Sallmann, A. and Pfister, R.; U.S. Patent 3,558,690; January 26, 1971; assigned to Geigy Chemical Corporation
Sallmann, A. and Pfister, R.; U.S. Patent 3,652,762; March 28, 1972; assigned to Ciba-Geigy Corporation

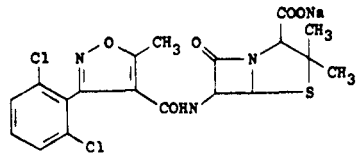
DICLOXACILLIN SODIUM

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
Dichlor-Stapenor	Bayer	W. Germany	1965
Dynapen	Bristol	U.S.	1968
Veracillin	Ayerst	U.S.	1968
Pathocil	Wyeth	U.S.	1968
Diclocil	Bristol	France	1968
Diclocil	Bristol	Italy	1971
Dycill	Beecham	U.S.	1975
Clocil	Bristol Banyu	Japan	–
Combipenix	Toyo Jozo	Japan	–
Constaphyl	Grunenthal	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-methyl-isoxazole-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 & 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.; U.S. Patent 3,239,507; March 8, 1966; assigned to Beecham Group Limited, England

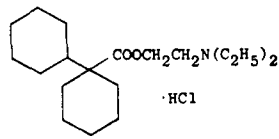
DICYCLOMINE HYDROCHLORIDE

Therapeutic Function: Antispasmodic

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

Common Name: Dicycloverin hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 67-92-5; 77-19-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Bentyl	Merrell National	U.S.	1950
Dyspas	Savage	U.S.	1974
Dicen	Mallard	U.S.	1980
Neoquess	O'Neal, Jones	U.S.	1981
A-Spas	Hyrex	U.S.	1983
Ametil	Corvi	Italy	—
Atumin	Merrell	W. Germany	—
Babyspasmil	Lacefa	Argentina	—
Benacol	Cenci	U.S.	—
Bentomine	Darby	U.S.	—
Bentylol	Inibsa	Spain	—
Clomin	S.C.S. Pharmalab.	S. Africa	—
Cyclobec	Pharbec	Canada	—
Dicycol	Ohio Medical	U.S.	—

Trade Name	Manufacturer	Country	Year Introduced
Esentil	Erba	Italy	–
Formulex	I.C.N.	Canada	–
Icramin	Toho Iyaku	Japan	–
Incron	Seiko	Japan	–
Kolantyl	Merrill	U.K.	–
Lomine	Riva	Canada	–
Mamiesan	Kyowa	Japan	–
Merbantal	Vitrum	Sweden	–
Merbenyl	Merrell	U.K.	–
Mydocalm	Lennon	S. Africa	–
Nomocramp	Salusa	S. Africa	–
Notensyl	C.T.S.	Israel	–
Or-Tyl	Ortega	U.S.	–
Panakiron	Sato	Japan	–
Protylol	Pro Doc	Canada	–
Spascol	Vangard	U.S.	–
Spasmoban	Trianon	Canada	–
Viscerol	Medic	Canada	–

Raw Materials

1-Phenylcyclohexane cyanide
β-Diethylaminoethanol
Sodium
Sulfuric acid
Ethanol
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 sodamide followed by alcoholysis and reesterification.

References

Merck Index 3083
Kleeman & 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.; U.S. Patent 2,474,796; June 28, 1949; assigned to The Wm. S. Merrell Company

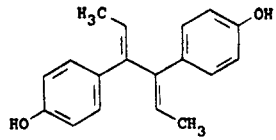
DIENESTROL

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	U.S.	1947
Cycladiene	Bruneau	France	1948
Agaldog	Vetoquinol	France	–
Bi-Star	Merit	U.S.	–
Dinestrol	Reid-Provident	U.S.	–
DV	Merrell Dow	U.S.	–
Estan	Schering	U.S.	–
Estraguard	Reid-Provident	U.S.	–
Farmacyrol	Farmaryn	W. Germany	–
Follidene	Recordati	Italy	–
Hormofemin	Medo	U.K.	–
Lucidon	Westerfield	U.S.	–
Oestrovis	Stotzer	Switz.	–
Para-Dien	Klimitschek	Austria	–
Reginol	Merz	W. Germany	–
Sexadien	A.F.I.	Norway	–

Raw Materials

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

Manufacturing Process

Preparation of γδ-Bis-(4-Hydroxylphenyl)-Hexane-γδ-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 U.S. Patent 2,464,203.

References

Merck Index 3085
Kleeman & 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; U.S. Patent 2,464,203; March 15, 1949; assigned to Boots Pure Drug Company Limited, England
Adler, E.; U.S. Patent 2,465,505; March 29, 1949; assigned to Hoffmann-La Roche Inc.

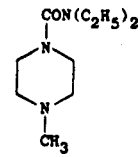
DIETHYLCARBAMAZINE CITRATE

Therapeutic Function: Anthelmintic

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

Common Name: –

Structural Formula:



(base)

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

Trade Name	Manufacturer	Country	Year Introduced
Hetrazan	Lederle	U.S.	1949

Trade Name	Manufacturer	Country	Year Introduced
Banocide	Burroughs-Wellcome	—	—
Difil	Evsco	U.S.	—
Filarcidin	Cidan	Spain	—
Filaribits	Norden	U.S.	—
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-methyl piperazine 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 1-methyl-4-piperazine-N,N-diethyl 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.; U.S. Patent 2,467,893; April 19, 1949; assigned to American Cyanamid Company
Kushner, S. and Brancone, L.; U.S. Patent 2,467,895; April 19, 1949; assigned to American Cyanamid Company

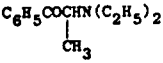
DIETHYLPROPION HCl

Therapeutic Function: Anorexic

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

Common Name: Amfepramone

Structural Formula:



(base)

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

Trade Name	Manufacturer	Country	Year Introduced
Tenuate	Merrell National	U.S.	1959
Tepanil	Riker	U.S.	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	Neth.	—
Lineal-Rivo	Rivopharm	Switz.	—
Linea Valeas	Valeas	Italy	—
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
Kleeman & Engel p. 37
PDR pp. 991, 1453, 1606
DOT 9 (6) 213 (1973)
I.N. p. 66
REM p. 891
Schutte, J.; U.S. Patent 3,001,910; September 26, 1961; assigned to Firma Temmler-Werke (W. Germany)

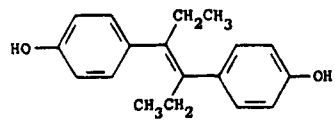
DIETHYLSTILBESTROL

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	U.S.	1946
Stilbetin	Squibb	U.S.	1950
Microest	Massengill	U.S.	1958
Vagestrol	Norwich Eaton	U.S.	1969
Acnestrol	Dermik	U.S.	–
Agostiben	Spofa	Czechoslovakia	–
Cyren A	Bayer	W. Germany	–
Desma	Tablicaps	U.S.	–
Des-Plex	Amfre-Grant	U.S.	–
Dicorvin	*Amfre-Grant*	U.S.	–
Distilbene	Ucepha	France	–
Estilbin	Dumex	Denmark	–
Estrosyn	Cooper	U.S.	–
Furacin-E	Eaton	U.S.	–
Gerex	Consul. Midland	U.S.	–
Makarol	Mallinckrodt	U.S.	–
Mase-Bestrol	Mason	U.S.	–
Menopax	Nicholas	U.K.	–
Micrest	Beecham	U.S.	–
Oestrogen	Holzinger	Austria	–
Oestrol	Veterinaria	Switz.	–
Oestromon	Merck	W. Germany	–
Pelestrol	Franklin	U.S.	–
Percutacrine	Besins-Iscovesco	France	–
Tylosterone	Lilly	U.S.	–

Raw Materials

p-Hydroxypropiophenone
Sodium hydroxide
Sodium
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 (diacetate of 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 Index 3115
Kleeman & 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.; U.S. Patent 2,421,401; June 3, 1947; assigned to Hoffmann-La Roche, Inc.

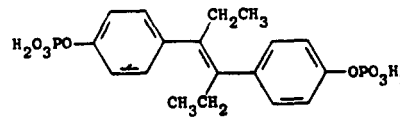
DIETHYLSTILBESTROL DIPHOSPHATE

Therapeutic Function: Estrogen; used in hormone therapy for prostate cancer

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	U.S.	1955
ST 52	Lucien	France	1955
Cytonal	VEB Berlin-Chemie	E. Germany	—
Honvan	Asta	W. Germany	—
Honvan	Funk	Spain	—
Honvan	W.B. Pharm.	U.K.	—
Honvan	Noristan	S. Africa	—
Honvan	Schering	Italy	—
Honvan	Asta-Kyorin	Japan	—
Stilbetin	Squibb	—	—
Stibol	A.C.O.	Sweden	—

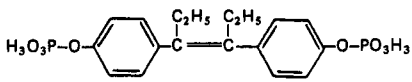
Raw Materials

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 2N-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 & Engel p. 433
PDR p. 1261
OCDS Vol. 1 p. 101 (1977)
I.N. p. 321
REM p. 989
Miescher, K. and Heer, J.; U.S. Patent 2,234,311; March 11, 1941; assigned to Ciba Pharmaceutical Products, Inc.

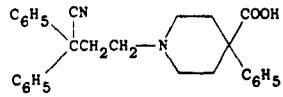
DIFENOXINE

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)

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-potassium butanolate in 60 parts of dimethylsulfoxide are added 1.7 parts of ethyl-1-(3-cyano-3,3-diphenylpropyl)-4-phenylisonipecotate hydro-

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

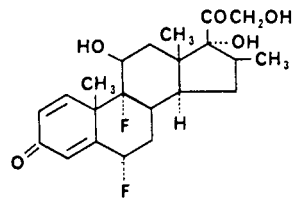
DIFLORASONE DIACETATE

Therapeutic Function: Topical corticosteroid antiinflammatory

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

Common Name: —

Structural Formula:



(base)

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

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

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-21-acetate: To approximately 1.3 g of hydrogen fluoride contained in a polyethylene bottle and maintained at -60°C was added 2.3 ml of tetrahydrofuran and then a solution of 500 mg (0.0012 mol) of 6α-fluoro-9β,11β-epoxy-16α-methyl-17α,21-dihydroxy-1,4-pregnadiene-3,20-dione-21-acetate in 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° 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 toluene sulfonic acid to give diflorasone diacetate.

References

Merck Index 3124
DFU 2 (4) 238 (1977)
Kleeman & 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.; U.S. Patent 3,557,158; January 19, 1971; assigned to The Upjohn Company
Ayer, D.E., Schlagel, C.A. and Flynn, G.L.; U.S. Patent 3,980,778; September 14, 1976; assigned to The Upjohn Co.

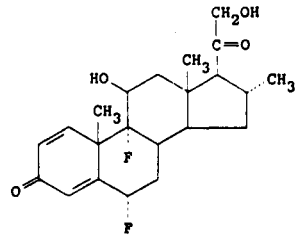
DIFLUCORTOLONE VALERATE

Therapeutic Function: Antiinflammatory

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

Common Name: –

Structural Formula:



(base)

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

Trade Name	Manufacturer	Country	Year Introduced
Nerisone	Schering	U.K.	1976
Temetex	Roche	U.K.	1976
Temetex	Roche	W. Germany	1977
Nerisone	Schering	France	1979
Nerisona	Schering	Italy	1979
Temetex	Roche	Italy	1980
Nerisona	Schering	Japan	1981
Texmeten	Roche	Japan	1981
Travocort	Schering	W. Germany	–

Raw Materials

16α-Methyl-6α,9α-difluoro-Δ^4-pregnene-11β,21-diol-3,20-dione-21-acetate
Bacterium *Bacillus lentus*
Valeric acid chloride

Manufacturing Process

16α-methyl-6α,9α-difluoro-Δ^4-pregnene-11β,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 m^3/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-Δ^4-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-$\Delta^{1,4}$-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 & 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.; U.S. Patent 3,426,128; February 4, 1969; assigned to Schering A.G. (West Germany)

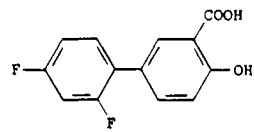
DIFLUNISAL

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	U.K.	1978
Unisal	Chibret	Switz.	1978
Dolobid	MSD	Italy	1979
Dolobis	MDS-Chibret	France	1981
Fluniget	Sharp & Dohme	W. Germany	1981
Dolobid	MSD	Canada	1982
Adomal	Malesci	Italy	1982
Dolobid	MSD	U.S.	1982
Citidol	C.T.	Italy	—
Diflonid	Dumex	Denmark	—
Diflunil	I.C.I.	—	—
Dugodol	Alkaloid	Yugoslavia	—

Trade Name	Manufacturer	Country	Year Introduced
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 & 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.; U.S. Patent 3,714,226; January 30, 1973; assigned to Merck & Co., Inc.

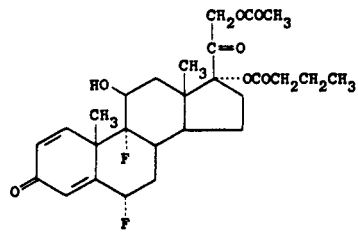
DIFLUPREDNATE

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

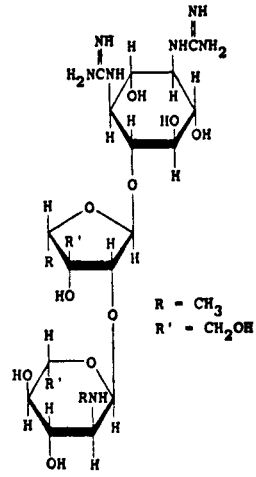
DIHYDROSTREPTOMYCIN SULFATE

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

Common Name: –

Structural Formula:



(base)

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

Trade Name	Manufacturer	Country	Year Introduced
Dihydrostrepto	MSD	U.S.	1948
Abiocine	Lepetit	France	–
Didromycin	Specia	France	–
Didrothenat	Grunenthal	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 & Hanburys	U.K.	–
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 & Engel p. 309
I.N. p. 328

Peck, R.L.; U.S. Patent 2,498,574; February 21, 1950; assigned to Merck & Co., Inc.
Carboni, R.A. and Regna, P.P.; U.S. Patent 2,522,858; September 19, 1950; assigned to Chas. Pfizer & Co., Inc.
Levy, G.B.; U.S. Patent 2,663,685; December 22, 1953; assigned to Schenley Industries, Inc.
Dolliver, M.A. and Semenoff, S.; U.S. Patent 2,717,236; September 6, 1955; assigned to Olin Mathieson Chemical Corp.
Sokol, H. and Popino, R.P.; U.S. Patent 2,784,181; March 5, 1957; assigned to American Cyanamid Co.
Kaplan, M.A.; U.S. 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.; U.S. Patent 2,950,277; August 23, 1960; assigned to Takeda Pharmaceutical Industries, Ltd.

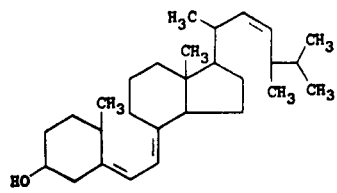
DIHYDROTACHYSTEROL

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	U.S.	1950
Calcamine	Sandoz	France	1949
D.H.T.	Roxane	U.S.	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 & Engel p. 309
PDR p. 1570
I.N. p. 329
REM p. 978
von Werder, F.; U.S. Patent 2,228,491; January 14, 1941; assigned to Winthrop Chemical Company, Inc.

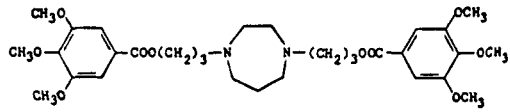
DILAZEP HYDROCHLORIDE

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:



(base)

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

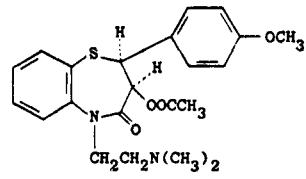
DILTIAZEM HYDROCHLORIDE

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: —

Structural Formula:



(base)

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

Trade Name	Manufacturer	Country	Year Introduced
Dilzem	Goedecke	W. Germany	1981
Cardizem	Marion	U.S.	1982
Cardizem	Nordic	Canada	1983
Tilazem	Parke Davis	—	—

Raw Materials

β-Diethylaminoethyl chloride
Sodium ethoxide
2-Aminothiophenol
4-Methoxybenzaldehyde
Acetic anhydride
Sodium bicarbonate
Hydrogen chloride
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 & 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., Ikezaki, M. and Takeo, S.; U.S. Patent 3,562,257; February 9, 1971; assigned to Tanabe Seiyaku Co., Ltd., Japan

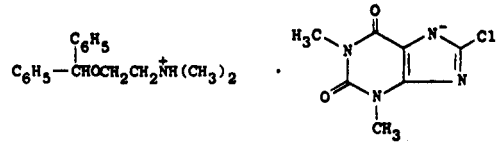
DIMENHYDRINATE

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	U.S.	1949
Dramamine	Searle	France	1957
Dramocen	Central	U.S.	1977
Dimate	Totag	U.S.	1980
Dramaban	Mallard	U.S.	1983
Amalmare	Saita	Italy	–
Amosyt	Leo	Sweden	–
Andrumin	Ethnor	Australia	–
Antemin	Streuli	Switz.	–
Anti-Em	Adeka	Turkey	–
Antivomit	Farmos	Finland	–
Aviomarine	Polfa	Poland	–
Betadorm A	Woelm Pharma	W. Germany	–
Bontourist	Katwijk	Neth.	–
Calm-X	Republic	U.S.	–
Dimenest	Fellows-Testagar	U.S.	–
Dipendrate	Kenyon	U.S.	–
Dramarr	Quimia	Spain	–
Dramavir	Vir	Spain	–
Dramavol	Barlowe Cote	Canada	–
Dromyl	A.F.Z.	Norway	–
Dymenol	Dymond	Canada	–
Emedyl	Montavit	Austria	–
Epha	Woelm	W. Germany	–
Gravol	Horner	Canada	–
Gravol	Carter Wallace	U.K.	–
Hydrate	Hyrex	U.S.	–
Lomarin	Geymonat	Italy	–
Mareosan	Bescansa	Spain	–
Marolin	Andreu	Spain	–
Motion Aid	Vangard	U.S.	–
Nauseal	Eri	Canada	–
Nauseatol	Sabek	Canada	–
Neptusan	Benzon	Denmark	–
Novomina	Robisch	W. Germany	–
Novodimenate	Novopharm	Canada	–
Paranausine	Couvreur	Belgium	–
Pastillas Azules	Llano	Spain	–
Reidamine	Reid-Provident	U.S.	–
Removine	Kerkhoff-Unicura	Neth.	–
Solbrine	Solac	France	–
Stada-Reisedragees	Stada	W. Germany	–
Travamin	Teva	Israel	–
Travamine	I.C.N.	Canada	–
Travel-Gum	Chemofux	Austria	–
Travin	Rondex	U.S.	–
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 & Engel p. 314
PDR pp. 1669, 1989
I.N. p. 334
REM p. 808
Cusic, J.W.; U.S. Patent 2,499,058; February 28, 1950; assigned to G.D. Searle & Co.
Cusic, J.W.; U.S. Patent 2,534,813; December 19, 1950; assigned to G.D. Searle & Co.

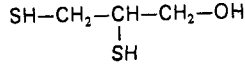
DIMERCAPROL

Therapeutic Function: Heavy metal antidote

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	U.S.	1944
Bal	Delalande	France	1950
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 & Engel p. 315
PDR p. 948
I.N. p. 335
REM p. 1224
Peppel, W.J. and Signaigo, F.K.; U.S. Patent 2,402,665; June 25, 1946; assigned to E.I. du Pont de Nemours & Company

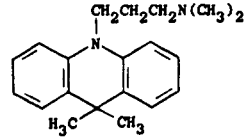
DIMETACRINE TARTRATE

Therapeutic Function: Antidepressant

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

Common Name: —

Structural Formula:



(base)

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
1-Chloro-3-dimethylaminopropane
Sodium amide
Tartaric acid

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/0.005 mm. $n_D^{29} = 1.5990$.

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 & 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.; U.S. Patent 3,284,454; November 8, 1966; assigned to Siegfried AG (Switzerland)

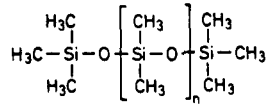
DIMETHICONE

Therapeutic Function: Antiflatulent

Chemical Name: Dimethylpolysiloxane

Common Name: Simethicone

Structural Formula:



n = 200 - 350

Chemical Abstracts Registry No.: 8050-81-5

Trade Name	Manufacturer	Country	Year Introduced
Silicote	Amer. Crit. Care	U.S.	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	Japan	–
Gasless	Hishiyama	Japan	–
Gaspanon	Kotani	Japan	–
Gasteel	Fuso	Japan	–
Gaszeron	Nichiiko	Japan	–
Gersmin	Kowa	Japan	–
Harop	Toyo	Japan	–
Kestomatine	Lircal	Italy	–
Lefax	Asche	W. Germany	–
Margarte	Mohan	Japan	–
Mylicon	Parke Davis	Italy	–
Mylicon	Stuart	U.S.	–
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	–
Trimax	Winthrop	Italy	–
Unicare	United	U.S.	–

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 mols) 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 copoly-

mer 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 & Engel p. 317
PDR p. 1826
Rem p. 774
Hyde, J.F.; U.S. Patent 2,441,098; May 4, 1948; assigned to Corning Glass Works

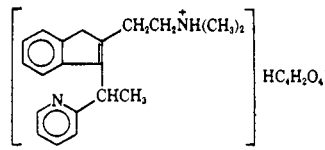
DIMETHINDENE MALEATE

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
Forhistal	Ciba	U.S.	1961
Fenostil	Zyma	U.K.	1963
Triten	Marion	U.S.	1971
Foristal	Ciba-Geigy-Takeda	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 & Engel p. 320
REM p. 1127
Huebner, C.F.; U.S. Patent 2,970,149; January 31, 1961; assigned to Ciba Pharmaceutical Products, Inc.

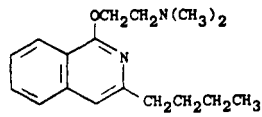
DIMETHISOQUIN

Therapeutic Function: Topical 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)

Trade Name	Manufacturer	Country	Year Introduced
Quotane	SKF	U.S.	1951
Quotane	Roger Bellon	France	1981
Isochinol	Chemipharm	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 2 N

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 & Engel p. 799
OCDS Vol. 1 p. 18 (1977)
I.N. p. 835
REM p. 1055
Ullyot, G.E.; U.S. Patent 2,612,503; September 30, 1952; assigned to Smith, Kline & French Laboratories

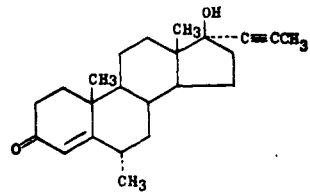
DIMETHISTERONE

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	U.S.	1965
Secrosteron	Allen & Hanburys	U.K.	—
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 6α-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 & 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.; U.S. 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.; U.S. Patent 2,939,819; June 7, 1960; assigned to The British Drug Houses Limited, England

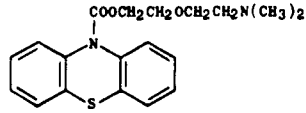
DIMETHOXANATE

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)

Trade Name	Manufacturer	Country	Year Introduced
Cothera	Ayerst	U.S.	1957
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 & Engel p. 319
OCDS Vol. 1 p. 390 (1977)
I.N. p. 336
von Seemann, C.; U.S. 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: $(CH_3)_2SO$

Chemical Abstracts Registry No.: 67-68-5

Trade Name	Manufacturer	Country	Year Introduced
Rimso	Research Industries	U.S.	1978
Damul	Pharm. Werk Meuselbach	E. Germany	—
Deltan	Serum & Impfinstitut	Switz.	—
Demasorb	Squibb	—	—
Demesco	MSD	—	—
Demsodrox	Nezel	Spain	—
Dermialgida	Andromaco	Spain	—
Dipirartril	Pons	Spain	—
Dromisol	MSD	—	—
Hyadur	Grunenthal	—	—
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.; U.S. Patent 2,581,050; January 1,1952; assigned to A.B. Centrallaboratorium Helsinki
Coma, J.G. and Gerttula, V.G.; U.S. Patent 3,045,051; July 17, 1962; assigned to Crown Zellerbach Corp.

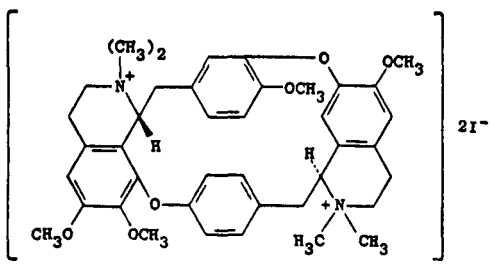
DIMETHYL TUBOCURARINE IODIDE

Therapeutic Function: Skeletal 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	U.S.	1949
Mecostrin	Squibb	U.S.	–
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 & Engel p. 319
I.N. p. 340
REM p. 923
Bray, M.D.; U.S. Patent 2,581,903; January 8, 1952; assigned to Eli Lilly and Company

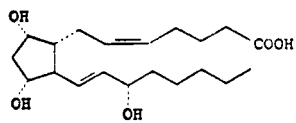
DINOPROST TROMETHAMINE

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

Structural Formula:



(base)

Chemical Abstracts Registry No.: 38562-01-5

Trade Name	Manufacturer	Country	Year Introduced
Prostin F2A	Upjohn	U.K.	1972
Prostin F2 Alpha	Upjohn	U.S.	1973
Prostalmon F	Ono	Japan	1974
Minprostin F2A	Upjohn	W. Germany	1975
Prostin F2 Alpha	Upjohn	Italy	1976
Pronalgon F	Sumitomo	Japan	1981
Amoglandin	Kabi Vitrum	Sweden	—
Enzaprost	Chinoin	Hungary	—
Enzaprost	Medica	Finland	—

Trade Name	Manufacturer	Country	Year Introduced
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 & Engel p. 321
OCDS Vol. 1 pp. 27, 33 (1977)
DOT 10 (4) 132 (1974) & 19 (6) 318 (1983)
I.N. p. 343
REM p. 950
Morozowich, W.; U.S. Patent 3,657,327; April 18, 1972; assigned to The Upjohn Company

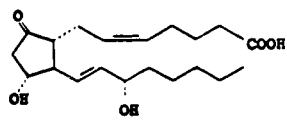
DINOPROSTONE

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	U.K.	1972

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

Raw Materials

Prostaglandin-A_2
Trimethylchlorosilane
Aluminum amalgam
Hexamethyldisilizane
Hydrogen peroxide

Manufacturing Process

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

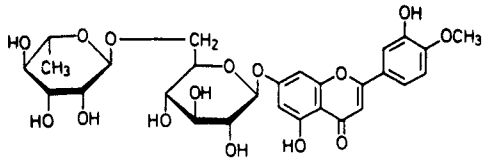
DIOSMIN

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.	–
Venex	Lusofarmaco	Portugal	–
Venosmine	Hommel	Switz.	–
Venotrex	Hommel	Switz.	–
Venusmin	Hommel	Switz.	–

Raw Materials

Hesperidin
Bromine
Acetic acid
Acetic anhydride
Sodium hydroxide

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

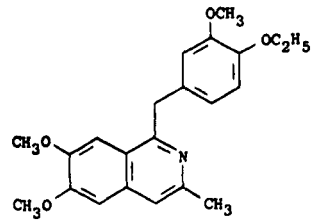
DIOXYLINE PHOSPHATE

Therapeutic Function: Vasodilator

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

Common Name: Dimoxyline

Structural Formula:



(base)

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

Trade Name	Manufacturer	Country	Year Introduced
Paveril	Lilly	U.S.	1951
Paverona	Lilly	Japan	—

Raw Materials

1-(3',4'-Dimethoxyphenyl)-2-propanone
Hydroxylamine HCl
Ammonia
3-Methoxy-4-ethoxyphenyl acetic acid
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 (0.2 mol) of α-methylhomoveratrylamine and 42.0 grams (0.2 mol) of 3-methoxy-4-ethoxyphenylacetic acid is heated at 190°-200°C for one hour. The reaction mixture is poured into about 100 cc 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 60 cc 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'-ethoxybenzylisoquinoline 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 & Engel p. 321
OCDS Vol. 1 p. 349 (1977)
I.N. p. 342
Shepard, E.R.; U.S. Patent 2,728,769; December 27, 1955; assigned to Eli Lilly and Co.