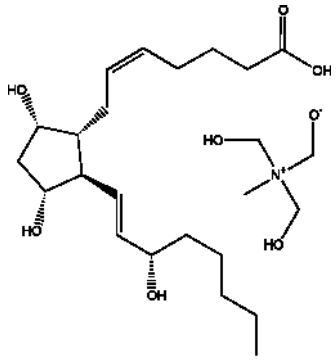
Therapeutic Function: Smooth muscle stimulant

Chemical Name: (5Z,9α,11α,13E,15S)-9,11,15-Trihydroxyprosta-5,13-dien-1-oic acid tromethamine salt

Common Name: Prostaglandin $F_{2\alpha}$ tromethamine

Chemical Abstracts Registry No.: 38562-01-5

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Prostin F2A	Upjohn	UK	1972
Prostin F2 α	Upjohn	US	1973
Prostalmon F	Ono	Japan	1974
Minprostin F2A	Upjohn	W. Germany	1975
Prostin F2 α	Upjohn	Italy	1976
Pronalgon F	Sumitomo	Japan	1981
Amoglandin	Kabi Vitrum	Sweden	-
Enzaprost	Chinoin	Hungary	-
Enzaprost	Medica	Finland	-
Lutalyse	Upjohn	-	-
Panacelan-F	Glaxo-Fuji	Japan	-
Zinoprost	Ono	Japan	-

Raw Materials

tris(Hydroxymethyl)aminomethane
Prostaglandin $F_{2\alpha}$

Manufacturing Process

A solution of tris(hydroxymethyl)aminomethane (1.645 grams) in 3.0 ml of water at 60°C is added with vigorous stirring to a solution of $PGF_{2\alpha}$, (5.00 grams) in 700 ml of acetonitrile which has just been brought to its boiling point. The vessel which contained the aqueous amine solution is rinsed with three 0.66 ml portions of water, each rinsing being added with vigorous stirring to the acetonitrile solution. The mixture is then cooled to 25°C by immersion of the vessel in cool water. At the cloud point, the vessel wall (glass) below the liquid surface is scratched vigorously with a glass rod. The mixture is then maintained at 25°C for 24 hours.

The resulting crystals are collected by filtration under nitrogen, washed on the filter with 50 ml of acetonitrile, and then dried by passing nitrogen at 50°C through the filter cake for one hour. Drying is completed in an oven at 70°C for 8 hours to give 5.965 grams of the tris(hydroxymethyl)aminomethane salt

of $PGF_{2\alpha}$ in free flowing crystalline form; MP 100°-101°C.

References

Merck Index 7781
Kleeman and Engel p. 321
OCDS Vol. 1 pp. 27, 33 (1977)
DOT 10 (4) 132 (1974) and 19 (6) 318 (1983)
I.N. p. 343
REM p. 950
Morozowich, W.; US Patent 3,657,327; April 18, 1972; assigned to The Upjohn Company

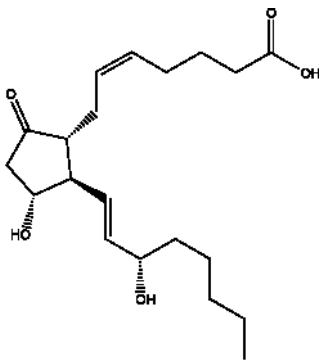
DINOPROSTONE

Therapeutic Function: Oxytocic, Abortifacient

Chemical Name: 11,15-Dihydroxy-9-oxoprosta-5,13-dien-1-oic acid

Common Name: Prostaglandin E_2; PGE_2

Structural Formula:



Chemical Abstracts Registry No.: 363-24-6

Trade Name	Manufacturer	Country	Year Introduced
Prostin E_2	Upjohn	UK	1972
Prostarmon E	Ono	Japan	1976
Prostin E_2	Upjohn	US	1977
Minprostin	Upjohn	W. Germany	1978

Raw Materials

Prostaglandin-A_2
Trimethylchlorosilane
Aluminum amalgam
Hexamethyldisilazane
Hydrogen peroxide

Manufacturing Process

Hexamethyldisilazane (1 ml) and trimethylchlorosilane (0.2 ml) are added with stirring to a solution of PGA_2 (250 mg) in 4 ml of tetrahydrofuran at 0°C under nitrogen. This mixture is maintained at 5°C for 15 hours. The mixture is then evaporated under reduced pressure. Toluene is added and evaporated twice. Then the residue is dissolved in 6 ml of methanol, and the solution is cooled to -20°C. Hydrogen peroxide (0.45 ml; 30% aqueous) is added. Then, 1N sodium hydroxide solution (0.9 ml) is added dropwise with stirring at -20°C. After 2 hours at -20°C, an additional 0.3 ml of the sodium hydroxide solution is added with stirring at -20°C. After another hour in the range -10°C to -20°C, an additional 0.1 ml of the sodium hydroxide solution is added. Then, 1.5 ml of 1 N hydrochloric acid is added, and the mixture is evaporated under reduced pressure. The residue is extracted with ethyl acetate, and the extract is washed successively with 1 N hydrochloric acid and brine, dried with anhydrous sodium sulfate and evaporated. The residue is dissolved in 5 ml of diethyl ether. To this solution is added 0.5 ml of methanol and 0.1 ml of water. Amalgamated aluminum made from 0.5 g of aluminum metal is then added in small portions during 3 hours at 25°C. Then, ethyl acetate and 3 N hydrochloric acid are added, and the ethyl acetate layer is separated and washed successively with 1 N hydrochloric acid and brine, dried with anhydrous sodium sulfate, and evaporated. The residue is chromatographed on 50 g of acid-washed silica gel, eluting first with 400 ml of a gradient of 50-100% ethyl acetate in Skellysolve B, and then with 100 ml of 5% methanol in ethyl acetate, collecting 25 ml fractions. Fractions 9 and 10 are combined and evaporated to give 18 mg of 11β-PGE_2. Fractions 17-25 are combined and evaporated to give 39 mg of PGE_2.

References

Merck Index 7780
Kleeman and Engel p. 323
OCDS Vol. 1 pp. 27, 30, 33, 35 (1977)
DOT 9 (10) 432 (1979); 11 (10) 388 (1975) and 14 (2) 74 (1978)
I.N. p. 343
REM p. 947
Pike, J.E. and Schneider, W.P.; US Patent 3,948,981; April 6, 1976; assigned to The Upjohn Co.

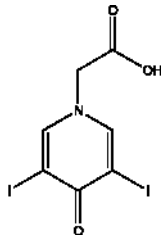
DIODONE

Therapeutic Function: Diagnostic aid

Chemical Name: 1(4H)-Pyridineacetic acid, 3,5-diiodo-4-oxo-, compd. with 2,2'-iminobis(ethanol) (1:1)

Common Name: Cardiotrast(um); Diodone; Iodopiraceti; Iodopyracet; Jodopyracet

Structural Formula:



Chemical Abstracts Registry No.: 101-29-1

Trade Name	Manufacturer	Country	Year Introduced
Iodopyracet	Winthrop	-	-

Raw Materials

Pyridine
Thionyl chloride
Chloroacetic acid
Diethanolamine
ICl

Manufacturing Process

2 mol of pyridine are reacted with thionyl chloride to give 4-pyridyl-pyridinium chloride. The last one is transformed into 4-1H-pyridone by adding of water at 150°C. Then it is added to 1 mol of iodomonochloride (ICl) to give 3,5-diidopyridone. It is converted in 3.5-diiodo-4-pyridone-N-acetic acid by addition of chloroacetic acid and sodium hydrate. 1 mol of 3.5-diiodo-4-pyridone-N-acetic acid is dissolved in a solution of 1 mol of diethanolamine in 60 ml of water while heating. The solution is made up to 100 ml with water. After evaporating the solution and recrystallizing, the salt is obtained in the form of white crystals. MP: 153°C.

References

Reitmann J.; US Patent No. 1,993,039; Mar. 5, 1935; Assigned to Winthrop Chemical Company, Inc., New York, N.Y., a corporation of New York

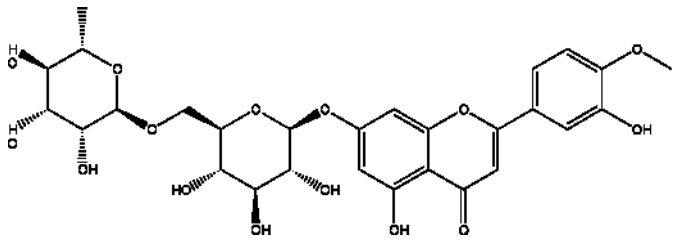
DIOSMIN

Therapeutic Function: Bioflavonoid

Chemical Name: 5,7-Dihydroxy-2-(3-hydroxy-4-methoxyphenyl)-4H-1-benzopyran-4-one-7-rutinoside

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 520-27-4

Trade Name	Manufacturer	Country	Year Introduced
Diosmil	Bellon	France	1971
Tovene	Kali-Chemie	W. Germany	1976
Dalfon	Servier	Italy	1977
Diosminil	Faes	Spain	-
Diovenor	Hommel	Switz.	-
Flebotropin	Bago	Argentina	-
Insuven	Lusofarmaco	Spain	-
Rioven	Hommel	Switz.	-
Varinon	Hommel	Switz.	-
Ven-Detrex	Hommel	Switz.	-
Venosmine	Hommel	Switz.	-
Venotrex	Hommel	Switz.	-
Venusmin	Hommel	Switz.	-

Raw Materials

Hesperidin
Acetic acid
Sodium hydroxide
Bromine
Acetic anhydride

Manufacturing Process

A mixture of 72 g hesperidin, 288 ml acetic anhydride and 300 ml glacial acetic acid were boiled in reflux with 15 ml pyridine as the catalyst for 144 hours until during the control of the reaction the band disappeared at a wave length between 264 to 280 nm, and a new maximum appeared at 330 nm. Thereafter in a rotation evaporator the reaction mixture was concentrated by evaporation under vacuum conditions.

The residue was absorbed in 1,200 ml ethyl acetate, admixed with 20 ml

ethanol and boiled for one hour under reflux action. The solution was filtered and compressed to dryness. The residue was dried in a vacuum drying cabinet. The yield amounted to 107.5 g.

35.8 g thereof were then dissolved in 280 ml glacial acetic acid and brominated with a solution of 6.05 g bromine in 30 ml glacial acetic acid. Thereafter the mixture compressed to dryness by means of the rotation evaporator, there being obtained a residue of 41.8 g. Such was dissolved in 150 ml methanol, admixed with a solution of 36 g sodium hydroxide in 180 ml water and stirred for one hour at 50°C.

The diosmin was precipitated out by adding 120 ml glacial acetic acid and stirring at 70°C for 30 minutes. The precipitate was filtrated in a suction filter or strainer, washed with methanol, water and again methanol and dried at 60°C in the drying cabinet. Raw yield: 17.0 g corresponding to 71% yield. Bromine content 0.51%.

10 g of the thus-obtained diosmin was dissolved in a solution of 24 g sodium hydroxide in 120 ml water, admixed with 100 ml methanol and 100 ml pyridine and stirred for one hour at 50°C. The diosmin was precipitated by the addition of 100 ml glacial acetic acid and stirred for 30 minutes at 70°C, filtered and washed with methanol and water and again methanol.

After drying at 60°C there was obtained a pure yield of 9.2 g diosmin (65% based upon the employed hesperidin) having a bromine content of 0.07%.

References

Merck Index 3300
Kleeman and Engel p. 324
DOT 12 (7) 263 (1976)
I.N. p. 344
Schmid, C., Glasbrenner, M. and Heusser, J.; US Patent 4,078,137; March 7, 1978; assigned to Hommel A.G. (Switz.)

DIOXYLINE PHOSPHATE

Therapeutic Function: Vasodilator

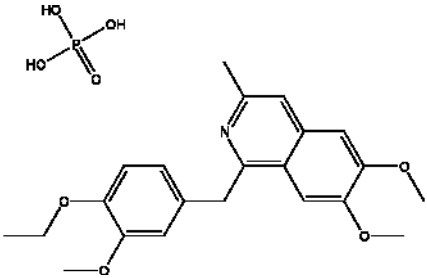
Chemical Name: 1-(4-Ethoxy-3-methoxybenzyl)-6,7-dimethoxy-3-methyl isoquinoline phosphate

Common Name: Dimoxyline

Chemical Abstracts Registry No.: 5667-46-9; 147-27-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Paveril	Lilly	US	1951
Paverona	Lilly	Japan	-

Structural Formula:



Raw Materials

1-(3',4'-Dimethoxyphenyl)-2-propanone
Hydroxylamine hydrochloride
3-Methoxy-4-ethoxyphenyl acetic acid
Ammonia
Phosphorus oxychloride
Sodium hydroxide

Manufacturing Process

A mixture of 150 grams of 1-(3',4'-dimethoxyphenyl)-2-propanone and 70 grams of hydroxylamine hydrochloride in 125 cc of water is stirred while a solution of 51.3 grams of sodium carbonate in 150 cc of water is added over the course of 15 minutes, and while maintaining the reaction mixture at 30°-40°C. The reaction mixture is stirred for an additional two and one-half hour period at room temperature, and is then diluted with an equal volume of water and extracted three times with 300 cc portions of ether. The combined ether extracts are washed with water, dried over anhydrous magnesium sulfate, and the ether is distilled off. The residue, comprising 1-(3',4'-dimethoxyphenyl)-2-propanone oxime, may be purified by fractional distillation in vacuo.

1-(3',4'-Dimethoxyphenyl)-2-propanone oxime thus prepared boiled at about 165°-175°C at 0.6 mm pressure. Analysis showed the presence of 7.23% of nitrogen, compared with the calculated amount of 6.69%.

A solution of 151 grams of 1-(3',4'-dimethoxyphenyl)-2-propanone oxime in 200 cc of absolute ethanol is treated with 5 grams of Raney nickel catalyst and ammonia in an autoclave at about 25 atm of pressure and at 75°-100°C. The reduction is complete in about one-half hour and the reaction mixture is filtered and fractionated under reduced pressure to recover the α-methylhomoveratrylamine formed by the reduction. α-Methylhomoveratrylamine thus prepared boiled at 163°-165°C at 18 mm pressure.

A mixture of 39.0 grams (0.2mol) of α-methylhomoveratrylamine and 42.0 grams (0.2mol) of 3-methoxy-4-ethoxyphenylacetic acid is heated at 190°-200°C for one hour. The reaction mixture is poured into about 100cc of petroleum ether, whereupon crystals of N-(α-methylhomoveratryl)-3-methoxy-4-ethoxyphenylacetamide separate. The precipitate is filtered off, and recrystallized from 50% methanol-water.

N-(α-methylhomoveratryl)-3-methoxy-4-ethoxyphenylacetamide thus prepared melted at about 135°-136°C. Analysis showed the presence of 68.05% carbon and 7.62% of hydrogen compared with the calculated amount of 68.19% carbon and 7.54% hydrogen.

A solution of 50 grams of N-(α-methylhomoveratryl)-3-methoxy-4-ethoxyphenylacetamide, prepared as set out above, in 200 cc of benzene, is treated with 8 cc of phosphorus oxychloride. The mixture is refluxed for about 3 hours, cooled and then is shaken with a solution composed of 15 grams of sodium hydroxide dissolved in 60cc of water. The aqueous layer is removed, and the benzene solution is washed with water. The washed benzene solution is dried over anhydrous magnesium sulfate, filtered and evaporated to dryness. The low-melting solid residue is 6,7-dimethoxy-3-methyl-1-(3'-methoxy-4'-ethoxybenzyl)-dihydroisoquinoline base.

To a solution of 50 grams of 6,7-dimethoxy-3-methyl-1-(4'-ethoxy-3'-methoxybenzyl)-dihydroisoquinoline base in 200 ml of dry benzene are added 150 ml of decalin, and the mixture is distilled until its temperature reaches 180°C. 1.5 grams of 5% palladium on carbon are then added. The mixture is stirred under reflux for about 6 hours to dehydrogenate the dihydroisoquinoline. On cooling, the reaction mixture is diluted with petroleum ether and the precipitated 6,7-dimethoxy-3-methyl-1-(3'-methoxy-4'-ethoxybenzyl)-isoquinoline is filtered off and recrystallized from dilute ethanol.

6,7-Dimethoxy-3-methyl-1-(3'-methoxy-4'-ethoxybenzyl)-isoquinoline thus prepared melted at 124°-125°C. Analysis showed the presence of 71.68% carbon and 7.07% hydrogen as compared with the calculated amount of 71.91% carbon and 6.85% hydrogen.

A solution of 5 grams of 6,7-dimethoxy-3-methyl-1-(4'-ethoxy-3'-methoxybenzyl)-isoquinoline in 100 cc of ethanol is treated with a solution of 1.5 grams of phosphoric acid in 10 cc of ethanol. 10 cc of water are added to effect complete solution, and the reaction mixture is then cooled and ether is added until precipitation of the salt is complete. The precipitate of 6,7-dimethoxy-3-methyl-1-(3'-methoxy-4'-ethoxybenzyl)-isoquinoline phosphate is filtered off and recrystallized from 85% ethanol by the addition of 2 volumes of ether.

References

Merck Index 3266
Kleeman and Engel p. 321
OCDS Vol. 1 p. 349 (1977)
I.N. p. 342
Shepard, E.R.; US Patent 2,728,769; December 27, 1955; assigned to Eli Lilly and Co.

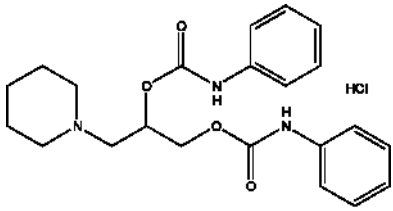
DIPERODON HYDROCHLORIDE

Therapeutic Function: Local anesthetic

Chemical Name: 1,2-Propanediol, 3-(1-piperidinyl)-, bis(phenylcarbamate) (ester), hydrochloride

Common Name: Diperocainum; Diperodon hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 537-12-2; 101-08-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Diothane Hydrochloride	HMR	-	-
Proctodon	Rowell	-	-

Raw Materials

Phenylisocyanate
Glycide
N-(1,2-Dihydroxypropyl)-piperidine
Piperidine

Manufacturing Process

15.0 g phenylisocyanate in 100 ml of anhydrous ether are added to 10 g of N-(1,2-dihydroxypropyl)-piperidine (prepared from glycide and piperidine) and the solution boiled for two hours, after which it is cooled and saturated with dry hydrogen chloride gas. The ether layer is then decanted off and the remaining insoluble product is dissolved in a hot mixture of acetone and ethyl acetate which on cooling precipitates white crystals of the hydrochloride of the ester of 1,2-propanediol, 3-(1-piperidinyl)-, bis(phenylcarbamate); MP 197°-198°C. A base form may be prepared by adding an equivalent of triethyl amine.

References

Rider T.H.; US Patent No. 2,004,132; June 11,1935

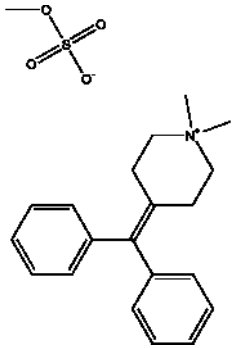
DIPHEMANIL METHYLSULFATE

Therapeutic Function: Spasmolytic

Chemical Name: 4-(Diphenylmethylene)-1,1-dimethylpiperidinium methylsulfate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 62-97-5

Trade Name	Manufacturer	Country	Year Introduced
Prantal	Schering	US	1952
Prantal	Unicet	France	1958
Demotil	Pharmacia	Sweden	-
Prentol	Essex Espana	Spain	-

Raw Materials

Bromobenzene
Dimethyl sulfate
Sulfuric acid
4-Benzoyl-N-methylpiperidine
Magnesium

Manufacturing Process

(A) Preparation of diphenyl-(N-Methyl-4-Piperidyl)carbinol: to a Grignard solution prepared from 4.9 grams of magnesium, 100 cc of ether and 31.4 grams of dry bromobenzene is added 18.5 grams of 4-benzoyl-N-methylpiperidine in 200 cc of dry ether. The reaction mixture is heated with stirring for 4 hours on the steam bath and then decomposed. The organic layer is separated and the aqueous layer extracted with benzene. The combined organic extracts are concentrated and the residue, diphenyl-(N-methyl-4-piperidyl)carbinol, recrystallized from benzene-petroleum ether, MP 130-131°C. The Grignard complex may also be decomposed with ice and hydrochloric acid and the insoluble hydrochloride of the carbinol isolated directly.

(B) Preparation of diphenyl-(N-Methyl-4-Piperidylidene)methane: the carbinol can be dehydrated with 60% sulfuric acid. In general, to one part of the carbinol there is added 10 parts of 60% sulfuric acid. The mixture after heating for 6 hours is poured onto cracked ice, the solution made alkaline with dilute sodium hydroxide and the oily basic layer extracted with ether. The ether extracts after washing with water are dried over sodium sulfate, and

after removing the ether, the residue is distilled in vacuo, MP 52°-53°C.

(C) Preparation of Final Product: The product from (B) is reacted with dimethyl sulfate in benzene to give the final product, MP 196°-197°C.

References

Merck Index 3313
Kleeman and Engel p. 325
I.N. p. 346
Sperber, N., Villani, F.J. and Papa, D.; US Patent 2,739,968; March 27, 1956; assigned to Schering Corporation

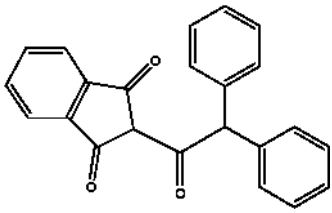
DIPHENADIONE

Therapeutic Function: Anticoagulant

Chemical Name: 2-(Diphenylacetyl)-1H-indene-1,3(2H)-dione

Common Name: 2-Diphenylacetyl-1,3-diketohydrindene; 2-Diphenylacetyl-1,3-indandione

Structural Formula:



Chemical Abstracts Registry No.: 82-66-6

Trade Name	Manufacturer	Country	Year Introduced
Dipaxin	Upjohn	US	1955
Didandin	Boots	-	-

Raw Materials

Dimethyl phthalate
Diphenylacetone
Sodium
Methanol

Manufacturing Process

A solution of sodium methoxide was prepared by adding 2.76 grams (0.12

mol) of sodium to 50 ml of absolute methanol and gently warming the mixture to effect complete solution of the sodium. To this was added 300 milliliters of dry benzene with vigorous stirring, whereafter excess methanol was removed by concentrating the mixture to a volume of about 100 ml. To the resulting sodium methoxide suspension was added a solution of 19.4 grams (0.1 mol) of dimethyl phthalate in 200 ml of dry benzene. The mixture was heated to boiling and a solution of 21 grams (0.1 mol) of diphenylacetone in 200 ml of dry benzene was added dropwise thereto. During addition approximately 200 ml of liquid, which consisted of benzene together with methanol formed during the course of the reaction, was distilled from the reaction mixture. After addition of the diphenylacetone, the mixture was heated under reflux for about 6 hours, cooled and stirred vigorously with 200 ml of 5% sodium hydroxide solution.

The light yellow solid which separated was collected by filtration; the filtrate was reserved for treatment as described below. Suspension in water of the solid, which weighed 12 grams, and acidification of the mixture with dilute hydrochloric acid produced a gum which soon crystallized. Recrystallization of this solid from ethanol gave 10.2 grams (30%) of 2-diphenylacetyl-1,3-indandione as a light yellow crystalline solid, which melted at 146-147°C.

The filtrate mentioned above consisted of 3 layers. An oily layer which was present between the aqueous and benzene layers was separated, acidified and extracted with ether. The aqueous layer was likewise separated, acidified and extracted with ether. The extracts were combined, dried and evaporated to yield a heavy gum which was crystallized from ethanol to give an additional 2.5 grams of product which melted at 146-147°C. The total yield of 2-diphenylacetyl-1,3-indandione was 12.7 grams (37%).

References

Merck Index 3315
Kleeman and Engel p. 326
I.N. p. 346
REM p. 1257
Thomas, D.G.; US Patent 2,672,483; March 16, 1954; assigned to The Upjohn Company

DIPHENHYDRAMINE HYDROCHLORIDE

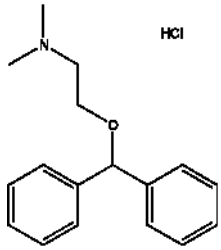
Therapeutic Function: Antihistaminic

Chemical Name: 2-Diphenylmethoxy-N,N-dimethylethanamine hydrochloride

Common Name: Benzhydramine hydrochloride

Chemical Abstracts Registry No.: 147-24-0; 58-73-1 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Benadryl	Parke Davis	US	1946
Benylin	Parke Davis	France	1964
Wehdryl	Hauck	US	1964
Sominex	Williams	US	1982
Aleryl	Farmos	Finland	-
Alledryl	Teva	Israel	-
Allerdryl	I.C.N.	Canada	-
Allergan	Bouty	Italy	-
Allergin	Nyegaard	Norway	-
Allergina	De Angeli	Italy	-
Bax	McKesson	US	-
Benadol	Taisho	Japan	-
Benadozol	Hokuriku	Japan	-
Benapon	Dainippon	Japan	-
Benasin	Kanto	Japan	-
Benhydramil	Barlow Cote	Canada	-
Benocten	Medinova	Switz.	-
Benzantine	Teva	Israel	-
Benzehist	PHARMEX	US	-
Bidramine	Adams	Australia	-
Bromanil	Schein	US	-
Broncho-Rivo	Rivopharm	Switz.	-
Carphenamine	Carroll	US	-
Cathejell	Montavit	Austria	-
Dabylen	Schieffelin	US	-
Dermistina	I.S.M.	Italy	-
Dermodrin	Montavit	Austria	-
Desentol	Leo	Sweden	-
Dibondrin	Montavit	Austria	-
Dihydral	SCS Pharmalab	S. Africa	-
Dimidril	Pliva	Yugoslavia	-
Dobacen	Homberger	Switz.	-
Dolestan	Much	W. Germany	-
Drama Ject	Mayrand	US	-
Draminol	Luar	US	-

Trade Name	Manufacturer	Country	Year Introduced
Drylistan	Sigmapharm	Austria	-
Expectoryn	Pharma-Plus	Switz.	-
Fenylhist	Mallard	US	-
Histaxin	Chemofux	Austria	-
Hyrexin	Hyrex	US	-
Insomnal	Welcker-Lyster	Canada	-
Kendiphen	Key	US	-
Lensen	Geneva	US	-
Mandrax	I.S.H.	France	-
Medidryl	Medica	Finland	-
Nautamine	Delagrange	France	-
Niramine	Rachelle	US	-
Noctomin	Medichemie	Switz.	-
Phentamine	Restan	S. Africa	-
Pheramin	Kanoldt	W. Germany	-
Prodryl	Progress	US	-
Restamin	Kowa	Japan	-
Reston	Kowa	Japan	-
Serundal D	Woelm	W. Germany	-
Somenox	Cooper	Switz.	-
Valdrene	Vale	US	-
Vilbin	Felbena	Switz.	-
Ziradryl	Parke Davis	US	-

Raw Materials

β-Dimethylaminoethanol
Sodium carbonate
Diphenylmethane
Bromine

Manufacturing Process

As described in US Patent 2,421,714: (a) benzhydryl bromide is first prepared as follows: 840 parts by weight of diphenylmethane is heated to 130°C with stirring. In the presence of a 200 watt electric light 6 inches from the flask, 880 parts of bromine is added slowly. Liberation of HBr occurs and addition requires 1 hour and 45 minutes. The temperature is maintained at 130°C for an additional 30 minutes. A fine stream of air is blown in to remove HBr and Br_2 while the reaction mixture cools. Benzene (180 parts) is added and the solution used immediately in (b) below.

If pure benzhydryl bromide is desired the above reaction mixture is dissolved in ether, washed with water, sodium carbonate solution and finally with water. The ether is removed, benzene added and distilled off and the benzhydryl bromide distilled in vacuo. Yield 85%.

(b) 490 parts β-dimethylaminoethanol and 530 parts of anhydrous sodium carbonate are heated to 110°C with stirring. The addition of the benzene-benzhydryl bromide mixture is then begun. The temperature is raised to 120°-125°C. As reaction takes place carbon dioxide is evolved, the addition requires

1½ hours. The mixture is kept at 125°C for 5 hours additional time. After cooling, 3,000 parts of water is added and the mixture stirred until the inorganic salts are dissolved. The mixture is transferred to a large separatory funnel and 1,500 parts of ether added. The ether solution is washed several times with water and then the ether layer extracted with 1 to 4 hydrochloric acid. The acid solution is treated with 30 parts of Darco and 30 parts Filter-Cel and filtered.

The free base is liberated from the acid solution with 20% sodium hydroxide solution and taken up in ether. The ether layer is washed with water, saturated with NaCl and then shaken with solid potassium hydroxide. The ether is removed by distillation, 200 parts of benzene added and distilled off. The residue is distilled in vacuo and the fraction 150°-165°C/2 mm is collected and amounts to 433 parts. The hydrochloride salt is prepared by dissolving the free base in anhydrous ether and slowly adding an alcoholic solution of hydrogen chloride. The solid is recrystallized from absolute alcohol-ether mixture or isopropanol-ether mixture and has a MP of 161-162°C.

References

Merck Index 3320
Kleeman and Engel p. 327
PDR pp. 695, 830, 872, 993, 1033, 1317, 1397, 1569, 1606, 1989, 1999
OCDS Vol. 1 p. 41 (1977)
I.N. p. 347
REM p. 1128
Martin, H., Hafliger, F., Gatzi, K. and Grob, A.; US Patent 2,397,799; April 2, 1946; assigned to J.R. Geigy AG, Switzerland
Rieveschl, G. Jr.; US Patent 2,421,714; June 3, 1947; assigned to Parke, Davis and Co.
Rieveschl, G. Jr.; US Patent 2,427,878; September 23, 1947;assigned to Parke, Davis and Company

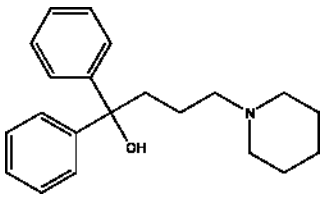
DIPHENIDOL

Therapeutic Function: Antinauseant

Chemical Name: α,α-Diphenyl-1-piperidinebutanol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 972-02-1

Trade Name	Manufacturer	Country	Year Introduced
Vontrol	SKF	US	1967
Cephadol	Nippon Shinyaku	Japan	1974
Ansumin	S.S. Pharm	Japan	-
Antiul	Tokyo Hosei	Japan	-
Avomol	Landerlan	Spain	-
Celmidol	Tobishi	Japan	-
Cerachidol	Ono	Japan	-
Cerrosa	Toyo	Japan	-
Deanosarl	Isei	Japan	-
Degidole	Nihon Yakuhin	Japan	-
Defenidolin	Taiyo	Japan	-
Gipsydol	Nihon Yakuhin	Japan	-
Maniol	Morishita	Japan	-
Meranom	Hokuriku	Japan	-
Midnighton	Takata	Japan	-
Pineroro	Maruko	Japan	-
Promodor	Torii	Japan	-
Satanolon	Tatsumi	Japan	-
Sofalead	Nikken	Japan	-
Solnomin	Zensei	Japan	-
Tatimil	Mohan	Japan	-
Wansar	Hoei	Japan	-
Yesdol	Toho Iyaku	Japan	-
Yophadol	Horita	Japan	-

Raw Materials

Ethyl bromide
Magnesium
N-[1-Chloropropyl-(3)]piperidine
Benzophenone

Manufacturing Process

2.6 grams magnesium, activated by means of iodine, is introduced into 20 cc of absolute ether and is caused to react with 0.6 cc of ethyl bromide. While warming gently, 16.2 grams (0.1 mol) of N-[1-chloropropyl-(3)]-piperidine in 40 cc of absolute ether are added and, after adding a further 0.5 cc of ethyl bromide, 14.5 grams (0.08 mol) of benzophenone in 50 cc of anhydrous ether are added in portions. The magnesium is used up fairly quickly and, after 10 hours, only traces are left. In working up, both with hydrochloric acid and with ammonium chloride, the hydrochloride of diphenyl-3-piperidinopropyl carbinol is precipitated as a dense precipitate. It is purified by recrystallization from chloroform-ethyl acetate. MP 212-214°C.

References

Merck Index 3323
Kleeman and Engel p. 300

PDR p. 1731
OCDS Vol. 1 p. 45 (1977)
DOT 3 (1) 32 (1967)
I.N. p. 323
REM p. 808
Miescher, K. and Marxer, A.; US Patent 2,411,664; November 26, 1946; assigned to Ciba Pharmaceutical Products, Inc.

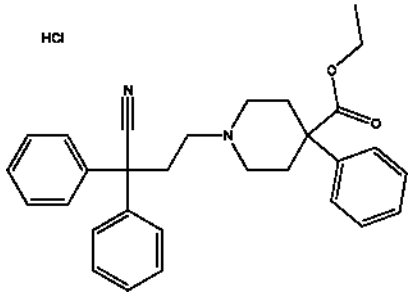
DIPHENOXYLATE HYDROCHLORIDE

Therapeutic Function: Antidiarrheal

Chemical Name: 1-(3-Cyano-3,3-diphenylpropyl)-4-phenyl-4-piperidinecarboxylic acid ethyl ester hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 3810-80-8; 915-30-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Lomotil	Searle	US	1960
Diarsed	Clin-Comar-Byla	France	-
Protector	I.F.L.	Spain	-
Reasec	Janssen	W. Germany	-
Retardin	Benzon	Denmark	-
Retardin	Leo	Sweden	-
Sedistal	Abic	Israel	-

Raw Materials

4-Phenylisonipecotic acid ethyl ester
2,2-Diphenyl-4-bromobutyronitrile

Manufacturing Process

A mixture of 23 parts of the ethyl ester of 4-phenylisonipecotic acid and 15 parts of 2,2-diphenyl-4-bromobutyronitrile in 19 parts of xylene is heated for 24 hours at 100-120°C and then cooled and filtered to remove the precipitate of the hydrobromide of the ethyl ester of 4-phenylisonipecotic acid. The filtrate is then extracted with dilute hydrochloric acid and the extract is rendered alkaline by addition of concentrated aqueous potassium hydroxide and extracted with ether. This ether extract is treated with gaseous hydrogen chloride. The resulting precipitate is collected on a filter. The hydrochloride of the ethyl ester of 2,2-diphenyl-4-(4'-carboxy-4'-phenyl-1'-piperidino)butyronitrile thus obtained melts at about 220.5-222°C. See meperidine hydrochloride for synthesis of 4-phenyl-isonipecotic acid ethyl ester.

References

Merck Index 3325
Kleeman and Engel p. 328
PDR pp. 993, 1569, 1690, 1999
OCDS Vol. 1 p. 302 (1977) and 2 331 (1980)
I.N. p. 348
REM p. 813
Janssen, P.A.J.; US Patent 2,898,340; August 4, 1959
Dryden, H.L. Jr. and Erickson, R.A.; US Patent 4,086,234; April 25, 1978; assigned to G.D. Searle and Co.

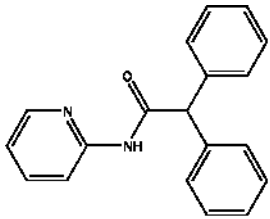
DIPHENPYRAMIDE

Therapeutic Function: Antiinflammatory

Chemical Name: 2-(Diphenylacetylamino)-pyridine

Common Name: Difenpiramide

Structural Formula:



Chemical Abstracts Registry No.: 51484-40-3

Trade Name	Manufacturer	Country	Year Introduced
Difenax	Zambeletti	Italy	1977

Raw Materials

Diphenylacetic acid chloride
2-Aminopyridine

Manufacturing Process

23 g (0.1 mol) diphenylacetic acid chloride dissolved in 300 cc anhydrous ethyl ether are slowly added dropwise to a solution of 19 g (0.2 mol) 2-aminopyridine in 300 cc anhydrous ethyl ether. The reaction mixture is agitated and the temperature is kept at between 5°C and 10°C with an ice bath. After the addition has been completed, the agitation of the mixture is continued and the temperature is allowed to rise to 20°C to 25°C.

After leaving to stand for a few hours, the gummy precipitate solidifies and becomes filterable. After separating off the precipitate, the ether is evaporated under reduced pressure to a volume of about 100 cc.

The ether is left to stand at a low temperature below 10°C when the remaining portion of the product precipitates and is filtered off and added to the first precipitate. The product thus obtained is thoroughly washed, first in water and then in a solution of sodium bicarbonate, and then again in water. After drying in air, the product is crystallized from anhydrous ethanol or from acetone and water. The analytical data correspond to calculated values. Yield is 18 g; MP 122°C to 124°C.

References

Merck Index 3123
DFU 2 (12) 793 (1977)
I.N. p. 323
Molteni, L., Tenconi, F. and Tagliabue, R.; US Patent 3,868,380; February 25, 1975

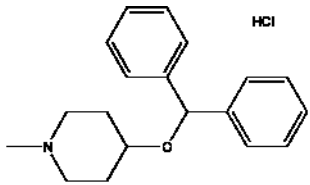
DIPHENYLPYRALINE HYDROCHLORIDE

Therapeutic Function: Antihistaminic

Chemical Name: 4-(Diphenylmethoxy)-1-methylpiperidine hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 132-18-3; 147-20-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Diafen	Riker	US	1955
Hispril	Nopco	US	1959
Lergoban	Riker	UK	1971
Allerzin	Virax	Australia	-
Anti-H10	S.M.B.	Belgium	-
Antinal	Arcana	Austria	-
Belfene	Bellon	France	-
Kolton Gelee	Promonta	W. Germany	-
Lyesipoll	Lyssia	W. Germany	-
Pirazone	UCB-Smit	Italy	-

Raw Materials

1-Methyl-4-piperidinol
Benzhydryl bromide
Hydrogen chloride

Manufacturing Process

A mixture of 46 grams of 1-methyl-4-piperidinol (0.4 mol), 49.4 grams of benzhydryl bromide (0.2 mol) and 100 ml of xylene was refluxed for approximately 24 hours. The reaction mixture separated into two phases with the upper phase containing the desired ether compound dissolved in xylene. The lower phase consisted of the hydrobromide salt of the excess 1-methyl-4-piperidinol. The upper phase was separated from the lower phase and the desired benzhydryl ether recovered in the crude state by distilling off the xylene under reduced pressure.

The crude benzhydryl ether was a clear reddish oil. It was dissolved in 75 ml of 20% hydrochloric acid and the aqueous acid solution then washed three times with 50 ml portions each of ethyl ether. The aqueous acid solution was then decolorized with activated carbon and thereafter slowly admixed with 75 ml of 28% aqueous ammonia. The benzhydryl ether separated as an oily material and was removed from the aqueous mixture by extraction with three 50 ml portions of ethyl ether.

On evaporation of the ethyl ether from the ethyl ether solution, the benzhydryl ether was recovered as a pale yellow oil. The benzhydryl ether was dissolved in 60 ml of isopropanol and the isopropanol solution acidified to a pH of 3 with dry hydrogen chloride-methanol solution. The acidic propanol solution was then diluted with ethyl ether until a faint turbidity was observed. In a short time, the crystalline hydrochloride salt of the benzhydryl ether separated from the propanol solution. The crystallized salt was recrystallized once from 75 ml of isopropanol with the aid of ethyl ether in order to further purify the material. A yield of the pure hydrochloride salt of 1-methylpiperidyl-4-benzhydryl ether of 24.5 grams was obtained. This was 39% of the theoretical yield. The pure material had a melting point of 206°C.

References

Merck Index 3347
Kleeman and Engel p. 328
PDR p. 1717
I.N. p. 349
REM p. 1128
Knox, L.H. and Kapp, R.; US Patent 2,479,843; August 23, 1949; assigned to Nopco Chemical Company

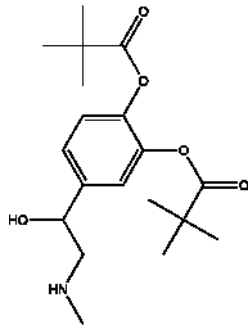
DIPIVEFRIN

Therapeutic Function: Adrenergic (ophthalmic)

Chemical Name: 2,2-Dimethylpropanoic acid 4-[1-hydroxy-2-(methylamino) ethyl]-1,2-phenylene ester

Common Name: Dipivalyl epinephrine

Structural Formula:



Chemical Abstracts Registry No.: 52365-63-6

Trade Name	Manufacturer	Country	Year Introduced
Propine	Allergan	W. Germany	1978
Propine	Allergan	US	1980
D-Epifrin	Allergan	-	-
Diopine	Allergan	-	-
Glaucothil	Thilo	W. Germany	-
Vistapin	Pharm-Allergan	W. Germany	-

Raw Materials

α-Chloro-3',4'-dihydroxyacetophenone
Methylamine

Pivaloyl chloride
Hydrogen

Manufacturing Process

First, 0.27 mol of α-chloro-3',4'-dihydroxyacetophenone are dissolved in 200 ml methanol with warming. Next, 100 ml of a 40% aqueous solution of methylamine is slowly added and the mixture stirred at 50°C to 55°C for 2 hours. The reaction mixture is then stirred an additional 24 hours at room temperature.

The crude product separates as a solid from the reaction medium and is recovered by filtration, and it is then washed thoroughly with ether and dissolved in 350 ml 1 N HCl. Then, approximately 250 ml of the aqueous solvent is removed with a rotary evaporator and the evaporation residue combined with 125 ml methanol and filtered through decolorizing charcoal. The product is precipitated as the HCl salt by the addition of 7 parts of acetone. The resulting crystalline material is removed by filtration dried at 40°C with vacuum, and has a melting point of about 242°C and is used without further purification.

Next, 25.3 g, 0.125 mol, of the above product are dissolved in 250 ml ethyl acetate and 0.125 mol perchloric acid as a 70% aqueous solution is slowly added thereto with continuous stirring. Then, an excess of pivaloyl chloride, 280 ml, is added and the mixture slowly warmed to reflux temperature. The reaction mixture is refluxed for about 5 hours and allowed to cool to room temperature with continuous stirring. The product is precipitated as the perchlorate salt by the addition of perchloric acid, $HClO_4$, in 500 ml ether. The product is isolated and purified by dissolving in 75 ml acetone and precipitating it with 150 to 200 ml of water.

To 20 g of the above compound dissolved in 300 ml 95% ethanol in a Parr reaction vessel is added 1.5 g Adams catalyst, platinum dioxide, and the mixture shaken under hydrogen at 50 psi for 1 hour at ambient temperature. The mixture is then filtered and the ethanol removed on a standard rotary evaporator. The resulting oil is dissolved in 200 ml ether and slowly added to 1,200 ml ether with continuous stirring. The product separates as crystals which are removed after 15 to 30 minutes by filtration. The compound melts at 146°C to 147°C and needs no further purification.

References

Merck Index 3356
Kleeman and Engel p. 329
OCDS Vol. 3 p. 22 (1984)
I.N. p. 350
REM p. 891
Hussain, A.and Truelove, J.E.; US Patents 3,809,714; May 7, 1974; and 3,839,584; October 1, 1974; both assigned to Inter Rx Research Corp.
Henschler, D., Wagner, J. and Hampel, H.; US Patent 4,085,270; April 18, 1978; assigned to Chemisch-Pharmazeutische Fabrik Adolf Klinge and Co. (W. Germany)

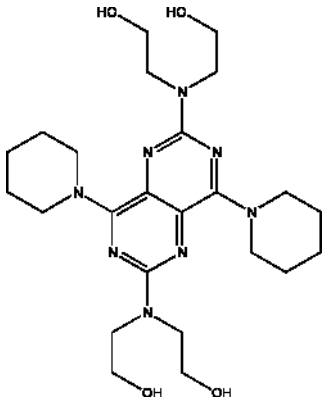
DIPYRIDAMOLE

Therapeutic Function: Coronary vasodilator

Chemical Name: 2,2',2'',2'''-(4,8-Dipiperidinopyrimido[5,4-d]pyrimidine-2,6-diyldinitrilo)tetraethanol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 58-32-2

Trade Name	Manufacturer	Country	Year Introduced
Persantine	Boehringer Ingelheim	US	1961
Natyl	Nativelle	France	1961
Persantin	Boehringer Ingelheim	UK	1961
Persantin	Thomae	W. Germany	1966
Agileese	Isei	Japan	-
Anginal	Yamanouchi	Japan	-
Atlantin	Dojin	Japan	-
Cardoxin	Rafa	Israel	-
Cleridium	Millot	France	-
Coribon	Radiumpharma	Italy	-
Coronamole	Nichiiko	Japan	-
Coronarine	Negma	France	-
Corosan	Saita	Italy	-
Coroxin	Malesci	Italy	-
Curantyl	Arzneimittelwerk Dresden	E. Germany	-
Dipyrida	Schurholz	W. Germany	-
Drisentin	Drifa	Turkey	-
Functiocardon	Krewel	W. Germany	-
Gulliostin	Taiyo	Japan	-
Isephanine	Kanto	Japan	-

Trade Name	Manufacturer	Country	Year Introduced
Justpertin	Horita	Japan	-
Padicor	Padil	Italy	-
Penselin	Sawai	Japan	-
Peridamol	Lab. Franc. Therap.	France	-
Perkod	Generod	France	-
Permilitin	Zensei	Japan	-
Piroan	Towa	Japan	-
Prandiol	Bottu	France	-
Protangix	Lefranco	France	-
Royalcor	Morgan	Italy	-
Santhimon	Santen	Japan	-
Stenocor	Chemipharma	Italy	-
Stimolcardio	Phanthox and Burck.	Italy	-
Tinol	Teikoku	Japan	-
Trancocard	Benvegna	Italy	-
Trombostaz	Yurtoglu	Turkey	-
Viscor	Italsuisse	Italy	-

Raw Materials

Urea
Acetoacetic ester
Potassium cyanate
Diethanolamine
Nitric acid
Hydrogen
Phosphorus oxychloride
Piperidine

Manufacturing Process

Urea may be reacted with acetoacetic ester and that product nitrated to give 5-nitro-orotec acid. That is hydrogenated, then reacted with urea and potassium cyanate to give tetrahydroxypyrimidopyrimidine. The tetrahydroxy compound is converted to the tetrachloro compound $POCl_3$. Reaction with diethanolamine and then with piperidine gives dipyridamole.

References

Merck Index 3366
Kleeman and Engel p. 330
PDR pp. 678, 830, 993, 1606, 1723, 1999
OCDS Vol. 1 p. 428 (1977)
I.N. p. 351
REM p. 854
Fischer, F.G., Roch, J and Kottler, A.; US Patent 3,031,450; April 24, 1962; assigned to Dr. Karl Thomae GmbH, Germany

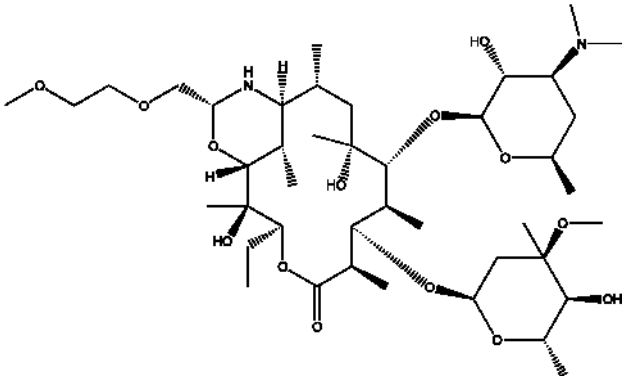
DIRITHROMYCIN

Therapeutic Function: Antibacterial

Chemical Name: (9S)-9-Deoxo-11-deoxy-9,11-[imino[(1R)-2-(2-methoxyethoxy)-ethylidene]oxy]erythromycin

Common Name: Dirithromycin

Structural Formula:



Chemical Abstracts Registry No.: 62013-04-1

Trade Name	Manufacturer	Country	Year Introduced
Dinabac	Eli Lilly	USA	-
Dynabac	Eli Lilly	France	-
Dynabac	Bock Pharmacal	USA	-
Dirithromycin	Hunan Jiudian Pharmaceutical Co.,Ltd.	China	-

Raw Materials

2-(2-Methoxyethoxy)acetaldehyde dimethyl acetal
4-Toluenesulfonic acid
Erythromycylamine

Manufacturing Process

The reactions were conducted for the synthesis of dirithromycin according to the following procedure. 2-(2-Methoxyethoxy)acetaldehyde dimethyl acetal (12 g, 2.7 eq) was placed in a three-neck flask equipped with a mechanical stirrer and dissolved in 60 ml of acetonitrile containing 4% water. p-Toluenesulfonic acid (200 mg, 0.04 eq) was added and the mixture was stirred under a nitrogen atmosphere for 3 hours at 30°C, after which, the temperature was adjusted to 23°C.

Erythromycylamine (20 g, 1 eq) was added over a 20 minute period and stirring continued for 12-16 hours at 23°C. The reaction mixture was cooled to 0°C for 2 hours and then filtered to recover dirithromycin crystals. The crystals were washed with cold acetonitrile and dryed in vacuo at 40°C. The

yield of final product was 84.5% with a potency of 95.4% (average of three reactions). Crystalline dirithromycin a condensation product of 2-(2-methoxyethoxy)acetaldehyde dimethyl acetal and erythromycylamine.

References

John M McGill, III; US Patent No. 5,578,713; Nov. 26, 1996; Assigned: Eli Lilly and Company (Indianapolis, IN)

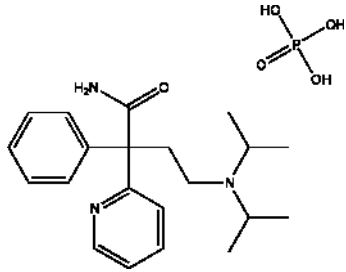
DISOPYRAMIDE PHOSPHATE

Therapeutic Function: Antiarrhythmic

Chemical Name: α-[2-[Bis(1-methylethyl)amino]ethyl]-α-phenyl-2-pyridineacetamide phosphate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 22059-60-5; 3737-09-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Rythmodan	Cassenne	France	1969
Ritmodan	Maestretti	Italy	1970
Rhythmodan	Roussel	UK	1972
Norpace	Searle	UK	1976
Norpace	Searle	W. Germany	1977
Norpace	Searle	US	1977
Rythmodul	Roussel	W. Germany	1977
Rythmodan	Hoechst-Roussel	Switz.	1978
Rythmodan	Roussel	Japan	1981
Dirytmin	Astra	Sweden	-
Disaloc	Medica	Finland	-
Rythmical	Unipharm	Israel	-
Rytmilen	Leiras	Finland	-

Raw Materials

Phenylacetonitrile
Sulfuric acid
2-Bromopyridine
Sodium hydroxide
Diisopropylaminoethyl chloride
Phosphoric acid
Sodium amide

Manufacturing Process

To a solution of 35.3 parts of phenylacetonitrile and 47.6 parts of 2-bromopyridine in 175 parts of dry toluene is added 53.4 parts of sodamide slowly with stirring over a period of 45 minutes. The resultant mixture is stirred at 100°C for 2 hours before it is cooled and the excess sodamide is decomposed by the addition of water. The toluene layer is separated and washed with water to remove excess alkali. The toluene solution is extracted with 6 N hydrochloric acid and the acid extract is made alkaline and then extracted with toluene. The toluene solution is dried over sodium sulfate and the solvent is evaporated. Recrystallization of the residue from alcohol-hexane gives α-phenyl-2-pyridineacetonitrile melting at about 87-88°C.

To a solution of 41 parts of α-phenyl-2-pyridineacetonitrile in 350 parts of dry toluene is added 9.2 parts of sodamide and the mixture is stirred and heated at 90°C for 30 minutes. Heating is stopped and a solution of 38.5 parts of 2-diisopropylaminoethyl chloride in 110 parts of dry toluene is added slowly over a period of 30 minutes. The mixture is stirred and refluxed for 6 hours before it is cooled and decomposed by the addition of water. The toluene layer is separated and washed with water and extracted with 6 N hydrochloric acid. The acid extract is made alkaline and extracted with toluene. The toluene solution is washed with water and dried and the solvent is evaporated. Distillation of the residue gives 4-diisopropylamino-2-phenyl-2-(2-pyridyl)-butyronitrile boiling at about 145°-160°C at 0.3 mm pressure.

A solution of 27.2 parts of 4-diisopropylamino-2-phenyl-2-(2-pyridyl)butyronitrile in 200 parts of concentrated sulfuric acid is heated on a steam bath for 4 hours and then poured onto ice. The resultant mixture is alkalized with 10 N sodium hydroxide, and the pH is adjusted to 6 by the addition of acetic acid. The solution is washed once with benzene before it is alkalized again with 10 N sodium hydroxide solution. The resultant mixture is extracted with benzene, and the solvent is evaporated from the benzene extract. The resultant residue is dissolved in ethanol and the alcohol solution is treated with charcoal and filtered. Evaporation of the solvent leaves a residue which is recrystallized from hexane to give 4-diisopropylamino-2-phenyl-2-(2-pyridyl)butyramide melting at about 94.5-95°C. It may be converted to the phosphate with phosphoric acid.

References

Merck Index 3378
Kleeman and Engel p. 332
PDR pp. 673, 830, 993, 1691
OCDS Vol. 2 p. 81 (1980) and 3,41 (1984)
DOT 6 (6) 213 (1970)
I.N. p. 352
REM p. 858

Cusic, J.W. and Sause, H.W.; US Patent 3,225,054; December 21, 1965; assigned to G.D. Searle and Co.

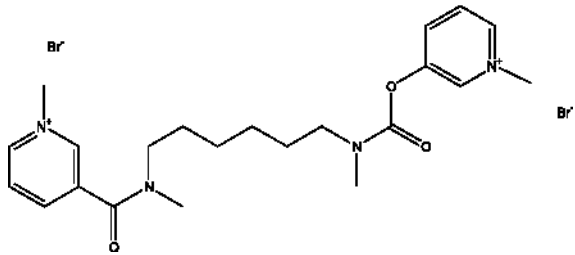
DISTIGMINE BROMIDE

Therapeutic Function: Cholinesterase inhibitor

Chemical Name: 3,3'-[1,6-Hexanediylbis[(methylimino)carbonyl]oxy]bis-[1-methylpyridinium] dibromide

Common Name: Hexamarium bromide

Structural Formula:



Chemical Abstracts Registry No.: 15876-67-2

Trade Name	Manufacturer	Country	Year Introduced
Ubretid	Hormonchemie	W. Germany	1966
Ubretid	Berk	UK	-
Ubretid	Lentia	W. Germany	-
Ubretid	Torii	Japan	-

Raw Materials

3-Oxypyridine
Sodium
Methanol
Hexamethylene-bis-(N-methyl carbamic acid chloride)
Methyl bromide

Manufacturing Process

2 parts of sodium are dissolved in 24 parts of methanol and to the solution of sodium methylate formed 8.25 parts of 3-oxypyridine and 90 parts of xylene (mixture of isomers) are added. Then the mixture is distilled in an atmosphere of nitrogen as protecting gas until the boiling point of xylene is reached and the methanol is completely removed. The remainder is brought together with a solution of 11.7 parts of hexamethylene-bis-(N-methyl carbamic acid chloride) in 45 parts of xylene and maintained 4 hours at a temperature of

80°C under vigorous stirring.

After having been cooled it is washed three times in water, three times in a 5% solution of caustic soda, and then another three times in water. The solution in xylene is dried over sodium sulfate and the xylene is completely distilled off in vacuo. Thus 11.0 parts of hexamethylene-bis-(N-methylcarbamic acid-3-pyridyl ester) are obtained.

7.3 parts of hexamethylene-bis-(N-methyl carbamic acid-3-pyridyl ester) are dissolved in 120 parts of acetone, then 22 parts of methyl bromide are added and the mixture is left to stand at room temperature until the reaction is finished, whereby crystals are precipitated. The reaction product after being drawn off and dried (9.9 parts) can be purified by dissolving in acetic acid and precipitating with methyl ethyl ketone. The hexamethylene-bis-(N-methyl carbamic acid-3-pyridyl ester bromomethylate) has a micro melting point between 147°C and 150°C.

References

Merck Index 3380
Kleeman and Engel p. 332
I.N. p. 353
Schmid, O.; US Patent 2,789,981; April 23, 1957; assigned to Oesterreichische Stickstoffwerke A.G. (Austria)

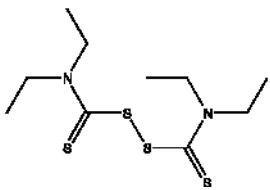
DISULFIRAM

Therapeutic Function: Alcohol deterrent

Chemical Name: Tetraethylthioperoxydicarbonic diamide

Common Name: Tetraethyl thiuram disulfide

Structural Formula:



Chemical Abstracts Registry No.: 97-77-8

Trade Name	Manufacturer	Country	Year Introduced
Esperal	Millot Solac	France	1950
Antabuse	Ayerst	US	1951
Abstenil	Sintesina	Argentina	-

Trade Name	Manufacturer	Country	Year Introduced
Abstinyl	Pharmacia	Sweden	-
Antabus	Tosse	W. Germany	-
Antabuse	Ethnor	Australia	-
Antabuse	Crinos	Italy	-
Antabuse D	Tokyo Tanabe	Japan	-
Antietil	Italfarmaco	Italy	-
Antivitium	Reder	Spain	-
Aversan	A.F.I.	Norway	-
Nocbin	Tokyo Tanabe	Japan	-
Ro-Sulfiram	Robinson	US	-
Tetidis	Krka	Yugoslavia	-

Raw Materials

Diethyl amine
Sodium hydroxide
Carbon bisulfide
Hydrogen peroxide

Manufacturing Process

Disulfiram may be made by the reaction of diethyl amine with carbon disulfide in the presence of sodium hydroxide. The $(C_2H_5)_2NCSSNa$ intermediate is oxidatively coupled using hydrogen peroxide to give disulfiram.

References

Merck Index 3382
Kleeman and Engel p. 333
PDR pp. 611, 830, 1606
OCDS Vol. 1 p. 223 (1977)
DOT 10 (9) 324 (1974)
I.N. p. 353
REM p. 1070
Adams, H.S. and Meuser, L.; US Patent 1,782,111; November 18, 1930; assigned to The Naugatuck Chemical Company
Bailey, G.C.; US Patent 1,796,977; March 17, 1931; assigned to The Roessler and Hasslacher Chemical Company

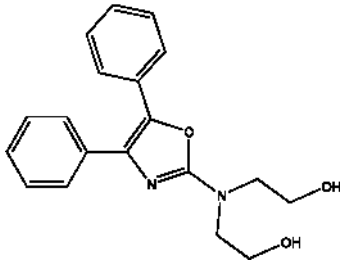
DITAZOL

Therapeutic Function: Antiinflammatory

Chemical Name: 2,2'-[(4,5-Diphenyl-2-oxazolyl)imino]diethanol

Common Name: Diethamphenazol

Structural Formula:



Chemical Abstracts Registry No.: 18471-20-0

Trade Name	Manufacturer	Country	Year Introduced
Ageroplas	Serona	Italy	1973

Raw Materials

2-Chloro-4,5-diphenyl oxazole
Diethanolamine

Manufacturing Process

A solution of 5.1 grams 2-chloro-4,5-diphenyl-oxazole, 6.3 grams diethanolamine and 50 ml absolute ethanol was refluxed for 4 hours. The solvent was stripped at 1 mm and the oily residue was added at 60°C to 100 ml 50% ethanol; by cooling the hydro-alcoholic solution, 4.5 grams of 2-bis(β-hydroxyethyl)amino-4,5-diphenyl-oxazole was obtained (yield, 69.5%). The product crystallized from ethyl ether + petroleum ether, with a MP of 96 to 98°C.

References

Merck Index 3386
DOT 10 (4) 135 (1974)
I.N. p. 354
Marchetti, E.; US Patent 3,557,135; January 19, 1971; assigned to Istituto Farmacologico Serono SpA, Italy

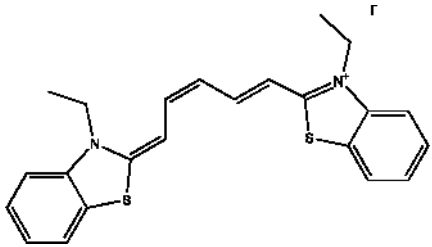
DITHIAZANINE IODIDE

Therapeutic Function: Anthelmintic

Chemical Name: 3-Ethyl-2-[5-[3-ethyl-2-(3H)-benzothiazolinylidene]-1,3-pentadienyl]benzothiazolium iodide

Common Name: 3,3'-Diethylthiacarbocyanine iodide

Structural Formula:



Chemical Abstracts Registry No.: 514-73-8

Trade Name	Manufacturer	Country	Year Introduced
Delvex	Lilly	US	1958
Abminthic	Pfizer	US	1959
Dilombrin	Pfizer	-	-
D.I.M.	Mediphar	Congo	-
Elmizin	Bouty	Italy	-
Nectocyd	Pfizer	-	-
Ossiurene	A.M.S.A.	Italy	-
Partel	Lilly	-	-
Termid	Lilly	-	-

Raw Materials

1-Methylbenzthiazole ethiodide
β-Ethyl thioacrolein diethyl acetal

Manufacturing Process

3.05 g of 1-methylbenzthiazole ethiodide, 1.11 g of β-ethyl thio acrolein diethyl acetal and 15 cc of pyridine were mixed and boiled gently under reflux for 15 minutes. The reaction mixture was then poured into an aqueous solution of potassium iodide. The dye was precipitated and was filtered off, and washed with ethyl alcohol and ether. Recrystallization from methyl alcohol solution yielded the dye as green needles. Melting point 248°C with decomposition.

References

Merck Index 3388
OCDS Vol. 1 p. 327 (1977)
I.N. p. 354
Kendall, J.D. and Edwards, H.D.; US Patent 2,412,815; December 17, 1946; assigned to Ilford, Ltd.

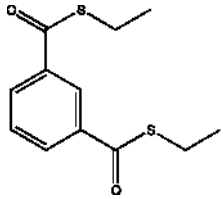
DITOPHAL

Therapeutic Function: Leprostatic

Chemical Name: 1,3-Dithioisophthalic acid, S,S-diethyl ester

Common Name: Ditophal

Structural Formula:



Chemical Abstracts Registry No.: 584-69-0

Trade Name	Manufacturer	Country	Year Introduced
ICI 15688	ICI	-	-
Etisul	Imperial Chemical Industries Limited	-	-

Raw Materials

Diethyl sulfate
Isophthalylchloride
Sodium hydrogen sulfide

Manufacturing Process

33 parts of diethyl sulphate are added to 20 parts of diethiolisophthalic acid (MP 245°-247°C prepared by the reaction of isophthalylchloride with sodium hydrogen sulphide) in 125 parts of 8% aqueous sodium hydroxide solution at 20°C and the mixture is then heated at 40°-50°C during one hour. The mixture is then cooled and extracted with 250 parts of benzene, in three portions. The benzene extract is washed with water and dried and the benzene is distilled. The residue is then distilled under reduced pressure to give diethyl dithioisophthalate, BP 210°-215°C/15 mm.

References

Driver G.W. et al.; G.B. Patent No. 791,734; Oct. 29, 1954

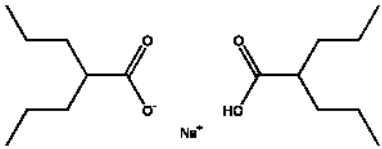
DIVALPROEX SODIUM

Therapeutic Function: Anticonvulsant

Chemical Name: Pentanoic acid, 2-propyl-, sodium (2:1)

Common Name: Divalproex sodium; Natrii hydrogenii valproas; Semisodium valproate; Sodium hydrogen valproate; Valproate semisodium

Structural Formula:



Chemical Abstracts Registry No.: ; 76584-70-8; 99-66-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Depakote	Abbott	-	-
Depakote Sprinkle	Abbott	-	-
Diproex ER	Neu-Foreva	India	-
Epival	Abbott	Canada	-

Raw Materials

Propylbromide
Cyanacetic acid
Sodium

Manufacturing Process

Dipropyl acetic acid or valproic acid may be prepared the next way. Propylbromide is mixed with cyanacetic acid in the presence of sodium ethylate, made from absolute ethanol and sodium. By that prepared α,α-dipropylcyanacetic acid ethyl ester is saponified with equimolecular amounts of NaOH to give dipropylacetonitril. The desired dipropylacetic acid is produced by saponification of dipropylacetonitryl with aquatic NaOH. It is colorless liquid. BP 219°-220°C.

Sodium salt of this acid may be prepared by adding of equivalent of NaOH.

References

Pharmazeutische Wirkstoffe; Synthesen Patente Anwendungen; von A. Kleemann und J. Engel; s.940, 1982, Georg Thime Verlag Stuttgart
Meunier H.E. et al.; US Patent No. 3,325,361; June 13, 1967; Assigned to Chemerton Corporation, Chicago, Ill., a corporation of Delaware

Dictionary of organic compounds v.1, p. 1052, 1946; ed. I. Heiebron and H.M. Bunbury; Jones and Jones

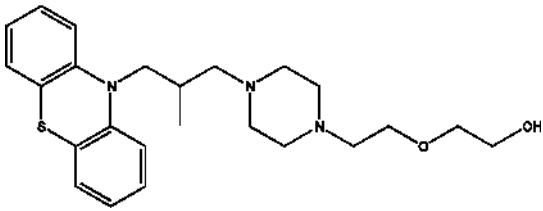
DIXYRAZINE

Therapeutic Function: Tranquilizer

Chemical Name: 2-[2-[4-[2-Methyl-3-(10H-phenothiazin-10-yl)propyl]-1-piperazinyl]ethoxy]ethanol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 2470-73-7

Trade Name	Manufacturer	Country	Year Introduced
Esucos	UCB Chemie	W. Germany	1962
Esucos	USB	Italy	1962
Esucos	USB	France	1964
Esocalm	Assia	Israel	-
Roscal	Rosco	Denmark	-

Raw Materials

Phenothiazine
Sodium amide
1-Chloro-2-methyl-3-bromopropane
1-[2-(2-Hydroxyethoxy)ethyl]piperazine

Manufacturing Process

To a suspension of sodamide in liquid ammonia and made from sodium in liquid ammonia, there is added fractionally and with stirring phenothiazine. After an hour there is added thereto, while maintaining the stirring, 1-chloro-2-methyl-3-bromopropane, then 700 cc of toluene. The ammonia is then driven off and heating under reflux is carried out for one hour.

After cooling, water is added and the solution then decanted. The toluene phase is then evaporated in vacuo to constant weight. The residue is constituted of 10-(2-methyl-3-chloro-propyl)-phenothiazine containing a

certain quantity of phenothiazine which has not reacted. As this product is not readily soluble in petroleum ether, it is possible to eliminate it by extraction by means of this solvent.

By operating in this manner 10-(2-methyl-3-chloro-propyl)phenothiazine is obtained. A mixture of l0-(2-methyl-3-chloro-propyl)phenothiazine and 1-[2-(2-hydroxyethoxy)ethyl]piperazine is then heated at 110°-120°C for 20 hours. After cooling, the reaction product is dissolved in 200 cc of benzene and the solution washed several times with water.

The benzene phase is then extracted by dilute hydrochloric acid. The acid aqueous phase is decanted, it is made distinctly alkaline and then extracted with benzene. The benzene extract is dried and evaporated in vacuo. The condensation product could not be crystallized. It may be converted into the dihydrochloride which, after recrystallization from isopropanol, melts at 192°C.

References

Merck Index 3403
Kleeman and Engel p. 334
OCDS Vol. 1 p. 384 (1977)
I.N. p. 356
Morren, H.; British Patent 861,420; February 22, 1961

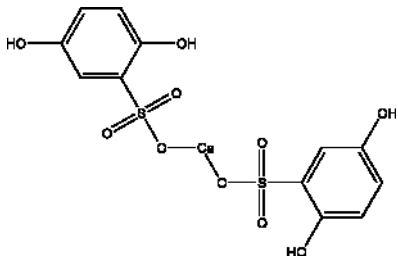
DOBESILATE CALCIUM

Therapeutic Function: Vasodilator

Chemical Name: 2,5-Dihydroxybenzenesulfonic acid calcium salt

Common Name: Hydroquinone calcium sulfonate

Structural Formula:



Chemical Abstracts Registry No.: 20123-80-2

Trade Name	Manufacturer	Country	Year Introduced
Doxium	Carrion	France	1971

Trade Name	Manufacturer	Country	Year Introduced
Dexium	Delalande	W. Germany	1971
Doxium	Delalande	Italy	1973
Dobesiphar	Farmila	Italy	-
Doxi-OM	O.M.	Switz.	-
Doxytrex	O.M.	Switz.	-
Romiven	Roche	-	-

Raw Materials

1,4-Benzoquinone
Calcium bisulfite

Manufacturing Process

To an ether solution of 108 grams 1,4-benzoquinone, maintained below 0°C, one adds an also very cold solution of 102 grams of pure calcium bisulfite as a 50% solution in distilled water. The addition is made carefully so as to maintain a very low temperature (0° to 4°C) in the vessel, and under stirring so as to mix the water and ether phase.

At the end of the addition, an almost colorless ether layer swims on the surface of the strongly colored water layer. After removal of the ether layer, the water layer is concentrated to dryness under vacuum and a stream of an inert gas. An earthy precipitate is formed, which after recrystallization yields 100 grams of hydroquinone calcium sulfonate, which decomposes without melting above 250°C.

The product consists of very small crystals having a powdery aspect and a pink color which deepens on contact with air. This product is very soluble in water and alcohol, and insoluble in ether.

References

Merck Index 3406
Kleeman and Engel p. 135
I.N. p. 356
Esteve-Subirana, A.; US Patent 3,509,207; April 28, 1970; assigned to Laboratories Om Societe Anonyme, Switzerland

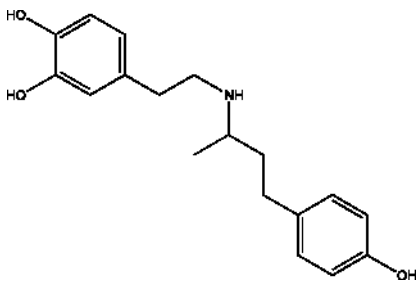
DOBUTAMINE

Therapeutic Function: Cardiotonic

Chemical Name: 3,4-Dihydroxy-N-[3-(4-hydroxyphenyl)-1-methylpropyl]-β-phenethylamine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 34368-04-2; 52663-81-4 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Dobutrex	Lilly	UK	1977
Dobutrex	Lilly	US	1978
Dobutrex	Lilly	W. Germany	1978
Dobutrex	Shionogi	Japan	1982
Dobutrex	Lilly	Italy	1983
Dobuject	Leiras	Finland	-
Inotrex	Lilly	-	-

Raw Materials

Homoveratrylamine	4-(p-Methoxyphenyl)-3-buten-2-one
Acetic acid	Hydrogen
Hydrogen bromide	Hydrogen chloride

Manufacturing Process

In a stainless steel hydrogenation bottle were placed 17.6 g (0.1 mol) of 4-(p-methoxyphenyl)-3-buten-2-one, 80 ml of ethyl acetate, and 1 g of Raney nickel catalyst. The hydrogenation bottle was attached to a Paar low-pressure hydrogenation apparatus and the solution was hydrogenated under an initial hydrogen pressure of 50 psi. The hydrogenation was carried out at room temperature and after about 12 hours one equivalent of hydrogen had been absorbed. The catalyst was filtered from the reduction mixture and 18.1 g (0.1 mol) of homoveratrylamine were added to the reduction mixture.

To the reduction mixture was then added 3.5 g of 5% palladium on carbon catalyst and the mixture was hydrogenated under a hydrogen pressure of 50 psi at room temperature for 12 hours. The catalyst was removed by filtration and the filtrate was evaporated to a small volume. The concentrated filtrate was dissolved in diethyl ether and the ethereal solution was saturated with anhydrous hydrogen chloride. The reduction product, 3,4-dimethoxy-N-[3-(4-methoxyphenyl)-1-methyl-n-propyl]phenethylamine was precipitated as the hydrochloride salt. The salt was filtered and recrystallized from ethanol

melting at about 147°C to 149°C.

To a solution of 101.2 g of the trimethoxy secondary amine, obtained as described above, in 3,060 ml of glacial acetic acid was added 1,225 ml of 48% hydrobromic acid and the reaction mixture heated at the reflux temperature for 4 hours. The reaction mixture was then cooled and evaporated to a small volume. The crystalline residue which formed was filtered and dried in vacuo. The dried crystalline residue was then triturated with ethyl acetate and redried to yield 97.3 g of crude crystalline material. The crude product was dissolved in 970 ml of warm water to obtain a yellow solution. To the solution was added successively by dropwise addition 75 ml of 1 N and 75 ml of 2 N hydrochloric acid. Following the dropwise addition, the solution was allowed to stir with ice cooling. The impurities which precipitated were removed by filtration through a gauze filter. Concentrated hydrochloric acid was then added dropwise. When approximately 50 to 75 ml of the concentrated acid had been added with ice bath cooling a pale yellow oil precipitated along with a while solid precipitate. With continued stirring of the cold solution, the pale yellow oil crystallized.

The cold solution was then allowed to stand overnight and all crystalline material filtered through a sintered glass filter. The filtrate was treated with an additional 300 ml of concentrated hydrochloric acid to yield a heavy white precipitate. The precipitate was filtered, dried and combined with the initial precipitate obtained as described above. The combined precipitated product, 3,4-dihydroxy-N-[3-(4-hydroxyphenyl)-1-methyl-n-propyl-β-phenethylamine hydrochloride, had a melting point of about 184°C to 186°C after recrystallization from boiling 4 N hydrochloric acid.

References

Merck Index 3407
DFU 2 (9) 579 (1977)
Kleeman and Engel p. 334 |
PDR p. 1047
OCDS Vol. 2 p. 53 (1980)
DOT 14 (10) 433 (1978)
I.N. p. 357
REM p. 882
Tuttle, R.R. and Mills, J.; US Patent3,987,200; October 19, 1976; assigned to Eli Lilly and Co.

DOCETAXEL

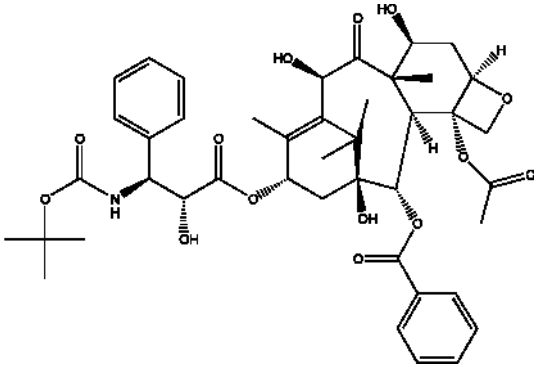
Therapeutic Function: Antitumor

Chemical Name: 10-Deacetyl-N-debenzoyl-N-[(1,1-dimethylethoxy)carbonyl] taxol

Common Name: Docetaxel; Docetaxol

Chemical Abstracts Registry No.: 114977-28-5

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Daxotel	Dabur Pharmaceuticals Ltd.	India	-
Docetaxel	Aventis Pharmaceuticals	USA	-
RP 56976	Aventis Pharmaceuticals	USA	-
Taxorene	Aventis Pharma	USA	-
Taxotere	Rhone-Poulenc Rorer	France	-

Raw Materials

Taxol
Chlorotriethylsilane
Zirconocene chloride hydride

Manufacturing Process

Taxol, a material occurring in nature, and extracted from Taxus brevifolia (i.e. the Pacific yew tree). It consists of the A, B and C variants. Taxol is not water soluble, thereby complicating its delivery in vivo for therapeutic purposes.

A sample of Taxol (14.7 g, 17 mmol) was dissolved in pyridine (150 mL) and chlorotriethylsilane (23.03 g, 147 mmol) was added. The reaction was stirred at 25°C under N_2. After 20 hours the reaction appeared complete by TLC analysis (7% MeOH/CH_2Cl_2). The mixture was concentrated to remove the pyridine. The residue was dissolved in CH_2Cl_2 and washed with water, 10% $CuSO_4$, $NaHCO_3$ and brine successively. The organic layer was dried over $MgSO_4$, and concentrated to yield 20.89 g of the crude 2,7'-bis(triethylsilyl) Taxol. A portion of crude 2',7-bis(triethylsilyl) Taxol (14.50 g, 13.4 mmol) was dissolved in dry THF (150 mL). Zirconocene chloride hydride (7.75 g, 30.2 mmol) was added. The reaction was stirred at 25°C under N_2. After 20 hours the reaction appeared complete by TLC analysis. The mixture was poured into

cold hexanes, and the resulting precipitated Zr complexes were filtered off. The solution was concentrated to yield 17 g of the crude 2,7'-bis(triethylsilyl) Taxol imine. A portion of crude 2',7-bis(triethylsilyl) Taxol imine (8.36 g) was dissolved in 1% HCl/EtOH (180 mL) and the reaction was stirred at 25°C for 20 hours. The reaction appeared complete by TLC analysis. The mixture was poured into 800 mL of water and washed with hexane (180 mL times 3). The aqueous layer was neutralized with $NaHCO_3$ to pH=7.0. The product was extracted with CH_2Cl_2. The organic layer was removed and concentrated to a solid. Silica gel chromatography (5% MeOH/CH_2Cl_2) yielded Taxol primary amine (2.41 g, 52% overall yield based on 5 g of Taxol used). Melting point 160°C-162°C.

A sample of Taxol primary amine (100 mg, 0.13 mmol) was dissolved in CH_2Cl_2 (10 mL) and HCl (15 mM in Et_2O; 10 ml, 150 mmol) was added. The reaction was stirred at 25°C for 2 minutes. The mixture was concentrated to remove the solvents. The residue was redissolved in CH_2Cl_2 and precipitated in hexane. Filtration yielded 85 mg of Taxol PA (PA-primary amine) HCl (83%). Melting point 65°C. A sample of Taxol PA HCl (50 mg, 0.064 mmol) was dissolved in 0.5 ml of water. It was neutralized to pH 7.0 by addition of saturated $NaHCO_3$, followed by extraction with CH_2Cl_2. The organic layer was concentrated and chromatographed (3% MeOH/CH2Cl2was used as mobile phase) to yield 30 mg of Taxol primary amine (63% yield). The ^1H NMR and LRMS data agree well with a standard sample of Taxol primary amine.

Trimethylsilyl- and trichlorethoxycarbonyl-protecting group can be used. A mixture of impure Taxol A, B, C can be converted Taxol primary amine, which then can be converted to Taxol A or docetaxel.

References

Murray C.K. et al.; US Patent No. 5,679,807; Oct. 21, 1997; Assigned: Hauser, Inc. (Boulder, CO)

DOCUSATE CALCIUM

Therapeutic Function: Stool softener

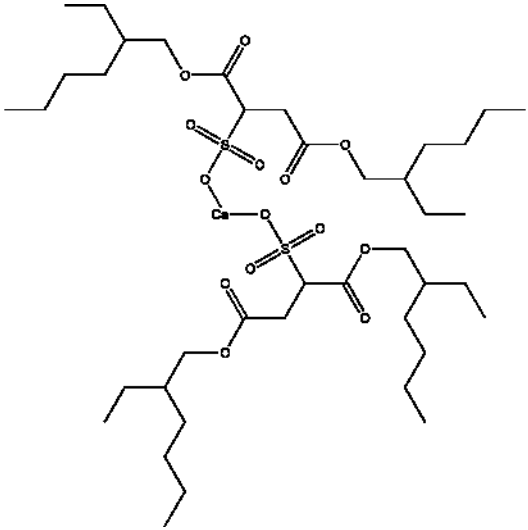
Chemical Name: Sulfobutanedioic acid 1,4-bis(2-ethylhexyl)ester calcium salt

Common Name: Dioctyl calcium sulfosuccinate

Chemical Abstracts Registry No.: 128-49-4

Trade Name	Manufacturer	Country	Year Introduced
Surfak	Hoechst	US	1959
Regutol	Schering	US	1981
Doxidan	Hoechst	-	-
Dioctocal	Schein	US	-

Structural Formula:



Raw Materials

Dioctyl sodium sulfosuccinate
Calcium chloride

Manufacturing Process

88 g of dioctyl sodium sulfosuccinate is first dissolved in 100 cc of isopropanol and 25 g of calcium chloride is dissolved in 50 cc of methanol. The solutions are then mixed and stirred for about 3 hours and then cooled with ice. The sodium chloride which precipitates in the cool mixture is removed by filtration and most of the alcohol is evaporated from the resulting filtrate with heat. The liquid remaining is poured into 88 cc of water, and the resulting precipitate washed with water until free of chloride ion. The washed calcium salt is then dried.

References

Merck Index 3408
PDR pp. 938, 945, 1606
I.N. p. 357
REM p. 805
Klotz, L.J.; US Patent 3,035,973; May 22, 1962; assigned to Lloyd Brothers, Inc.

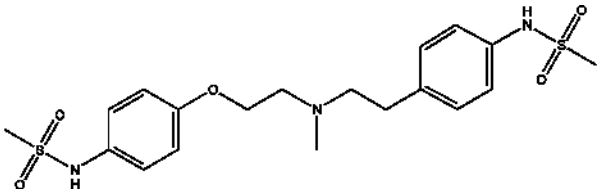
DOFETILIDE

Therapeutic Function: Antiarrhythmic

Chemical Name: Methanesulfonamide, N-(4-(2-(methyl(2-(4-((methylsulfonyl)amino)phenoxy)ethyl)amino)ethyl)phenyl)-

Common Name: Dofetilide

Structural Formula:



Chemical Abstracts Registry No.: 115256-11-6

Trade Name	Manufacturer	Country	Year Introduced
Dofetilide	Reyoung Pharma. Co., Ltd.	China	-
Tikosyn	Pfizer	USA	-
Xelide	Pfizer	USA	-

Raw Materials

N-Methyl-4-nitrophenethylamine
2-[4-Nitrophenoxy]ethyl chloride
Hydrogen
Methanesulfonic anhdyride
Potassium carbonate
Sodium iodide
Nickel Raney

Manufacturing Process

To a solution of N-methyl-4-nitrophenethylamine (1.5 g) (J.O.C., [1956], 21, 45) and 2-[4-nitrophenoxy]ethyl chloride (1.55 g) (C.A., [1955], 49, 3163e) in acetonitrile (50 ml) was added potassium carbonate (1.25 g) and sodium iodide (1.2 g) and the suspension was stirred at reflux for 72 hours. After evaporation to dryness, the residual oily solid was partitioned between a 2 N aqueous sodium bicarbonate solution and ethyl acetate. After two further extractions with ethyl acetate, the organic portions were combined, washed with a saturated aqueous brine solution, dried over magnesium sulfate, filtered and evaporated. The resultant orange solid (2.7 g) was crystallised from ethanol to give 1-(4-nitrophenoxy)-2-[N-methyl-N-(4-nitrophenethyl)amino]ethane (1.9 g), m.p. 74°C.

A solution of 1-(4-nitrophenoxy)-2-[N-methyl-N-(4-nitrophenethyl)amino]ethane (1.5 g) in ethanol (100 ml) was stirred for 16 hours at room temperature under three atmospheres of hydrogen in the presence of Raney nickel. The reaction mixture was filtered and evaporated to dryness. The residual oil was re-dissolved in ether, filtered and evaporated to give a yellow solid (1.1 g), which was crystallised from ethyl acetate/petroleum ether (b.p. 60-80°C) to give 1-(4-aminophenoxy)-2-[N-(4-aminophenethyl)-N-methylamino]ethane (0.9 g), m.p. 73-74°C.

A solution of 1-(4-aminophenoxy)-2-[N-(4-aminophenethyl)-N-methylamino]ethane (0.75 g) and methanesulphonic anhdyride (1.0 g) in dry methylene chloride (50 ml) was stirred at room temperature overnight. After evaporation, the resultant oil was partitioned between a 2 N aqueous sodium bicarbonate solution and ethyl acetate. After two further extractions with ethyl acetate, the organic portions were combined, dried over magnesium sulfate, filtered and evaporated. The resultant colourless solid (1.2 g) was crystallised from ethyl acetate/methanol to give methanesulfonamide, N-(4-(2-(methyl(2-(4-((methylsulfonyl)amino)phenoxy)ethyl)amino)ethyl)phenyl)-, (0.6 g), m.p. 147-149°C.

References

Cross P.E. et al.; US Patent No. 5,079,248; Jan. 7, 1992 ; Assigned to Pfizer Inc. (New York, NY)

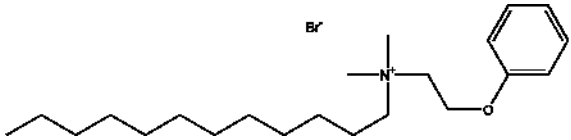
DOMIPHEN BROMIDE

Therapeutic Function: Topical antiinfective

Chemical Name: N,N-Dimethyl-N-(2-phenoxyethyl)-1-dodecanaminium bromide

Common Name: Phenododecinium bromide

Structural Formula:



Chemical Abstracts Registry No.: 538-71-6

Trade Name	Manufacturer	Country	Year Introduced
Bradosol	Ciba	US	1958
Bradex-Vioform	Ciba	W. Germany	-
Brado	Ciba Geigy	Japan	-
Bradoral	Ciba	Italy	-
Neo-Bradoral	Ciba	Switz.	-
Oradol	Ciba Geigy	Japan	-

Raw Materials

β-Phenoxyethyl dimethylamine
Dodecyl bromide

Manufacturing Process

7 parts of β-phenoxyethyl-dimethylamine are heated for 2 hours on the boiling water-bath with 11 parts of dodecyl bromide. A good yield of β-phenoxy-ethyl-dimethyl-dodecyl-ammonium bromide is obtained which, after recrystallization from acetone, melts at 112°C. It is a white crystalline powder which dissolves easily in water to give a neutral reaction.

References

Merck Index 3424
Kleeman and Engel p. 335
I.N. p.. 359
Hartmann, M. and Bosshard, W.; US Patent 2,581,336; January 8, 1952; assigned to Ciba Pharmaceutical Products, Inc.

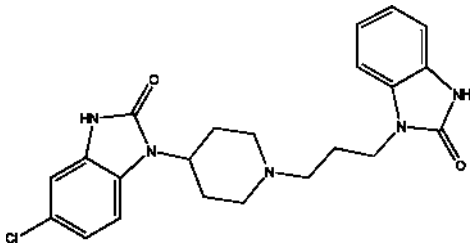
DOMPERIDONE

Therapeutic Function: Antiemetic

Chemical Name: 5-Chloro-1-[1-[3-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)-propyl]-4-piperidinyl]-1,3-dihydro-2H-benzimidazol-2-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 57808-66-9

Trade Name	Manufacturer	Country	Year Introduced
Motilium	Cilag	Switz.	1979
Motilium	Janssen	W. Germany	1979
Motilium	Janssen	Italy	1981
Motilium	Janssen	UK	1982
Nauselin	Kyowa Hakko	Japan	1982
Motilium	Janssen-Le Brun	France	1983
Euciton	Roux-Ocefa	Argentina	-
Moperidona	Sidus	Argentina	-

Raw Materials

1-(3-Chloropropyl)-1,3-dihydro-2H-benzimidazol-2-one
5-Chloro-1,3-dihydro-l-(4-piperidinyl)-2H-benzimidazol-2-one

Manufacturing Process

A mixture of 2.3 parts of 1-(3-chloropropyl)-1,3-dihydro-2H-benzimidazol-2-one, 2.5 parts of 5-chloro-1,3-dihydro-l-(4-piperidinyl)-2H-benzimidazol-2-one, 3.2 parts of sodium carbonate, 0.1 part of potassium iodide and 80 parts of 4-methyl-2-pentanone is stirred and refluxed for 24 hours. The reaction mixture is cooled to room temperature and water is added. The undissolved product is filtered off and purified by column chromatography over silica gel using a mixture of trichloromethane and 10% methanol as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from 4-methyl-2-pentanone. The product is filtered off and recrystallized from a mixture of N,N-dimethylformamide and water, yielding 1.3 parts (30%) of 5-chloro-1-[1-[3-(1,3-dihydro-2-oxo-2H-benzimidazol-1-yl)propyl]-4-piperidinyl]-1,3-dihydro-2H-benzimidazol-2-one; MP 242.5°C.

References

Merck Index 3425
DFU 2 (10) 661 (1977)
Kleeman and Engel p. 335
OCDS Vol. 3 p. 174 (1984)
DOT 17 (1) 19 (1981)
I.N. p. 360
Vanderberk, J., Kennis, L.E.J., Van der Aa, M.J.M.C. and Van Heertum, A.H.M.T.; US Patents 4,066,772; January 3, 1978; 4,110,333; August 29, 1978; 4,126,687; November 21, 1978; 4,126,688; November 21, 1978; 4,160,836; July 10, 1979 and 4,175,129; November

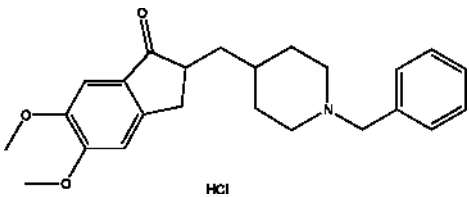
DONEPEZIL HYDROCHLORIDE

Therapeutic Function: Anti-Alzheimer's disease

Chemical Name: 1H-Inden-1-one, 2,3-dihydro-5,6-dimethoxy-2-((1-(phenylmethyl)-4-piperidinyl)methyl)-, hydrochloride

Common Name: Donepezil hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 120011-70-3

Trade Name	Manufacturer	Country	Year Introduced
Aricept	Pfizer	France	-
Aricept	Eisai Co.	Japan	-
Aricept	Wyeth-Ayerst	USA	-
Donecept	Protec	-	-
Donepezil hydrochloride	Eisai-Pfizer	USA	-
Eranz	Wyeth-Ayerst	USA	-
Memorit	Unipharm	Israel	-

Raw Materials

5,6-Dimethoxy-1-indanone
1-Benzyl-4-piperidinecarboaldehyde
Hexamethyl-phosphoric amide
Butyl lithium
Diisopropylamine
Palladium on carbon

Manufacturing Process

This reaction was conducted in an argon atmosphere. 2.05 ml of diisopropylamine was added to 10 ml of anhydrous THF, followed by addition of 9.12 ml of a 1.6 M solution of n-butyl lithium in hexane at 0°C. The mixture was stirred at 0°C for 10 min and then cooled to -78°C, and a solution of 2.55 g of 5,6-dimethoxy-1-indanone in 30 ml of anhydrous THF and 2.31 ml of hexamethyl-phosphoric amide were added thereto. The mixture was stirred at -78°C for 15 min, and a solution of 2.70 g of 1-benzyl-4-piperidinecarboaldehyde in 30 ml of anhydrous THF was added thereto. The temperature of the mixture was gradually raised to room temperature, followed by stirring for 2 hr. An aqueous 1% ammonium chloride solution was added thereto, and the organic phase was separated. The water phase was extracted with ethyl acetate, and the organic phases were combined with each other. The combined organic phase was washed with a saturated saline solution, dried over magnesium sulfate, and concentrated in vacuo. The resulting residue was purified by making use of a silica gel column (methylene chloride:methanol=500:1-100:1). The eluate was concentrated in vacuo, and the residue was dissolved in methylene chloride. A 10% solution of hydrochloric acid in ethyl acetate was added to the resulting solution, followed by concentration in vacuo to obtain a crystal, which was recrystallized from methanol/IPE to obtain 3.40 g (yield: 62%) 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-ylidenyl]methylpiperidine HCl; melting point 237°-238°C.

4 g of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-ylidenyl]methylpiperidine was dissolved in 16 ml of THF, followed by addition of 0.04 g of 10% palladium-carbon. The mixture was hydrogenated at room temperature under atmospheric pressure for 6 hr. The catalyst was filtered off, and the filtrate was concentrated in vacuo. The residue was purified by making use of a silica gel column (methylene chloride:methanol=50:1). The eluate was concentrated in vacuo, and the residue was dissolved in methylene chloride. A 10% solution of hydrochloric acid in ethyl acetate was added to the resulting solution, followed by concentration in vacuo to obtain a crystal, which was recrystallized from methanol/IPE to obtain 0.36 g (yield: 82%) of the 1-

benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl-methylpiperidine]-hydrochloride (donepezil HCl) having the melting point: 211°C-212°C (dec.).

Later it was described the synthesis of the donepezil HCl from 5,6-dimethoxy-2-(pyridin-4-yl)methylene-indan-1-one by the reaction with H_2 over platinum dioxide at room temperature in acetic acid-methanol mixture to give 4-[(5,6-dimethoxy-1-indanon)-2-yl]methylpiperidine. The last one yielded donepesyl HCl by refluxing with benzyl bromide and triethylamine for 4 hours with the following addition of methanolic HCl (10%).

References

Sugimoto H. et al.; US Patent No. 4,895,841; Jan. 23, 1990; Assigned: Eisai Co., Ltd. (Tokyo, JP)
Imai A. et al.; US Patent No. 5,985,864; Nov. 16, 1999; Assigned: Eisai Co., Ltd. (Tokyo, JP)
Vidyadhar J.S. et al.; US Patent No. 6,649,765 B1; Nov. 18, 2003; Assigned: USV Limited, BSD MARG. (Maharashtra, IN)

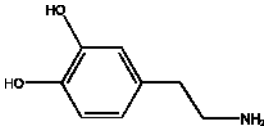
DOPAMINE

Therapeutic Function: Cardiotonic

Chemical Name: Pyrocatechol, 4-(2-aminoethyl)-

Common Name: Dopamine; Hydroxytyramine

Structural Formula:



Chemical Abstracts Registry No.: 51-61-6

Trade Name	Manufacturer	Country	Year Introduced
Dopmin	Orion Corporation	Finland	-

Raw Materials

3,4-Dimethoxyphenylethyl amine hydrochloride
Hydrochloric acid

Manufacturing Process

To 5 g of 3,4-dimethoxyphenylethyl amine HCl was added 20 ml of concentrated HCl. The mixture was heated at 150°C for 2 hours. Then it was

cooled to ambient temperature and decolored with a charcoal, filtered and deluted with ethanol. The resulting crystals was isolated and re-crystallized from acetone. The melting point of 3,4-dihydroxyphenylethylamine hydrochloride is 174°-175°C. The free base may be prepared from this product by adding of equivalent of NaOH or any other alkali.

References

Rosenmund K.W.; Kaiserliches Patentamt No 247906, kl.12q, gr. 32; 10 June 1912
Shopf, Bayerle; Lieb. Ann. Chem. 513, 196 (1934)

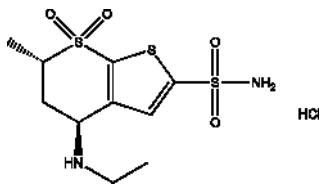
DORZOLAMIDE HYDROCHLORIDE

Therapeutic Function: Antiglaucoma

Chemical Name: 4H-Thieno(2,3-b)thiopyran-2-sulfonamide, 5,6-dihydro-4-(ethylamino)-6-methyl-, 7,7-dioxide, monohydrochloride, (4S,6S)-

Common Name: Dorzalamide hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 130693-82-2

Trade Name	Manufacturer	Country	Year Introduced
Biodrop	Sidus	Argentina	-
Cosopt	Merck Frosst Canada and Co.	Canada	-
Trusopt	Merck Sharp and Dohme	-	-

Raw Materials

Chlorosulfonic acid
Thionyl chloride
Sodium borohydride
Boron trifluoride etherate
Maleic acid
Carbon (Darco KB)

Manufacturing Process

Step A: Sulfuric Acid Ritter Procedure

To a mechanically stirred, cooled (-5°5°C) solution of 6-methyl-7,7-dioxo-4,5,6,7-tetrahydro-7γ^6-trieno-[2,3b]thiopyran-4-ol (hydroxysulfone) (25.0 g, 0.114 mol; 98:2 trans/cis) in acetonitrile (300 mL) was slowly added concentrated sulfuric acid (18 M, 86 mL, 1.52 mol) over a 0.5 h period while maintaining the internal temperature at -5°-5°C. The mixture was allowed to warm to 20°5°C and was stirred at this temperature for 12-18 h, or until the reaction was judged to be complete by HPLC. The reaction was considered complete when less than 1% of hydroxysulfone remained. At the end of the reaction the trans/cis ratio of the acetamidosulfone - (N-(6-methyl-7,7-dioxo-4,5,6,7,-tetrahydro-7γ^6-trieno-[2,3b]thiopyran-4-yl)propionamidewas 92.4:7.6.

After the reaction was complete, the reaction mixture was slowly added to a mechanically stirred, pre-cooled (0°-5°C) quench mixture of ethyl acetate (1.7 L) and water (800 mL). At the same time, 50% (w/w) aqueous sodium hydroxide (185 mL) was added to the quench mixture at such a rate that the pH was maintained between 3-5 and the internal temperature was maintained below 25°C. The pH was then further adjusted to 7.0-7.5 with additional sodium hydroxide, and the mixture stirred for 1 h at 30°C. The mixture was filtered to remove the sodium sulfate, and the filter cake washed with ethyl acetate (300 mL). The filtrate and cake washes were combined, and the mixture partitioned. The aqueous (lower) phase was extracted once with ethyl acetate. The organic (upper) phases were combined and then concentrated in vacuo (10 mBar, 50°C) to a volume of 100 mL. Hexane (300 mL) was added slowly, and the mixture stirred for 1 h at 20°-22°C. The mixture was filtered, and the product cake washed with hexane (1 bed volume). The product was air-dried, then dried in vacuo (100 mBar, nitrogen sweep, 30°-35°C) to constant weight. Yield: 31.0 g (95% based on HPLC wt % purity) of crude acetamidosulfone as a white solid. The crude product also contains a small amount of acetamide and sodium acetate.

Step B: Sulfonylation Procedure

To mechanically stirred, cooled (0°C) chlorosulfonic acid (70 mL, 1.05 mol) was added the crude acetamidosulfonamide (29.7 g, 0.114 mol; 93:7 trans/cis) portionwise at a rate to maintain the internal temperature <20°C. The dark sulfonylation reaction mixture was heated to 50°C for 12 h, or until the reaction was judged to be complete by HPLC. During the reaction hydrogen chloride (0.114 mol) was evolved.

Assay Procedure: An aliquot (0.1 mL) is diluted to 100.0 mL with H_2O and then analyzed by the following HPLC method. Instrument: Spectra Physics 8800. Column: 4.1 times 250 mm Ultrasphere C-8 (Altex Inc.). Eluent A: H_2O (0.1% v/v H_3PO_4). Eluent B: MeCN. Gradient: 97:3 to 35:65 A:B over 25 min. Flow Rate: 2.0 mL/min. Temperature: 45°C. Injection: 10.0 µL. Detection: UV (230 nm). Retention Times: Sulfonic Acid (cis/trans isomers) 5.0 min, Acetamidosulfone (cis isomer) 9.0 min, Acetamidosulfone (trans isomer) 10.0 min. The sulfonylation reaction was considered to be complete when less than 1% of acetamidosulfone (vs. the sulfonic acid - 6-methyl-7,7-dioxo-4,5,6,7,-

tetrahydro-7γ6-trieno-[2,3b]thiopyran -2-sulfonic acid) remained.

Step C: Chlorosulfonylation Procedure

After the Step B reaction was complete, the mixture was cooled to 20°C. Thionyl chloride (70 mL, 0.96 mol) was then slowly added at a rate to control the evolution of hydrogen chloride (0.114 mol) and sulfur dioxide (0.114 mol). Following the addition, the mixture was heated to 50°C for 6 h, or until the reaction was judged to be complete by HPLC. Assay Procedure: An aliquot (0.1 mL) is diluted to 50.0 mL with acetonitrile and then immediately analyzed by the above HPLC method (to minimize hydrolysis of the sufonyl chloride product). Retention Times: Sulfonic Acid (cis/trans isomers) 5.0 min, Sulfonyl Chloride - 6-methyl-7,7-dioxo-4,5,6,7,-tetrahydro-7γ6-trieno-[2,3b]thiopyran-2-sulfonylchloride (cis/trans isomers) 19 min. The reaction was considered to be complete when less than 1% of the sulfonic acid (vs. the sulfonyl chloride product) remained. After the reaction was complete, the mixture was cooled to 15°-20°C, and then metered slowly into vigorously stirred water (1.4 L), pre-cooled to 0°-5°C, at a rate to maintain the temperature <5°C; the internal temperature must not be allowed to rise above 5°C to minimize hydrolysis of the sulfonyl chloride product. After the addition of ca. 10% of the reaction mixture, the quench mixture can be further cooled to -5°5°C. During the quench, significant amounts of hydrochloric acid and sulfurous acid are generated. The mixture was stirred for 1 h at 0°-5°C, was filtered, and the product cake then washed with cold (5°C) water (1 L). The cake was sucked well to remove as much water as possible. Yield: 68 g of crude sulfonyl chloride as a moist solid (ca. 40 wt % water), which was used immediately in the next step.

Step D: Amidation Procedure

To a mechanically stirred, cooled (-10°5°C) solution of concentrated aqueous ammonia (15 M, 43 mL, 0.65 mol) in tetrahydrofuran (THF, 300 mL) was added the crude sulfonyl chloride (68 g wet, ca. 40.9 g, 0.114 mol) portionwise at a rate that maintained the internal temperature below 0°C. After the addition was complete, the mixture was stirred at 0°-5°C for 1 h, or until the reaction was judged to be complete by HPLC. Assay Procedure: An aliquot (0.1 mL) is diluted to 50.0 mL with acetonitrile and then immediately analyzed by the HPLC method described above (to minimize hydrolysis of the sufonyl chloride starting material). The reaction was considered complete when less than 1% of sulfonyl chloride (vs. the acetamidosulfonamide - N-(6-methyl-7,7-dioxo-4,5,6,7-tetrahydro-7γ6-trieno-[2,3b]thiopyran-4-yl)-propionamide) remained. After the reaction was complete, the pH of the mixture was adjusted to 3-5 by the dropwise addition of concentrated sulfuric acid (18 M, ca. 12.2 mL, 0.218 mol) while maintaining the internal temperature below 20°C. The mixture was allowed to settle, and the layers separated. The aqueous (lower) phase was extracted with THF (70 mL). The two organic layers were combined and then diluted with water (250 mL). The solution was then concentrated by distillation to a volume of 125 mL. During the concentration the product spontaneously crystallized. The slurry was diluted with water to a volume of 250 mL and the mixture then stirred for 12-18 h at 20°-25°C. The mixture was filtered, and the product cake washed with water (150 mL). The product was air-dried, then dried in vacuo (100 mBar, nitrogen sweep, 55°C) to constant weight. Yield: 29.5 g (76% yield from hydroxysulfone) of acetamidosulfonamide as a white crystalline solid.

Step E: Reduction via Borane Generated in situ Procedure

To a mechanically stirred, cooled (0°-5°C) slurry of acetamidosulfonamide (29.5 g, 87.1 mmol; 95:5 trans/cis) and sodium borohydride (16.9 g, 447 mmol) in dry THF (290 mL) was added neat boron trifluoride etherate (8.13 M, 73 mL, 593 mmol) over a 0.5 h period while maintaining the internal temperature below 5°C. Hydrogen is generated during the reaction as sodium borohydride and/or diborane reacts with the sulfonamide protons. After the addition was complete the mixture was stirred for 5 h at 0°-5°C and then at 30°-35°C for 12-18 h, or until the reaction was judged to be complete by HPLC. The reaction was considered to be complete when less than 1% of acetamidosulfonamide (vs. the aminosulfonamide - 4-ethylamino-6-methyl-7,7-dioxo-4,5,6,7-tetrahydro-7γ^6-trieno-[2,3b]thiopyran-2-sulfonicacid amide) remained. After the reaction was complete, the reaction mixture was slowly added to a mechanically stirred, pre-cooled (0°-5°C) solution of 1 M aqueous sulfuric acid (400 mL) at such a rate that the internal temperature was maintained below 20°C. Hydrogen is generated during the quench. The mixture was stirred for 2 h at 20°-25°C, or until the generation of hydrogen ceased. The mixture was then concentrated by distillation (1 atm) to a volume of 400 mL. The resultant aqueous solution was cooled to 10°C and the pH cautiously adjusted to 4-5 by the dropwise addition of 50% aqueous sodium hydroxide (ca. 37 mL, 0.7 mol) while the internal temperature was maintained below 20°C. Ethyl acetate (600 mL) was added and the pH further adjusted to 7.5-8.0 by the addition of saturated aqueous sodium bicarbonate (ca. 75 mL, 90 mmol). The mixture was filtered to remove the sodium sulfate generated during the initial pH adjustment, and the filter cake washed with ethyl acetate (100 mL). The filtrate and cake wash were combined and the resultant mixture partitioned. The aqueous (lower) phase was extracted with ethyl acetate (100 mL). The organic layers were combined and then washed with brine (100 mL). This solution containing the crude aminosulfonamide product (ca. 27.9 g) was used "as is" in the next step.

Step F: Maleate Salt Formation Procedure

The ethyl acetate solution containing aminosulfonamide (ca. 27.9 g, 86 mmol; 95:5 trans/cis) from step 5 was concentrated by distillation (1 atm) to a volume of 70 mL. Acetone (250 mL) was added and the concentration repeated to a volume of 70 mL. The operation was repeated, this time concentrating to a volume of 160 mL. Maleic acid (9.98 g, 86 mmol) was added. The mixture was stirred until the salt crystallized, and was then stirred for 12-18 h at 20°-22°C. The mixture was filtered, and the product cake washed with acetone (1 bed volume). The product was air-dried, then dried in vacuo (100 mBar, nitrogen sweep, 75°C) to constant weight. Yield: 33.0 g (92%) of the maleate salt as a white crystalline solid. HPLC: 99:1 trans/cis (above method).

Step G: Crude Hydrochloride Salt Formation

To a mechanically stirred mixture of ethyl acetate (250 mL) and saturated aqueous sodium bicarbonate (120 mL) was added maleate salt (33.0 g, 75 mmol; 99:1 trans/cis). The mixture was stirred at 20°-25°C until all of the solid dissolved, and the two phases became clear. The mixture was allowed to settle and the layers then separated. The aqueous (lower) phase was extracted with ethyl acetate (50 mL). The organic layers were combined and

then washed with saturated aqueous sodium chloride (50 mL). To the well stirred ethyl acetate solution was slowly added concentrated hydrochloric acid (12 M, 6.25 mL, 75 mmol). During the addition the product crystallized. The mixture was concentrated in vacuo (200 mBar, 45°C), replacing the ethyl acetate as necessary, until the water content of the solution was less than 0.1 mg/mL at a volume of 150 mL. The mixture was cooled to 20°-22°C and then stirred for 12-18 h at this temperature. The mixture was filtered, and the product cake washed with ethyl acetate (2 times 25 mL). The product was air-dried, then dried in vacuo (100 mBar, nitrogen sweep, 45°-50°C) to constant weight. Yield: 26.4 g (98% yield; 64% overall yield from hydroxysulfone) of the crude aminosulfonamide hydrochloride salt as a white crystalline solid. HPLC: >99% (above HPLC method).

Step H: Recrystallization Procedure

A mechanically stirred suspension of crude amino-sulfonamide hydrochloride salt (26.4 g, 73 mmol) in water (70 mL) was heated at 90°-95°C until all of the solid dissolved. To the hot solution was added activated carbon (Darco KB, 0.26 g), and the mixture stirred for 15 min at 90°-95°C. The mixture was filtered hot (85°-90°C) through a well-washed bed of filter aid (SuperCel). The filter cake was washed with boiling water (9 mL). The filtrate and cake wash were combined, and the product allowed to crystalize as well-stirred solution was cooled to 60°C. The mixture was stirred for 1 h at 60°C, or until the product had convened to the thermodynamically more stable hemihydrate crystal form. The mixture was then slowly cooled to 3°C, and then stirred for 1 h at this temperature. The mixture was filtered cold, using the mother liquors to rinse the cake. The product was air-dried, then dried in vacuo (100 mBar, nitrogen sweep, 45°-50°C) to constant weight. Yield: 24.2 g (92% yield; 59% overall yield from hydroxysulfone) of pure aminosulfonamide hydrochloride salt (dorsolamide) as a white crystalline solid. HPLC: 99.9 area % (254 nm), 99.6 wt % vs an external standard, >99% (4S,6S) as the N-TFA derivative. Specific Rotation: α_{589} =-17.1° (c=1.00, H_2O). MP: 238°C.

References

Blacklock T. et al.; US Patent No. 5,688,968; Nov. 18, 1997; Assigned to Merck and Co., Inc., Rahway, N.J.

DOXAPRAM HYDROCHLORIDE

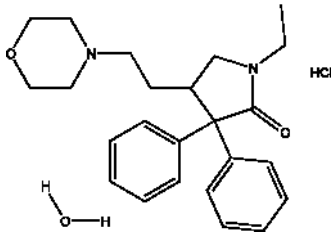
Therapeutic Function: Respiratory stimulant

Chemical Name: 1-Ethyl-4-(2-morpholinoethyl)-3,3-diphenyl-2-pyrrolidinone hydrochloride monohydrate

Common Name: -

Chemical Abstracts Registry No.: 7081-53-0; 309-29-5 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Dopram	Robins	US	1965
Doxapril	Farmalabor	Italy	1967
Dopram	Martinet	France	1969
Dopram	Robins	UK	1971
Dopram	Kissei Pharmaceutical Co., Ltd.	Japan	1976
Dopram	Brenner	W. Germany	1977
Stimulexin	Robins	US	-

Raw Materials

Diphenylacetonitrile	1-Ethyl-3-chloropyrrolidine
Morpholine	Sodium amide
Sulfuric acid	Hydrogen chloride

Manufacturing Process

(A) Preparation of α-(1-ethyl-3-pyrrolidyl)-α,α-diphenylacetonitrile: A suspension of the sodium salt of diphenylacetonitrile was formed by the dropwise addition at 50°C of 193 grams (1.0 mol) of diphenylacetonitrile to a stirred suspension of 43 grams (1.1 mols) of sodium amide in 1 liter of dry toluene. After addition was complete, the mixture was refluxed for 4 hours and then, to the refluxing mixture, 1.0 mol of 1-ethyl-3-chloropyrrolidine was added at a rapid dropwise rate with continuous stirring. After addition was complete, stirring and refluxing were continued for 3 hours. The mixture was then cooled and extracted with one normal hydrochloric acid. The aqueous layer together with an oil layer were separated, made basic with dilute sodium hydroxide, and extracted with ether. The ethereal solution was dried over sodium sulfate and concentrated and the residue was distilled in vacuo. The material crystallized from a 4:1 ethanol-water mixture.

(B) Preparation of 4-(β-chloroethyl)-3,3-diphenyl-1-ethyl-2-pyrrolidinone: A solution of α,α-diphenyl-α-(1-ethyl-3-pyrrolidyl)-acetonitrile in 70% sulfuric acid was heated at 130-140°C for 48 hours, poured onto ice, made basic with sodium hydroxide, and extracted with chloroform. The chloroform solution was acidified with hydrogen chloride gas, dried over sodium sulfate and concentrated. The residue was refluxed in 500 ml of thionyl chloride for 3 hours; the resulting solution was concentrated in vacuo; and the residue was

crystallized from isopropyl ether.

(C) Preparation of doxapram hydrochloride [3,3-diphenyl-1-ethyl-4-(2-morpholino-ethyl)-2-pyrrolidinone hydrochloride monohydrate]: A solution of 25 grams (0.076 mol) of 4-(2-chloroethyl)-3,3-diphenyl-1-ethyl-2-pyrrolidinone and 13.3 grams (0.153 mol) of morpholine in 500 ml of absolute ethanol was heated at 95°-120°C for 21 hours in a closed system and concentrated in vacuo. The residue was dissolved in 300 ml of two normal hydrochloric acid and extracted with 150 ml of ethyl acetate. A solid crystallized (13 g) during the extraction and was removed by filtration. MP 217°-219°C. The acid extracts were made basic with sodium hydroxide and extracted with ether, and the ether solution was concentrated in vacuo and the residue was suspended in six normal hydrochloric acid. Additional crystalline product formed and was recrystallized from two normal hydrochloric acid. Yield, 10 grams; MP 217°-219°C. Total yield, 23 grams (70%).

References

Merck Index 3433
Kleeman and Engel p. 337
PDR p. 1456
OCDS Vol. 2 p. 236 (1980)
DOT 2 (2) 55 (1966)
I.N. p. 362
REM p. 867
Lunsford, C.D. and Cale, A.D. Jr.; US Patent 3,192,230; June 29, 1965; assigned to A.H. Robins Company, Inc.

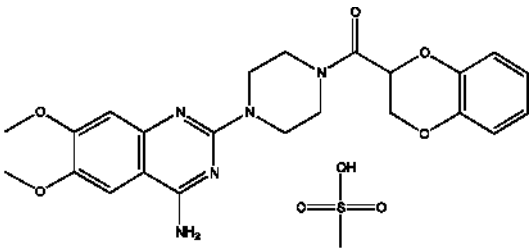
DOXAZOSIN MESYLATE

Therapeutic Function: Adrenergic blocker

Chemical Name: Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-((2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl)-, monomethanesulfonate

Common Name: Doxazosin mesylate

Structural Formula:



Chemical Abstracts Registry No.: 77883-43-3

Trade Name	Manufacturer	Country	Year Introduced
Alfadil	Roerig/Pfizer	Sweden	-
Cardura	Pfizer	USA	-
Cardura	Astra	Canada	-
Cardura	Invicta /Pfizer	Ireland	-
Cardura	Roerig/Pfizer	Italy	-
Cardura	Roerig/Pfizer	Netherlands	-
Cardura	Roerig/Pfizer	S. Africa	-
Cardura	Roerig/Pfizer	UK	-
Carduran	Roerig/Pfizer	Australia	-
Carduran	Roerig/Pfizer	Norway	-
Carduran	Roerig/Pfizer	Spain	-
Carduran	Roerig/Pfizer	Norway	-
Cardular	Roerig/Pfizer	Germany	-
Doksura	Fako Ilaclaria AS	Turkey	-
Doxazosin mesylate	Chemo Iberica	Spain	-
Prostadilat	Roerig/Pfizer	Austria	-

Raw Materials

4-Amino-2-chloro-6,7-dimethoxyquinazoline
N-(1,4-benzodioxan-2-carbonyl)piperazine
Methyl sulfate

Manufacturing Process

4-Amino-2-chloro-6,7-dimethoxyquinazoline (140 g) and N-(1,4-benzodioxan-2-carbonyl)piperazine (150 g) were stirred together under reflux in n-butanol (2 L) for 3.5 hours. The mixture was then cooled to 80°C, the solid product collected, washed with cold n-butanol (2 times 250 ml), and dried. The crude product was dissolved in hot (80°C) dimethylformamide (530 ml) and water (130 ml), filtered, concentrated in vacuo to about 300 ml, then cooled and ether (1.8 L) added. The solid so obtained was collected and washed with ether to give 4-amino-2-[4-(1,4-benzodioxan-2-carbonyl)piperazin-1-yl]-6,7-dimethoxyquinazoline hydrochloride (215 g), melting point 289°C-290°C. Mesylate may be prepared by usual method from hydrochloride with methylsulphonic acid.

References

Campbell S.P.; US Patent No. 4,188,390; Feb. 12, 1980; Assigned: Pfizer Inc. (New York, NY)

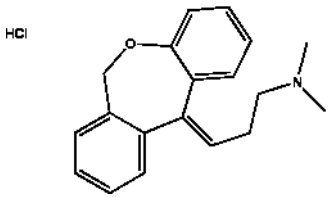
DOXEPIN HYDROCHLORIDE

Therapeutic Function: Tranquilizer

Chemical Name: N,N-Dimethyl-3-dibenz[b,e]oxepin-11-(6H)-ylidene-1-propanamine hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 1229-29-4; 1668-19-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Sinequan	Pfizer	US	1969
Sinequan	Pfizer	UK	1969
Aponal	Boehringer Mannheim	W. Germany	1970
Sinequan	Pfizer	W. Germany	1970
Sinequan	Pfizer	Italy	1971
Sinequan	Pfizer	France	1971
Adapin	Pennwalt	US	1973
Doksapan	Eczacibasi	Turkey	-
Dolat	Yurtoglu	Turkey	-
Doxal	Orion	Finland	-
Doxedyn	Medica	Finland	-
Gilex	Ikapharm	Israel	-
Novoxapin	Ester	Spain	-
Quitaxon	Phartec	France	-
Toruan	Boehringer Mannheim	-	-

Raw Materials

1,3-Dibromopropane
Triphenylphosphine
Hydrogen bromide
Dimethylamine
6,11-Dihydrodibenz-(b,e)oxepin-11-one
Butyl lithium

Manufacturing Process

(A) Preparation of 3-bromopropyltriphenylphosphonium bromide: Triphenylphosphine, 1.0 kg, and 770 grams of 1,3-dibromopropane are dissolved in 2.0 liters of xylene and the solution is stirred under a nitrogen atmosphere at 130°C. After 20 hours the mixture is cooled, and the crystalline product, which precipitates, is collected and washed with 20 liters of benzene. After drying in vacuo the product weighs 1,578 grams, MP 229°-230°C;

titration for bromide ion: Found, 17.1%; calculated, 17.2%.

(B) Preparation of 3-dimethylaminopropyltriphenylphosphonium bromide hydrobromide: A solution of 595 grams of anhydrous dimethylamine and 1,358 grams of 3-bromopropyl-triphenylphosphonium bromide in 4 liters of ethanol is warmed to 70°C until solution is complete and the solution then is allowed to stand at room temperature for 20 hours. Volatile components are removed by distillation in a vacuum and the residue is suspended in 2.0 liters of ethanol and is redistilled to remove excess amine. The residue is dissolved in 3.0 liters of warm ethanol and gaseous hydrogen bromide is passed into the solution until the mixture is acidic. After filtration the solution is concentrated to a volume of 3.0 liters, is cooled, whereupon the product precipitates, and the precipitate is collected; it weighs 1,265 grams, MP 274-281°C. Recrystallization from ethanol raises the MP to 280.5°-282.5°C. Bromide ion titration: Found, 31.2%; calculated 31.3%.

(C) Preparation of doxepin: 1,530 grams of the product from step (B) is suspended in 4.5 liters dry tetrahydrofuran and 6.0 mols of butyl lithium in heptane is added during 1 hour. After an additional 30 minutes, 483 grams of 6,11-dihydrodibenz-(b,e)oxepin-11-one, prepared as described in Belgian Patent 641,498, is added to the deep red solution and the reaction was maintained at reflux for 10 hours. Water, 500 ml, is added at room temperature and the solvent is removed in vacuo. The crude residue is treated with 10% hydrochloric acid until acidic (pH 2) and then 1.5 liters benzene is added. After stirring, the mixture separates into 3 phases (an insoluble hydrochloride salt product phase, an aqueous phase and an organic phase).

The benzene layer is removed by decantation and the remaining mixture is rendered basic with 10% sodium hydroxide solution and is extracted with three 1,500 ml portions of benzene. The benzene extracts are washed, then dried with anhydrous sodium sulfate and concentrated in a vacuum leaving a residue of 1,530 grams, gas and thin layer chromatography analysis show this to be a cis/trans mixture (approx. 4:l) of 11-dimethylaminopropylidene-6,11-dihydrodibenz-(b,e)oxepin (90% yield). This mixture has substantially more activity pharmacologically than the cis/trans mixture obtained by the Grignard route disclosed in the Belgian Patent 641,498. This base is then converted to the hydrochloride with HCl.

References

Merck Index 3434
Kleeman and Engel p. 338
PDR pp. 1397,1530
OCDS Vol. 1 p. 404 (1977)
DOT 6 (2) 53 (1970)
I.N. p. 362
REM p. 1094
Chas. Pfizer and Co., Inc.; British Patent 1,085,406; October 4, 1967
Bloom, B.M. and Tretter, J.R.; US Patent 3,420,851; January 7, 1969; assigned to Chas. Pfizer and Co., Inc.
Stach, K.; US Patent 3,438,981; April 15, 1969; assigned to C.F. Boehringer and Soehne GmbH (Germany)

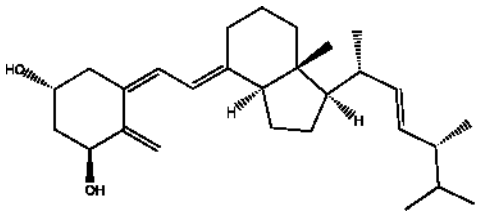
DOXERCALCIFEROL

Therapeutic Function: Calcium regulator

Chemical Name: 9,10-Secoergosta-5,7,10(19),22-tetraene-1,3-diol, (1α,3β,5Z,7E,22E)-

Common Name: Doxercalciferol; 1α-Hydroxyergocalciferol; 1α-Hydroxyvitamin D_2

Structural Formula:



Chemical Abstracts Registry No.: 54573-75-0

Trade Name	Manufacturer	Country	Year Introduced
Hectorol	Bone Care Intern.	-	-

Raw Materials

Ergosterol
Selenium dioxide
Ammonia
Acetic anhydride
Trimethylphosphite
Acetic acid
Hydrogen peroxide
Lithium
N,N'-Dibromodimethylhydantoin

Manufacturing Process

Isoergosterone (m.p. 105-106°C) was prepared from ergosterol by the method described in Shepherd et al., J. Amer. Chem. Soc. 77, 1212 (1955). To a solution of isoergosterone in 80 ml t-butanol and 1 ml acetic acid, 1.5 g SeO_2 were added, and the mixture was refluxed under nitrogen for 16 hours. The solvent was then evaporated in vacuo, the residue was redissolved in 150 ml ethanol and 7 ml of 28% aqueous $(NH_4)_2S$ was added. This solution was refluxed for 1.5 hours and then kept at room temperature overnight. After evaporation of the solvent under reduced pressure and addition of $CHCl_3$ the resulting slurry was filtered through a short Al_2O_3-column to remove the Se powder. Concentration of the filtrate and separation of the products on a silicic acid column gave ca. 1.5 g (30% yield) of 1,4,6,25-ergostatetraen-3-one of satisfactory purity which was identified by the spectral dates.

To a solution of 1.5 g of the 1,4,6,25-ergostatetraen-3-one in 200 ml MeOH and 50 ml dioxane, 1 ml 10% NaOH and 6 ml 30% H_2O_2 were added. The reaction mixture was kept at room temperature overnight. The solvent was

then evaporated under reduced pressure, and the product that separated was collected by suction filtration, washed with water and dried in vacuo. The solid obtained was redissolved in $CHCl_3$ and applied to a column of 100 g silicic acid prepared in $CHCl_3$. Elution with $CHCl_2$ gave 1.2 g (77%)of 1α,2α-epoxy-4,6,22-ergostatnene-3-one which, upon crystallization from methanol/acetone yielded material having the melting point 143°-145°C.

A solution of 600 mg of the epoxide in 70 ml freshly distilled THF was added (all at once) to 70 ml liquid ammonia containing 2 g of 30% lithium dispersion. The reaction mixture was refluxed for 10 min and then 15 g NH_4Cl was added in small portions over a 20 min. After evaporation of the ammonia, water was added, and the mixture was extracted with ether. The ether layer was dried over Na_2SO_4, evaporated, and the residue was applied to a 120 g silicic acid column poured as a slurry in 20% ether in Skellysolve B. The column was eluted with 100 ml of 20% ether in Skellysolve B (straight run aliphatic naphthas (essentially normal hexane) derived from petroleum oil having a boiling range of 60-68°C, (marketed by Skelly Oil Co.) followed by 250 ml of 50%, and 250 ml of 70% ether in Skellysolve B and finally with 250 ml of ether, 250 ml of 20%, ethyl acetate in ether and 200 ml of 50% ethyl acetate in ether. 12 ml fractions were collected. Crystallization of the material in tubes 69-90 (200 mg) from Skellysolve B and ethyl acetate gave the dihydroxy compound, 1α-hydroxy-7,8-dihydroergosterol having the melting point 180-182°C.

200 mg of the 1α-hydroxy-7,8-dihydroergosterol was acetylated by dissolving in pyridine (10 ml) and acetic anhydride (10 ml). The acetylation was done at 80°C for 24 hours. The reaction mixture was extracted with diethylether and H_2O (pH 4 with H_2SO_4). The ether phase was collected and the aqueous phase was extracted twice with diethylether and dried under nitrogen gas. The collected material was subjected to silicic acid column chromatography and 130 mg (54% yield) of the diacetate, 1α-acetoxy-7,8-dihydroergosteryl acetate was recovered.

To 100 mg of the 1α-acetoxy-7,8-dihydroergosteryl acetate dissolved in 6 ml Skellysolve B, at 70°C, 4.3 mg of N,N'-dibromodimethylhydantoin was added. The solution was refluxed with stirring for 15 min, then cooled in an ice bath and filtered. The filtrate was taken up in 2 ml xylene and added dropwise to a solution of 0.2 ml trimethylphosphite and 1 ml xylene preheated to 135°C. The reaction mixture was kept at 135-140°C for 2 hours. After evaporation of the solvent under reduced pressure the residue was chromatographed on $AgNO_3$-impregnated silicic acid. Elution with 5% ether in Skellysolve B gave ca. 10 mg (10% yield) of 1α-hydroxyergosteryl diacetate.

A solution of 4 mg of the 1α-hydroxyergosteryl diacetate in 200 ml ether was irradiated (Hanovia high pressure quarty mercury vapor lamp) at 0°C for 2 min in accordance with the procedure of Blunt and DeLuca (Biochemistry 8:671, 1969). The products were separated into two fractions on $AgNO_3$-impregnated silicic acid. The nonpolar fraction contained the desired 1α,3β-diacetoxy previtamin D_2, exhibiting UV absorption at λ_{max} 260 nm and λ_{min} 235 nm. After heating in 95% EtOH at 80°C for 2 hours the absorption shifted to λ_{max} 265 nm and λ_{min} 228 nm and the absorbance was enhanced indicating conversion of the previtamin to the vitamin D_2 skeleton. Two drops of 0.9 N KOH in MeOH were then added and the mixture was kept at 60°C for 10 min.

Evaporation of the ethanol under a stream of N2, addition of H_2O and extraction with $CHCl_3$, drying (Na_2SO_4) and evaporation of $CHCl_3$ gave a residue which was applied to a 20 g Sephadex LH-20 column in $CHCl_3$: Skellysblve B (1:1) and eluted with the same solvent. Collection of 3.2 ml fractions gave, in fractions 25-33, the pure 1α-hydroxyergocalciferol with λ_{max} 265 nm and λ_{min} 228 nm.

References

DeLuca H.F., Schnoes H.K.; US Patent No. 3,907,843; Sept. 23, 1975; Assigned to Wisconsin Alumni Research Foundation, Madison, Wis.

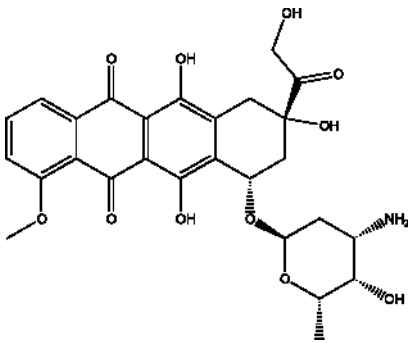
DOXORUBICIN

Therapeutic Function: Cancer chemotherapy

Chemical Name: (8S-cis)-10-[(3-Amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-5,12-naphthacenedione

Common Name: 14-Hydroxydaunomycin

Structural Formula:



Chemical Abstracts Registry No.: 23214-92-8; 25316-40-9 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Adriblastina	Farmitalia	Italy	1971
Adriamycin	Farmitalia	UK	1971
Adriblastina	Farmitalia	W. Germany	1972
Adriablastine	Roger Bellon	France	1974
Adriacin	Kyowa Hakko	Japan	1974
Adriamycin	Adria	US	1974

Raw Materials

Glucose
Bacterium Streptomyces peucetius var. caesius

Manufacturing Process

Two 300 ml Erlenmeyer flasks, each containing 60 ml of the following culture medium for the vegetative phase, were prepared: peptone 0.6%; dry yeast 0.3%; hydrated calcium carbonate 0.2%; magnesium sulfate 0.01%; the pH after sterilization was 7.2. Sterilization has been effected by heating in autoclave to 120°C for 20 minutes. Each flask was inoculated with a quantity of mycelium of the mutant F.I.106 (the new strain thus obtained has been given the code F.I.106 of the Farmitalia microbiological collection and has been called Streptomycespeucetius var. caesius) corresponding to 1/9 of a suspension in sterile water of the mycelium of a 10 day old culture grown in a big test tube on the following medium: saccharose 2%; dry yeast 0.1%; bipotassium phosphate 0.2%; sodium nitrate 0.2%; magnesium sulfate 0.2%; agar 2%; tap water up to 100%. The flasks were then incubated at 28°C for 48 hours on a rotary shaker with a stroke of 30 mm at 220 rpm.

2 ml of a vegetative medium thus grown were used to inoculate 300 ml Erlenmeyer flasks with 60 ml of the following medium for the productive phase: glucose 6%; dry yeast 2.5%; sodium chloride 0.2%; bipotassium phosphate 0.1%; calcium carbonate 0.2%; magnesium sulfate 0.01%; ferrous sulfate 0.001%; zinc sulfate 0.001%; copper sulfate 0.001%; tap water to 100%. The glucose was previously sterilized separately at 110°C for 20 minutes. The resulting pH was 7. This was sterilized at 120°C for 20 minutes and incubated at 28°C under the same conditions by stirring, as for the vegetative media.

The maximum concentration of the antibiotic was reached on the 6th day of fermentation. The quantity of adriamycin produced at this time corresponds to a concentration of 15 μg/ml.

References

Merck Index 3435
Kleeman and Engel p. 338
PDR p. 557
DOT 8 (4) 132 (1972) and 16 (5) 170 (1980)
I.N. p. 362
REM p. 1149
Arcamone, F., Cassinelli, G., di Marco, A. and Gaetani, M.; US Patent 3,590,028; June 29, 1971; assigned to Societa Farmaceutici Italia, Italy
Smith, T.H., Fujiwara, A.N., Henry, D.W. and Lee, W.W.; US Patent 4,012,448; March 15, 1977; assigned to Stanford Research Institute
Arcamone, F., di Marco, A. and Penco, S.; US Patents 4,058,519; November 15, 1977; and 4,098,798; July 4, 1978; both assigned to Societa Farmaceutici Italia S.p.A. (Italy)

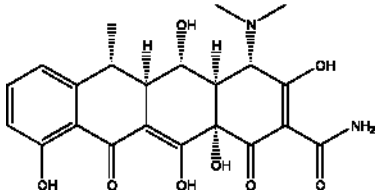
DOXYCYCLINE

Therapeutic Function: Antibiotic

Chemical Name: 4αS-(Dimethylamino)-1,4,4aα,5,5aα,6,11,12a-octahydro-3,5α,10,12,12aα-pentahydroxy-6α-methyl-1,11-dioxo-2-naphthacenecarboxamide

Common Name: 6-Deoxy-5-oxytetracycline

Structural Formula:



Chemical Abstracts Registry No.: 564-25-0

Trade Name	Manufacturer	Country	Year Introduced
Cyclidox	Protea	Australia	-
Doxitard	Mack	W. Germany	-
Doxy	Wolff	W. Germany	-
Doxy 200	Engelhard	W. Germany	-
Doxylin	A.L.	Norway	-
Doxy-Puren	Klinge	W. Germany	-
Doxyremed	Remed Econerica	W. Germany	-
Dumoxin	Dumex	Denmark	-
Dura Doxal	Durachemie	W. Germany	-
Geobiotico	Asia	Spain	-
Hiramicin	Pliva	Yugoslavia	-
Liviatin	Juste	Spain	-
Medomycin	Medica	Finland	-
Mespatin	Merckle	W. Germany	-
Novelciclina	Lifasa	Spain	-
Tenutan	Chinoin	Hungary	-

Raw Materials

Methacycline
Hydrogen

Manufacturing Process

Hydrogen was introduced into a standard hydrogenation vessel containing 10 grams 6-deoxy-6-demethyl-6-methylene-5-oxytetracycline hydrochloride

(methacycline), 150 ml methanol and 5 grams 5% rhodium on carbon. The pressure was maintained at 50 psi while agitating at room temperature for 24 hours. The catalyst was then filtered off, the cake washed with methanol and the combined filtrates were evaporated to dryness. The dry solids were slurried in ether, filtered and the cake dried. The resulting solids exhibited a bioactivity of 1,345 units per mg versus K. pneumoniae.

Water (35 ml) was employed to dissolve 8.5 grams of the above product and the pH was adjusted to 6.0 with triethylamine, sufficient dimethyl formamide being added to maintain the solids in solution. Cellulose powder (2 kg) was slurried in water-saturated ethyl acetate and packed into a tower of about 3½ inches diameter, to a height of 3 ft. The product solution was then chromatographed over this column, developing with about 12 liters water-saturated ethyl acetate. The first product fraction to come from the tower yielded 1.85 grams 6-epi-6-deoxy-5-oxytetracycline. The next fraction contained 2.0 grams of 6-deoxy-6-demethyl-6-methylene-5-oxytetracycline. The third fraction yielded 0.8 grams 6-deoxy-5-oxytetracycline.

References

Merck Index 3436
Kleeman and Engel p. 339
PDR p. 1424
DOT 3 (3) 114 (1967) and 4 (3) 102 (1968)
I.N. p. 363
REM p. 1205
Blackwood, R.K., Rennhard, H.H., Beereboom, J.J. and Stephens, C.R. Jr.; US Patent 3,200,149; August 10, 1965; assigned to Chas. Pfizer and Co., Inc.

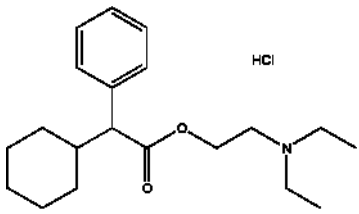
DROFENINE HYDROCHLORIDE

Therapeutic Function: Spasmolytic

Chemical Name: Benzeneacetic acid, α-cyclohexyl-, 2-(diethylamino)ethyl ester, hydrochloride

Common Name: Drofenine hydrochloride; Hexahydroadiphenine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 548-66-3; 1679-76-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Trasentine A	Ciba	-	-
Trasentine H	Ciba	-	-

Raw Materials

Diphenylacetic acid 2-(diethylamino)ethyl ester
Platinum

Manufacturing Process

17.4 parts of diphenylacetic acid 2-(diethylamino)ethyl ester were solved in 200 parts of acetic acid and hydrogenated over platinum catalyst. After the calculated volume of hydrogen was passed, the catalyst was filtered off and the solvent was removed to dryness. Ether, water and a potassium carbonate solution were added to the remaining oil and were thoroughly shaken. The ether layer was washed with water and dried over potassium carbonate. The solvent was removed, the remaining oil was distilled in vacuum to give 2-(diethylamino)ethyl α-phenylcyclohexaneacetate; BP 150°-160°C/0.2 mm Hg.

In practice it is usually used as hydrochloride.

References

Swiss Patent No. 219,301; Jan. 31, 1942; Assigned to Gesselschaft fur Chemische Industrie in Basel, Basel (Schweiz.)

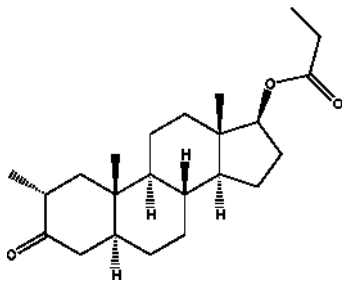
DROMOSTANOLONE PROPIONATE

Therapeutic Function: Cancer chemotherapy

Chemical Name: 2α-Methyl-17β-(1-oxopropoxy)-5α-androstan-3-one

Common Name: 2-Methyldihydrotestosterone propionate

Structural Formula:



Chemical Abstracts Registry No.: 521-12-0; 58-19-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Drolban	Lilly	US	1961
Masterone	Recordati	Italy	1962
Masterid	Gruenenthal	W. Germany	1969
Permastril	Cassenne	France	1969
Masteril	Syntex	UK	-
Mastisol	Shionogi	Japan	-
Metormon	I.F.L.	Spain	-

Raw Materials

Dihydrotestosterone
Ethyl formate
Sodium hydride
Propionic anhydride

Manufacturing Process

A suspension of 10 grams of dihydrotestosterone in 500 cc of anhydrous benzene free of thiophene was mixed with10 cc of ethyl formate and 3 grams of sodium hydride and the mixture was stirred for 5 hours under an atmosphere of nitrogen and at a temperature of approximately 25°C. The resulting suspension was filtered, the resulting mixture of the sodium salt of the hydroxymethylene compound and the excess of sodium hydride was washed with benzene and dried. This mixture was slowly added to a vigorously stirred solution of 20 cc of concentrated hydrochloric acid in 500 cc of water, and the stirring was continued for 30 minutes at the end of which the precipitate was collected and well washed with distilled water. After drying in vacuo, there was obtained 9.7 grams of 2-hydroxymethylene-dihydrotestosterone.

A mixture of 1 gram of 2-hydroxymethylene-dihydrotestosterone, 10 cc of pyridine and 2 cc of propionic anhydride was allowed to react at room temperature for 16 hours and then poured into water. The resulting suspension was heated for 1 hour on the steam bath to hydrolyze the excess of propionic anhydride, cooled and extracted with methylene dichloride. The extract was consecutively washed with dilute hydrochloric acid, sodium bicarbonate solution and water, dried over anhydrous sodium sulfate and evaporated to dryness under vacuum. There was thus obtained the dipropionate of 2-hydroxymethylenedihydrotestosterone which was treated with hydrogen, in methanol solution.

When the uptake of hydrogen ceased, the catalyst was filtered and the solution was evaporated to dryness under vacuum. The residue was dissolved in a mixture of benzene-hexane, transferred to a chromatographic column with neutral alumina and the product was eluted with mixtures of benzene-hexane, gradually increasing the proportion of benzene in the mixture. Crystallization of the eluates from acetone-hexane yielded the propionate of 2α-methyldihydrotestosterone.

References

Merck Index 3443

Kleeman and Engel p. 342
OCDS Vol. 1 p. 173 (1977)
I.N. p. 366
REM p. 998
Ringold, H.J. and Rosenkranz, G.; US Patent 2,908,693; October 13, 1959; assigned to Syntex SA, Mexico
Ringold, H.J. and Rosenkranz, G.; US Patent 3,118,915; January 21, 1964; assigned to Syntex Corporation, Panama

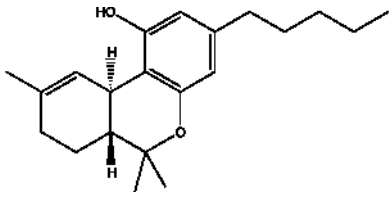
DRONABINOL

Therapeutic Function: Appetite stimulant

Chemical Name: 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aR,10aR)-

Common Name: Dronabinol; δ^9-Tetrahydrocannabinol

Structural Formula:



Chemical Abstracts Registry No.: 1972-08-3

Trade Name	Manufacturer	Country	Year Introduced
Deltanyn	Pharmos	USA	-
Dronabinol	Unimed Pharmaceuticals, Inc.	USA	-
Marinol	Unimed Pharmaceuticals, Inc.	USA	-
Marinol	Boehringer Ingelheim	-	-
Marinol	Sanofi	France	-
Marinol	Roxane	USA	-

Raw Materials

Fine powdered marijuana plant material
Hexanes GR from EM Sciences
Silica gel

Manufacturing Process

δ-9-Tetrahydrocannabinol (THC, also known as dronabinol) is the main biologically active component in the Cannabis plant extracted from the resin of Cannabis sativa (marihuana, hashish).

One kg of the fine powdered marijuana plant material [average % of THC was about 5.21%] was macerated with 6 L hexanes (Hexanes GR from EM Sciences) in a percolator (9" in diameter from the top and 20" long, cone shaped) for 24 hours at room temperature and filtered. The macerate was reextracted with 5 L hexanes for another 24 hours. The hexane extracts were combined and evaporated under reduced pressure at low temperature to give 110.7 g residue (11.07% extractives). The % of THC in the hexane extract was 41.21%.

Column Chromatography.

The hexane extract (110.7 g) was mixed with 150 g silica gel (silica gel 60, Art.# 9385-3) and 50 ml hexane. The air dried slurry was transferred to the top of a silica gel column (800 g silica gel 60, particle size 0.04-0.063 mm, from EM Science, Art.# 9385-3). The column was eluted with hexane:ether mixtures in a manner of increasing polarities. Fractions were collected and TLC screened (analytical silica gel plates, developing system: Hexane:Ether (80:20), Visualizing agent: Fast blue). The fractions collected with hexane (3 L) and hexane-ether (95:5, 2 L) were discarded. The following fractions collected with hexane-ether (95:5, 3 L) and hexane-ether (9:1, 5 L) were combined and evaporated to yield 77.2 g of residue. GC analysis of the residue showed THC concentration to be 54.74%.

Fractional Distillation

A portion (30.5 g) of the residue collected above was subjected to fractional distillation under reduced pressure (0.1-0.15 mm/Hg). The temperature was slowly raised to 125°C and the materials collected were kept separate. The temperature was then raised between 140°-160°C where the major fraction was collected (14 g). GC analysis showed >96% THC. Further purification on a silica gel column gives THC with at least 98% purity. An improvement of this process includes the use of high pressure liquid chromatography (HPLC). The preparation of dronabinol and related compounds have employed acid-catalyzed electrophilic condensation of a 5-alkylresorcinol such as 5-n-pentylresorcinol (commonly known as olivetol) and a menthadienol, followed by cyclization; yield of desired product is about 17-22% (Petrzilka et al., Helv. Chim. Acta, 52, 1102 (1969)).

References

Elsohly et al.; US Patent No. 6,365,416 B1; Apr. 2, 2002; Assigned to the University of Mississippi, University, MS (US)
Elsohly et al.; US Patent No. 6,730,519; May 4, 2004; Assigned to the University of Mississippi, University, MS (US)

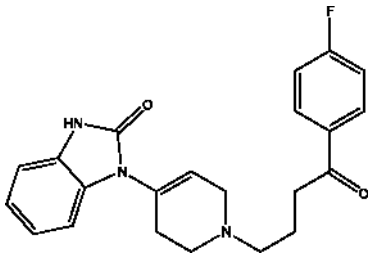
DROPERIDOL

Therapeutic Function: Tranquilizer

Chemical Name: 1-[1-[4-(4-Fluorophenyl)-4-oxobutyl]-1,2,3,6-tetrahydro-4-pyridinyl]-1,3-dihydro-2H-benzimidazol-2-one

Common Name: Dehydrobenzperidol

Structural Formula:



Chemical Abstracts Registry No.: 548-73-2

Trade Name	Manufacturer	Country	Year Introduced
Dehydrobenzperidol	Janssen	W. Germany	1963
Sintodian	Carlo Erba	Italy	1965
Droleptan	Janssen	UK	1965
Droleptan	Janssen	France	1966
Inapsine	McNeil	US	1970
Thalamonal	Sankyo	Japan	1972
Dridol	Leo	Sweden	-
Halkan	Thekan	France	-
Leptofen	Erba	Italy	-
Neurolidol	Abic	Israel	-

Raw Materials

γ-Chloro-4-fluorobutyrophenone
1-(1,2,3,6-Tetrahydro-4-pyridyl)-2-benzimidazolinone

Manufacturing Process

A mixture of 10 parts of γ-chloro-4-fluorobutyrophenone, 5.5 parts of 1-(1,2,3,6-tetrahydro-4-pyridyl)-2-benzimidazolinone, 4 parts of sodium carbonate, and 0.1 part of potassium iodide in 176 parts of 4-methyl-2-pentanone is stirred and refluxed for 64 hours. The cooled reaction mixture is filtered and the solvent is evaporated from the filtrate to leave an oily residue which is dissolved in toluene. The toluene solution is filtered and the solvent is evaporated. The resultant residue is recrystallized from a mixture of 32 parts of ethyl acetate and 32 parts of diisopropyl ether to give 1-[1-[(4-

fluorobenzoyl)propyl]-1,2,3,6-tetrahydro-4-pyridyl]-2-benzimidazolinone hydrate melting at about 145°-146.5°C.

References

Merck Index 3444
Kleeman and Engel p. 341
PDR p. 954
OCDS Vol. 1 p. 308 (1977)
DOT 9 (6) 235 (1973)
I.N. p. 365
REM p. 1087
Janssen, P.A.J. and Gardocki, J.F.; US Patent 3,141,823; July 21, 1964; assigned to Research Laboratorium Dr. C. Janssen NV, Belgium
Janssen, P.A.J.; US Patent 3,161,645; December 15, 1964; assigned to Research Laboratorium Dr. C. Janssen NV, Belgium

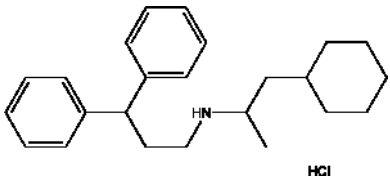
DROPRENILAMINE HYDROCHLORIDE

Therapeutic Function: Coronary vasodilator

Chemical Name: N-(2-Cyclohexyl-1-methylethyl)-γ-phenylbenzene-propanamine monohydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 57653-27-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Valcor	Maggioni	Italy	1979

Raw Materials

3,3-Diphenylpropylamine
Cyclohexylacetone
Hydrogen

Manufacturing Process

The flask of a Parr hydrogenation apparatus was charged with 10.5 g of 3,3-

diphenylpropylamine, 7.7 g of cyclohexylacetone, 50 ml methanol and 150 mg of platinum dioxide. Hydrogen at a pressure of 3 atmospheres was introduced and the mixture stirred. Upon absorption of the theoretical amount of hydrogen, stirring is discontinued, the catalyst is filtered off and the solution is evaporated to dryness. The residue is taken up with ether and the hydrochloride is precipitated with HCl in alcoholic solution. The product, as collected on a filter and washed with ether, is recrystallized from isopropanol. Yield: 17 g (92.5% of theory). MP: 175°C to 177°C.

References

Merck Index 3445
DFU 2 (11) 720 (1977)
OCDS Vol. 3 p. 47 (1984)
I.N. p. 366
Carissimi, M., Ravenna, F. and Picciola, G.; British Patent 1,461,240; January 13, 1977; assigned to Maggioni and Co. S.p.A. (Italy)

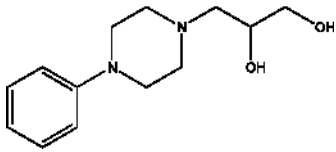
DROPROPIZINE

Therapeutic Function: Antitussive

Chemical Name: 1,2-Propanediol, 3-(4-phenyl-1-piperazinyl)-

Common Name: Dropropizine; Fenpropazina

Structural Formula:



Chemical Abstracts Registry No.: 17692-31-8

Trade Name	Manufacturer	Country	Year Introduced
Ribex	Formenti	-	-
Dropropizine	Shanghai Chemfrom Chemical Co., Ltd.	-	-
Dropropizine	Zandu	-	-
Catabex	UCB S. A.	-	-
Ditustat	Tecnifar	-	-
Ditustat	Ivax Pharmaceuticals S.R.O.	-	-
Ribex-Tosse	Pfizer C. Health Div. Salute	-	-
Vibral	Sintofarma	-	-

Raw Materials

1,2-Epoxy-3-hydroxypropane (glycide)
1-Phenylpiperazine

Manufacturing Process

34 g 1,2-epoxy-3-hydroxypropane (glycide) in 50 ml of water were added to 64.8 g 1-phenylpiperazine in 80 ml of ethanol at the temperature not higher 50°C. The mixture was stood at night, then it was evaporated to dryness in vacuum and the stark product was recrystallized from 100 ml of acetone to give 60 g 1-phenyl-4-(2,3-dihydroxypropyl)piperazine (dropropizine) MP 105°C; BP 205°C/1 mm Hg.

References

Mooren H.; Austrian Patent No. 227,269; 10 May 1963

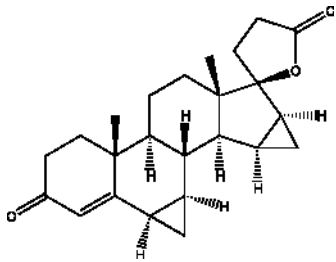
DROSPIRENONE

Therapeutic Function: Aldosterone antagonist

Chemical Name: (6R,7R,8R,9S,10R,13S,14S,15S,16S,17S)-1,3',4',6,6a,7,8,9,10,11,12,13,14,15,15a,16-Hexadecahydro-10,13-dimethylspiro-(17H-dicyclopropa(6,7:15,16)cyclopenta(a)phenanthrene-17,2'(5'H)-furan)-3,5'(2H)-dione

Common Name: Dihydrospirenone; Drospirenone

Structural Formula:



Chemical Abstracts Registry No.: 67392-87-4

Trade Name	Manufacturer	Country	Year Introduced
Yasmin	Berlex	-	-
Yirala	Schering	-	-

Raw Materials

Trimethyl sulfoxonium iodide
Sodium hydride
15α,16α-Methylene-3-oxo-4,6-androstadiene-[17(beta-1')-spiro-5']perhydrofuran-2'-one

Manufacturing Process

2.75 g of trimethyl sulfoxonium iodide is stirred in 57 ml of dimethyl sulfoxide with 341 mg of 80% sodium hydride oil suspension for 2 h at room temperature. The almost clear solution is combined under nitrogen with 2.0 g of 15α,16α-methylene-3-oxo-4,6-androstadiene-[17(β-1')-spiro-5']perhydrofuran-2'-one and agitated for 24 h at room temperature. The mixture is then stirred into ice water, the thus-obtained precipitate is filtered off, washed with water, and taken up in methylene chloride. After drying and evaporation, the residue is purified by repeated preparative layer chromatography, thus obtaining 520 mg of 6β,7β,15α,16α-dimethylene-3-oxo-4-androstene-[17(β-1')-spiro-5']perhydrofuran-2'-one (drospirenone).

References

Wiechert R. et al.; US Patent No. 4,129,564; Dec. 12, 1978; Assigned: Schering, A.G. Patentabteilung, Berlin, Fed. Rep. of Germany

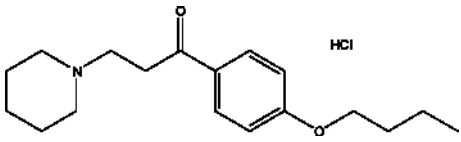
DYCLONINE HYDROCHLORIDE

Therapeutic Function: Local anesthetic

Chemical Name: 1-(4-Butoxyphenyl)-3-(1-piperidinyl)-1-propanone hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 536-43-6; 586-60-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Dyclone	Dow	US	1956
Resolve	Merrell Dow	US	1980
Epicain Ace	S.S. Pharm	Japan	-
Epirocain	Eisai	-	-

Raw Materials

p-n-Butoxyacetophenone	Piperidine hydrochloride
Paraformaldehyde	Hydrogen chloride

Manufacturing Process

A mixture of 17.6 grams of p-n-butoxyacetophenone, 12.1 grams of piperidine hydrochloride, 4.5 grams paraformaldehyde, 0.25 cc concentrated hydrochloric acid, 52.5 cc nitroethane, 7.5 cc of 95% ethanol, and 15 cc of toluene was boiled under reflux for one hour, removing water formed in the reaction by means of a condensate trap. The mixture was then cooled. The crystals which formed were collected by filtration, washed with anhydrous ether and recrystallized from methyl ethyl ketone. The crystals thus obtained, which melted at 174-175°C, were shown by analysis to be 4-n-butoxy-β-piperidinopropiophenone hydrochloride.

References

Merck Index 3459
Kleeman and Engel p. 343
PDR p. 592
I.N. p. 369
REM p. 1056
Bockstahler, E.R.; US Patent 2,771,391; November 20, 1956; assigned to Allied Laboratories, Inc.
Florestano, H.J., Jeffries, S.F., Osborne, C.E. and Bahler, M.E.; US Patent 2,868,689; January 13, 1959; assigned to Allied Laboratories, Inc.

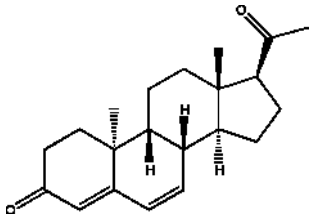
DYDROGESTERONE

Therapeutic Function: Progestin

Chemical Name: 9β,10α-Pregna-4,6-diene-3,20-dione

Common Name: 10α-Isopregnenone; 6-Dehydro-retro-progesterone

Structural Formula:



Chemical Abstracts Registry No.: 152-62-5

Trade Name	Manufacturer	Country	Year Introduced
Duphaston	Duphar	UK	1961
Duphaston	Duphar	France	1962
Duphaston	Philips Roxane	US	1962
Dufaston	I.S.M.	Italy	1963
Duphaston	Thomae Duphar	W. Germany	1966
Gynorest	Mead Johnson	US	1968
Duphaston	Ethnor	Australia	-
Terolut	Ferrosan	Denmark	-

Raw Materials

Retroprogesterone
Chloranil

Manufacturing Process

A solution of 7.5 grams of retroprogesterone in 500 ml of freshly distilled tertiary butyl alcohol was refluxed with 12.75 grams of finely powdered chloranil, while stirring, for 5 hours in a nitrogen atmosphere. After cooling, 2 liters of water were added and extraction was performed three times with 200 ml of methylene dichloride. The combined extracts were then diluted with 1 liter of petroleum ether (40-60°C) washed successively with 100 ml of diluted Na_2SO_4, four times with 75 ml of 1 N NaOH, and then water to neutral reaction.

By drying this solution on Na_2SO_4, and evaporating to dryness (last part in vacuo) 3.7 grams of crystalline residue was obtained. This residue was then dissolved in benzene. Filtration in benzene filtered through 35 grams of alumina (according to Brockmann was done and then the alumina was eluted with benzene. Evaporation of the benzene yielded 3.11 grams of crystalline residue. By crystallization with 15 ml of acetone at room temperature (at lower temperatures a by-product crystallized out) 900 mg of crystals, with a melting point of 165°-170°C were obtained. Transfer of the acetone mother liquor into a mixture of ethanol and hexane yielded 1.7 grams of a solid substance with a melting point of 130° to 145°C. This solid was then recrystallized with acetone at room temperature, yielding 600 mg of a solid with a melting point of 166° to 171°C. The two fairly pure fractions (600 mg and 900 mg) yielded, after crystallization with a mixture of acetone and hexane, finally 1.0 gram of 6-dehydroretroprogesterone, melting point 169° to 170°C. From the mother liquors an additional fraction of 0.44 gram with a melting point of 168° to 169°C was obtained.

References

Merck Index 3460
Kleeman and Engel p. 343
I.N. p. 369
Reerink, E.H., Westerhof, P. and Scholer, H.F.L.; US Patent 3,198,792; August 3, 1965; assigned to North American Philips Company, Inc.

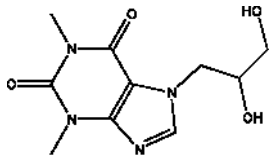
DYPHYLLINE

Therapeutic Function: Smooth muscle relaxant

Chemical Name: 7-(2,3-Dihydroxypropyl)-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione

Common Name: (1,2-Dihydroxy-3-propyl)theophylline; Diprophylline

Structural Formula:



Chemical Abstracts Registry No.: 479-18-5

Trade Name	Manufacturer	Country	Year Introduced
Neothylline	Lemmon	US	1948
Neutraphylline	Houde	France	1949
Droxine La	Dermik	US	1979
Diprophyline	Wakodo Seiyaku	Japan	1981
Oxystat	Hyrex	US	1983
AFI-Phyllin	A.F.I.	Norway	-
Aristophyllin	Kwizda	Austria	-
Astamasit	Showa	Japan	-
Asthmolysin	Kade	W. Germany	-
Astrophyllin	Astra	-	-
Austrophyllin	Petrasch	Austria	-
Coeurophylline	Barlow Cote	Canada	-
Corphyllin	Nippon Shinyaku	Japan	-
Difilina	Liade	Spain	-
Dilor	Savage	US	-
Diasthmol	Trima	Israel	-
Dyflex	Econo-Rx	US	-
Diurophylline	Monal	France	-
Dihydrophylline	Tokyo Hosei	Japan	-
Lufyllin	Mallinckrodt	US	-
Neophyllin-M	Eisai	Japan	-
Neospect	Lemmon	US	-
Neothylline	Lemmon	US	-
Neo-Vasophylline	Katwijk	Netherlands	-
Prophyllen	Streuli	Switz.	-
Protophylline	Rougier	Canada	-

Trade Name	Manufacturer	Country	Year Introduced
Rominophyllin	Grelan	Japan	-
Silbephylline	Berk	UK	-
Sintofillina	Sintetica	Switz.	-
Solufyllin	Pharmacia	Sweden	-
Theourin	Kanto	Japan	-
Thefylan	Pharmacia	Sweden	-

Raw Materials

Theophylline
Sodium hydroxide
1-Chloro-2,3-dihydroxypropane

Manufacturing Process

180 grams of theophylline is dissolved in 500 cc of boiling water. To this solution is added 40 grams of sodium hydroxide or 56 grams of potassium hydroxide slowly and with constant stirring.

When solution is complete, 120 grams of 1-chloro-2,3-dihydroxypropane is slowly added. The thus provided mixture is brought to boiling and heating is continued until a temperature of 110°C is reached.

The resultant liquid is evaporated under reduced pressure to remove all traces of water. The resulting syrupy liquid is allowed to stand with occasional stirring until crystallization takes place. The compound is purified by recrystallization from alcohol. The product melts at 155°-157°C.

References

Merck Index 3465
Kleeman and Engel p. 329
PDR pp. 1603,1877
I.N. p. 350
REM p. 872
Jones, J.W. and Maney, P.V.; US Patent 2,575,344; November 20, 1951;assigned to the State of Iowa