D

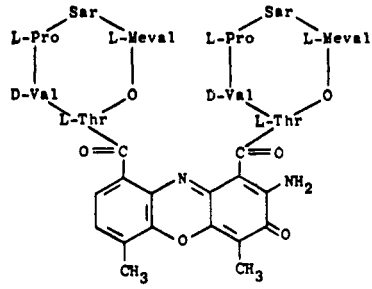
DACTINOMYCIN

Therapeutic Function: Cancer chemotherapy

Chemical Name: Complex actinomycin, see structural formula

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 & Dohme	U.S.	1965
Lyovac	Merck Sharp & Dohme	W. Germany	1966
Cosmegen	Merck Banyu	Japan	1969
Cosmegen	Merck Sharp & 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 & Engel p. 265
PDR p. 1151
I.N. p. 282
REM p. 1148
Waksman, S.A. and Woodruff, H.B.; U.S. Patent 2,378,876; June 19, 1945; assigned to Merck & Co., Inc.

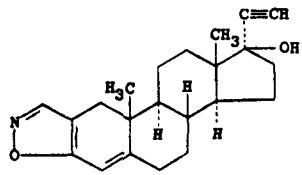
DANAZOL

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	U.K.	1974
Danocrine	Sterling Winthrop	U.S.	1976
Winobanin	Winthrop	W. Germany	1976
Danatrol	Winthrop	Switz.	1976
Bonzol	Tokyo Tanabe	Japan	1983
Chronogyn	Winthrop	U.S.	—
Cyclomen	Winthrop	Canada	—

Trade Name	Manufacturer	Country	Year Introduced
Danatrol	Sterwin Espanola	Spain	–
Ladogal	Ross	U.S.	–
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; $[\alpha]_D^{25} = +7.5 \pm 0.2°$ (in 95% ethanol); ultraviolet maximum at 286 mμ (E = 11,300).

References

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

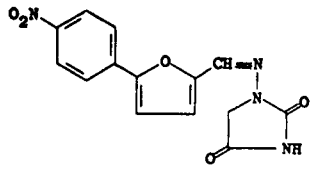
DANTROLENE SODIUM

Therapeutic Function: Skeletal 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:



(base)

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

Trade Name	Manufacturer	Country	Year Introduced
Dantrium	Norwich Eaton	U.S.	1974
Dantrium	Eaton	U.K.	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 & 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.; U.S. Patent 3,415,821; December 10, 1968; assigned to The Norwich Pharmacal Company

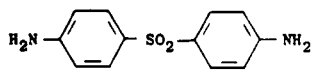
DAPSONE

Therapeutic Function: Antibacterial (leprostatic)

Chemical Name: 4,4'-Sulfonylbisbenzamine

Common Name: bis(4-Aminophenyl)sulfone; Diaphenylsulfone

Structural Formula:



Chemical Abstracts Registry No.: 80-08-0

Trade Name	Manufacturer	Country	Year Introduced
Avlosulfon	Ayerst	U.S.	1957
Dapsone	Jacobus	U.S.	—
Disulone	Specia	France	—
Maloprim	Wellcome	U.K.	—
Novophone	—	—	—
Protogen	Yoshitomi	Japan	—
Sulfona Oral	Esteve	Spain	—
Udolac	I.C.I.	U.K.	—

Raw Materials

p-Chloronitrobenzene
Acetamidobenzene sodium sulfonate
Stannous chloride
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 & Engel p. 267
PDR p. 951
OCDS Vol. 1 p. 139 (1977) & 2 p. 112 (1980)
I.N. p. 284
Weijiard, J. and Messerly, J.P.; U.S. Patent 2,385,899; October 2, 1945; assigned to Merck & Co., Inc.

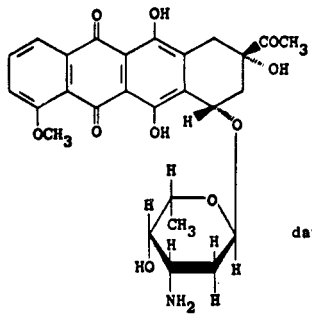
DAUNORUBICIN

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 & Baker	U.K.	1971
Cerubidine	Ives	U.S.	1979
Cerubidine	Rhone-Poulenc	Canada	—
Ondena	Bayer	—	—
Rubomycin	Medexport	U.S.S.R.	—

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
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 μg/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

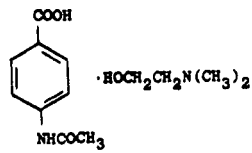
DEANOL ACETAMIDOBENZOATE

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	U.S.	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 solu-

tion 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 & Engel p. 267
I.N. p. 285
REM p. 1136
British Patent 879,259; October 11, 1961; assigned to Riker Laboratories, Inc.

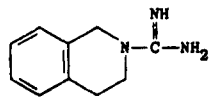
DEBRISOQUIN

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	U.K.	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) & 2 p. 374 (1980)
DOT 16 (4) 137 (1980)
I.N. p. 286
Wenner, W.; U.S. Patent 3,157,573; November 17, 1964; assigned to Hoffmann-LaRoche, Inc.

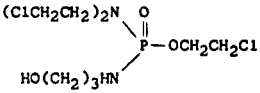
DEFOSFAMIDE

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.; U.S. Patent 3,035,080; May 15, 1962; assigned to Asta-Werke A.G. Chemische Fabrik (W. Germany)

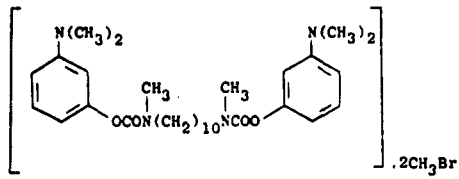
DEMECARIUM BROMIDE

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	U.S.	1959
Tonilen	Frumtost	Spain	—
Tosmilen	Chibret	France	—
Tosmilen	Chugai	Japan	—
Tosmilen	Linz	Austria	—
Tosmilen	Lentia	W. Germany	—
Tosmilen	Astra	U.K.	—

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-dimethylaminophenylester-bromomethylate) 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 & Engel p. 270
PDR p. 1182
I.N. p. 290
REM p. 898
Schmid, O.; U.S. Patent 2,789,981; April 23, 1957; assigned to Oesterreichische Stickstoffwerke AG, Austria.

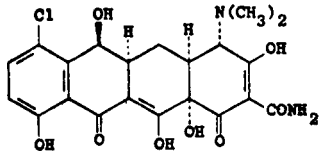
DEMECLOCYCLINE HYDROCHLORIDE

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:



(base)

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

Trade Name	Manufacturer	Country	Year Introduced
Declomycin	Lederle	U.S.	1959
Ledermycine	Lederle	Japan	1970
Ledermycine	Lederle	France	1971
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	Biotraching	Italy	–
Fidocin	Farmaroma	Italy	–
Isodemetil	Isola Ibi	Italy	–
Latomicina	Farber-R.E.F.	Italy	–
Ledermicina	Lederle	Italy	–
Magis-Ciclina	Tiber	Italy	–
Meciclin	Citobios	Switz.	–

Trade Name	Manufacturer	Country	Year Introduced
Mexocine	Specia	France	–
Mirciclina	Francia	Italy	–
Neo-Cromaciclin	Panther-Osfa	Italy	–
Perciclina	Atral	Portugal	–
Provimicina	Lifasa	Spain	–
Temet	Colli	Italy	–
Tetradek	S.I.T.	Italy	–
Tollercin	Scalari	Italy	–
Veraciclina	A.F.I.	Italy	–

Raw Materials

Bacterium *S. aureofaciens*
Corn starch

Manufacturing Process

According to U.S. 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 U.S. 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 & 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.; U.S. Patent 2,878,289; March 17, 1959; assigned to American Cyanamid Company
Szumski, S.A.; U.S. Patent 3,012,946; December 12, 1961; assigned to American Cyanamid Company
Goodman, J.J. and Matrishin, M.; U.S. Patent 3,019,172; assigned to American Cyanamid Company
Goodman, J.J.; U.S. Patent 3,050,446; August 21, 1962; assigned to American Cyanamid Company
Neidleman, S.L.; U.S. Patent 3,154,476; October 27, 1964; assigned to Olin Mathieson Chemical Corporation

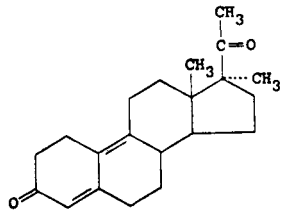
DEMEGESTONE

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
Methyl iodide
Acetic acid
Chromic acid
Lithium
Ammonia
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-$\Delta^{1,3,5(10),16}$-pregnatetraene-20-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 $[\alpha]_D^{20} = +75° \pm 1°$ (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 $[\alpha]_D^{20} = +168.5° \pm 3.5°$ (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 0°C. 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 $[\alpha]_D^{20} = -270° \pm 4.5°$ (c = 0.5% in ethanol) were obtained.

References

Merck Index 2860
Kleeman & 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.; U.S. Patent 3,453,267; July 1, 1969; assigned to Roussel-Uclaf, France
Joly, R., Warnant, J. and Farcilli, A.; U.S. Patent 3,547,959; December 15, 1970; assigned to Roussel-UCLAF, France

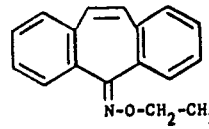
DEMEXIPTILINE HCl

Therapeutic Function: Antidepressant

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

Common Name: —

Structural Formula:



(base)

Chemical Abstracts Registry No.: –

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.; U.S. Patent 3,963,778; June 15, 1976; assigned to Bayer A.G. (W. Germany)

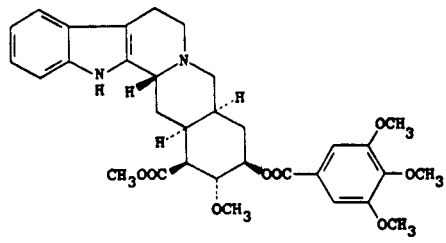
DESERPIDINE

Therapeutic Function: Antihypertensive

Chemical Name: 17α-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	U.S.	1957
Enduronyl	Abbott	U.S.	–
Harmonyl	Abbott	U.S.	–
Harmonyl	Abbott	U.K.	–
Oreticyl	Abbott	U.S.	–
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 & Engel p. 272
PDR pp. 515, 526, 543

OCDS Vol. 1 p. 320 (1977)
I.N. p. 296
REM p. 909
Ulshafer, P.R.; U.S. Patent 2,982,769; May 2, 1961; assigned to Ciba Pharmaceutical

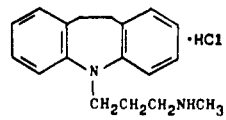
DESIPRAMINE HYDROCHLORIDE

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	U.K.	1963
Norpramine	Merrell	U.S.	1964
Pertofrane	U.S.V.	U.S.	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	U.S.	—
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 & 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
Biel, J.H. and Judd, C.I.; U.S. Patent 3,454,554; July 8, 1969; assigned to Colgate-Palmolive Co.

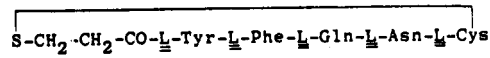
DESMOPRESSIN

Therapeutic Function: Antidiuretic

Chemical Name: 1-(3-Mercaptopropionic acid)-8D-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	U.K.	1975
Minirin	Ferring	W. Germany	1976
DDAVP	U.S.V.	U.S.	1978
Desmopressin	Kyowa	Japan	1979
Minirin DDAVP	Valeas	Italy	1979
Adiuretin	Spofa	Czechoslovakia	—
Defirin	Ferring	Sweden	—
Desurin	Ferring	Sweden	—
Minirin	Protea	Australia	—
Stimate	Armour	U.S.	—

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

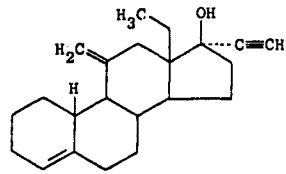
DESOGESTREL

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	Organon	W. Germany	1981
Marvelon	Organon	U.K.	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-Δ^4-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) & 19 (10) 570 (1983)

I.N. p. 297
Van den Broek, A.J.; U.S. Patent 3,927,046; December 16, 1975; assigned to Akzona, Inc.

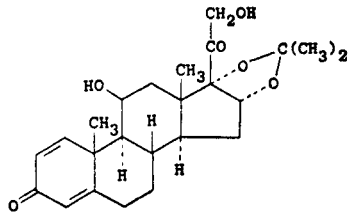
DESONIDE

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	U.S.	1972
Tridesilon	Dome	U.K.	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 on 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 (3 x 25 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 & 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.; U.S. Patent 2,990,401; June 27, 1961; assigned to American Cyanamid Company
Diassi, P.A. and Principe, P.A.; U.S. Patent 3,549,498; December 22, 1970; assigned to E.R. Squibb & Sons, Inc.

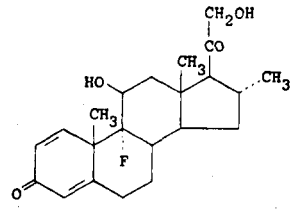
DESOXIMETASONE

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
Topicort	Hoechst	U.S.	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 m^3/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-Δ^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 & Engel p. 277
PDR p. 946
I.N. p. 297
REM p. 972
Kieslich, K., Kerb, U. and Raspe, G.; U.S. Patent 3,232,839; February 1, 1966; assigned to Schering AG, Germany

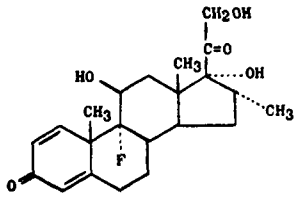
DEXAMETHASONE ACETATE

Therapeutic Function: Glucocorticoid

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

Common Name: –

Structural Formula:



(base)

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

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

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 U.S. 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 & Engel p. 278
PDR pp. 695, 928, 1156, 1286, 1569, 1606, 1723
OCDS Vol. 1 p. 199 (1977)
I.N. p. 299
REM p. 972
Fried, J.; U.S. Patent 2,852,511; September 16, 1958; assigned to Olin Mathieson Chemical Corporation
Muller, G., Bardoneschi, R. and Jolly, J.; U.S. Patent 3,007,923; November 7, 1961; assigned to Les Laboratories Francais de Chimiotherapie, France

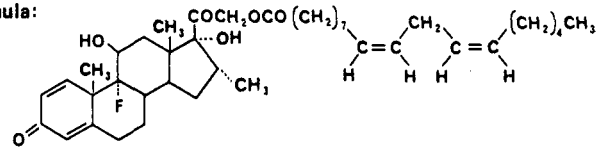
DEXAMETHASONE-21-LINOLEATE

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: –

Structural Formula:



Chemical Abstracts Registry No.: 39026-39-6

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

Raw Materials

9α-Fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione
Methane sulfonyl 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 (10 g, 25.5 mmol) in 20 ml pyridine and 12 ml acetone at -10°C, a cold solution of methane sulfonyl chloride (3 ml, 38.5 mmol) in 8 ml acetone was added dropwise. The addi-

tion was completed within about 3 hours and the mixture was then left standing in the cold for a further 1.5 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 1.5 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 & 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)

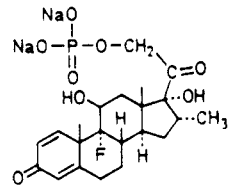
DEXAMETHASONE PHOSPHATE

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&D	U.S.	1959
Hexadrol Phosphate	Organon	U.S.	1965
Maxidex	Algon	U.S.	1975
Dexacen 4	Central	U.S.	1977
Aacidexam	Aaciphar	Belgium	–
Cebedex	Chauvin-Blache	France	–
Cebefrasone	Chauvin-Blache	France	–
Chibro-Cardon	Chibret	France	–
Colvasone	Norbrook	U.K.	–
Cortcetine	Chauvin-Blache	France	–
Dalaron	O'Neal Jones	U.S.	–
Decaderm	Frosst	Australia	–

Trade Name	Manufacturer	Country	Year Introduced
Decadron	Banyu	Japan	—
Decalibour	MSD	France	—
Dekort	Deva	Turkey	—
Delladec	O'Neal Jones	U.S.	—
Desalark	Farm. Milanese	Italy	—
Dexacort	Ikapharm	Israel	—
Dexaderme	Chauvin-Blache	France	—
Dexa-Helvacort	Helvepharm	Switz.	—
Dexamed	Medice	W. Germany	—
Dexasone	Legere	U.S.	—
Eta-Cortilen	S.I.F.I.	Italy	—
Megacort	Lancet	Italy	—
Orgadrone	Sankyo	Japan	—
Penthasone	Pentagone	Canada	—
Savacort	Savage	U.S.	—
Soldesam	Farm. Milanese	Italy	—
Solone	Liade	Spain	—
Soludecadron	MSD	France	—
Solurex	Hyrex	U.S.	—
Spersadex	Dispersa	Switz.	—
Vasodex	Smith, Miller & Patch	Puerto Rico	—

Raw Materials

Phosphoric acid
Triethylamine
9α-Fluoro-11β,17α,21-trihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione-21-methane sulfonate
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-3,20-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 & 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.; U.S. Patent 2,939,873; June 7, 1960; assigned to Merck & Co., Inc.

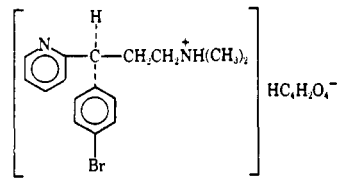
DEXBROMPHENIRAMINE MALEATE

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	U.S.	1959
Dexbrom	Zenith	U.S.	—
Disophrol	Schering	U.S.	—
Drixoral	Schering	U.S.	—
Ebalin	Allergopharma	W. Germany	—

Raw Materials

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

Manufacturing Process

The following is taken from U.S. 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 thereof 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 & Engel p. 283
PDR p. 1999
OCDS Vol. 1 p. 77 (1977)

I.N. p. 302
REM p. 1132
Walter, L.A.; U.S. 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: See dexbrompheniramine maleate substituting -Cl for -Br.

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

Trade Name	Manufacturer	Country	Year Introduced
Polaramine	Schering	U.S.	1958
Celestamine	Cetrane	France	—
Destral	Tiber	Italy	—
Dexchlor	Schein	U.S.	—
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,N-dimethylpropylamine-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 U.S. Patent 3,030,371.

References

Merck Index 2908
Kleeman & Engel p. 284
PDR pp. 1606, 1648
OCDS Vol. 1 p. 77 (1977)
I.N. p. 302
REM p. 1127
Walter, L.A.; U.S. Patents 3,061,517; October 30, 1962; and 3,030,371; April 17, 1962; both assigned to Schering Corporation

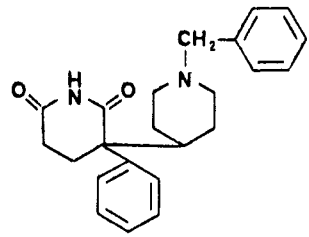
DEXETIMIDE

Therapeutic Function: Anticholinergic

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

Common Name: Dexbenzetimide; dextrobenzetimide; benzetimide

Structural Formula:



(base)

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 1-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-3-phenyl-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) & 9 (6) 247 (1975)
I.N. p. 302
Janssen, P.A.J.; U.S. Patent 3,125,578; March 17, 1964; assigned to Research Laboratorium Dr. C. Janssen NV (Belgium)

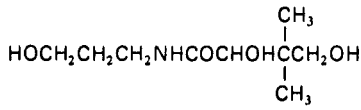
DEXPANTHENOL

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	U.S.	1957
Cozyme	Travenol	U.S.	1958
Motilyn	Abbott	U.S.	1960
Beducene	Roche	—	—
Dexol	Legere	U.S.	—
Intrapan	Elkins-Sinn	U.S.	—
May-Vita	Mayrand	U.S.	—
Pantene	Shionogi	Japan	—
Pantenyl	Kay	U.S.	—
Panthenol-Drobena	Drobena	W. Germany	—
Panthoderm	U.S.V.	U.S.	—
Pantol	Toa-Eiyo-Yamanouchi	Japan	—
Thenalton	Fulton	Italy	—
Tonestat	A.V.P.	U.S.	—
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-γ-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 & Engel p. 284
PDR pp. 563, 872, 1033, 1083
I.N. p. 302
REM p. 813
Schnider, O.; U.S. Patent 2,413,077; December 24, 1946; assigned to Hoffmann-La Roche Inc.

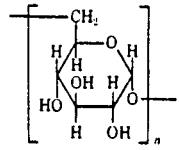
DEXTRAN 40

Therapeutic Function: Plasma extender

Chemical Name: Polymeric glucose (see structural formula) of molecular weight 40,000

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 9004-54-0

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

Raw Materials

Sucrose
Bacterium *Leuconostoc mesenteroides*

Manufacturing Process

Sucrose is subjected to the action of the bacterium *Leuconostoc 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.; U.S. Patent 2,644,815; July 7, 1953; assigned to Aktiebolaget Pharmacia, Sweden
Shurter, R.A.; U.S. Patent 2,717,853; September 13, 1955; assigned to Commercial Solvents Corp.
Behrens, U. and Ringpfeil, M.; U.S. Patent 3,044,940; July 17, 1962; assigned to Vebserum-Werk Bernburg (W. Germany)
Novak, L.J. and Stoycos, G.S.; U.S. Patent 2,841,578; July 1, 1958; assigned to Commonwealth Eng. Co. of Ohio
Novak, L.J. and Witt, E.E.; U.S. Patent 2,972,567; February 21, 1961; assigned to Commonwealth Eng. Co. of Ohio

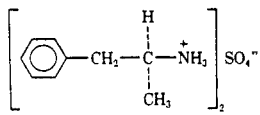
DEXTROAMPHETAMINE SULFATE

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	U.S.	1944
Domofate	Haag	U.S.	1954
Dexalme	Meyer	U.S.	1954
Amsusatain	Key	U.S.	1954
Evrodex	Evron	U.S.	1955
Cendex	Dentral	U.S.	1956
D-Ate	Lemmon	U.S.	1957
Perke One	Ascher	U.S.	1966
Dexaspan	U.S.V.	U.S.	1969
Dexa Sequels	Lederle	U.S.	1970
Dexamplex	Lemmon	U.S.	1976
Adiparthrol	Syntex-Medical	Switz.	—

Trade Name	Manufacturer	Country	Year Introduced
Amfe-Dyn	Pharma-Dyn	Italy	–
d-Amfetasul	Pitman-Moore	U.S.	–
Curban	Pasadena	U.S.	–
Dexamine	Streuli	Switz.	–
Obetrol	Rexar	U.S.	–
Simpamina	Recordat	Italy	–
Stil-2	Castillon	Spain	–

Raw Materials

dl-α-Methylphenethylamine
d-Tartaric acid
Sodium hydroxide
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.; U.S. Patent 2,276,508; March 17, 1942; assigned to Smith, Kline & French Laboratories

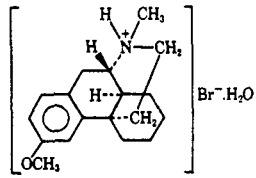
DEXTROMETHORPHAN HYDROBROMIDE

Therapeutic Function: Antitussive

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

Common Name: Racemethorphan hydrobromide

Structural Formula:



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

Trade Name	Manufacturer	Country	Year Introduced
Symptom 1	Parke Davis	U.S.	1977
Romilar HBR	Block	U.S.	1954
Methorate	Upjohn	U.S.	1958
Dormethan	Dorsey	U.S.	1958
Tusasade	Westerfield	U.S.	1964
Benylin	Parke Davis	U.S.	1978
Delsym	Pennwalt	U.S.	1982
Cremacoat	Vicks	U.S.	1983
Agrippol	Herdt & Charton	Canada	–
Albatussin	Bart	U.S.	–
Ambenyl-D	Marion	U.S.	–
Balminil-DM	Rougier	Canada	–
Broncho-Grippol	Herdt & Charton	Canada	–
Calmasan	Syntex-Pharm	Switz.	–
Calmerphan-L	Siegfried	Switz.	–
Cardec	Schein	U.S.	–
Codimal	Central	U.S.	–
Comtrex	Bristol-Myers	U.S.	–
Congespirin	Bristol-Myers	U.S.	–
Contratuss	Eri	Canada	–
Coryban D	Pfipharmecs	U.S.	–
Co Tylenol	McNeil	U.S.	–
Coughcon	Santen	Japan	–
Demo-Cineol	Sabex	Canada	–
Dextphan	Hishiyama	Japan	–
Extuson	Ferrosan	Denmark	–
Histalet DM	Reid-Roweli	U.S.	–
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	U.S.	–
Pedia Care	McNeil	U.S.	–
Pulmex-DM	Therapex	Canada	–
Quelidrine	Abbott	U.S.	–
Rivodex	Rivopharm	Switz.	–
Robidex	Robins	U.S.	–
Scot-Tussin	Scot-Tussin	U.S.	–
Sedatuss	Trianon	Canada	–
Sedotus	Farge	Italy	–
Sisaal	Towa	Japan	–
Sorbutuss	Dalin	U.S.	–
St. Joseph Cough Syrup	Plough	U.S.	–
Testamin	Toyama	Japan	–
Triaminicol	Dorsey	U.S.	–

Trade Name	Manufacturer	Country	Year Introduced
Trimpus	Zensei	Japan	–
Tussar D.M.	U.S.V.	U.S.	–
Tussidyl	Tika	Sweden	–
Tussi-Organidin	Wallace	U.S.	–
Val-Atux	Farm. Milanese	Italy	–

Raw Materials

D,L-3-Hydroxy-N-methyl-morphinan
Phenyl trimethyl ammonium chloride
D-Tartaric acid
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-trimethyl-ammonium-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.; U.S. Patent 2,676,177; April 20, 1954; assigned to Hoffmann-La Roche Inc.

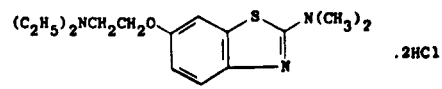
DIAMTHAZOLE DIHYDROCHLORIDE

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
Asterol	Roche	U.S.	1951
Athelor	Roche	—	—
Atelora	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 & Engel p. 313
I.N. p. 333
Steiger, N. and Keller, O.; U.S. Patent 2,578,757; December 18, 1951; assigned to Hoffmann-La Roche, Inc.

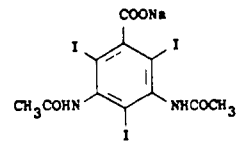
DIATRIZOATE SODIUM

Therapeutic Function: Diagnostic aid (radiopaque medium)

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

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	U.S.	1955
MD-50	Mallinckrodt	U.S.	1980
Urovist Sodium	Berlex	U.S.	1983
Trignost	Teva	Israel	—
Urovison	Schering	W. Germany	—
Visotrast	Fahlberg-List	E. Germany	—

Raw Materials

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

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 & 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.; U.S. Patent 3,076,024; January 29, 1963; assigned to Sterling Drug, Inc.

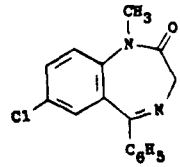
DIAZEPAM

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	U.S.	1963
Valium	Roche	W. Germany	1963
Valium	Roche	U.K.	1963
Valium	Roche	France	1964
Novazam	Genevrier	France	1983
Aliseum	Zova	Italy	—
Amiprol	U.S. 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	U.K.	—
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	U.K.	–
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	Neth.	–
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	U.K.	–
Pacitran	Grossmann	Mexico	–
Pacitran	Lafi	Brazil	–
Pax	Lennon	S. Africa	–
Paxel	Elliott-Marion	Canada	–
Pro-Pam	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	U.K.	–
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	U.K.	–
Somasedan	Celtia	Argentina	–
Sonacon	Delmar	Canada	–
Sonacon	Chugai	Japan	–
Stresolid	Dumex	Denmark	–
Stress-Pam	Sabex	Canada	–
Tensium	D.D.S.A.	U.K.	–
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	–

Trade Name	Manufacturer	Country	Year Introduced
Vival	A.L.	Norway	–
Vivol	Horner	Canada	–
Zepam	Aksu	Turkey	–

Raw Materials

2-Amino-5-chlorobenzophenone-β-oxime
Chloroacetyl chloride
Phosphorus trichloride
Sodium hydroxide
Diazomethane

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 vacuo. 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 2-chloroacetamido-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 vacuo 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 U.S. Patent 3,136,815. Purification of diazepam is discussed in U.S. Patent 3,102,116.

References

Merck Index 2967
Kleeman & Engel p. 288
PDR pp. 1506, 1517, 1999
OCDS Vol. 1 p. 365 (1977) & 2 p. 452 (1980)
DOT 9 (6) 236 (1973); 18 (8) 380 (1982) & 19 (3) 170 (1983)
I.N. p. 309
REM p. 1062

Chase, G.; U.S. Patent 3,102,116; August 27, 1963; assigned to Hoffmann-La Roche Inc.
Reeder, E. and Sternbach, L.H.; U.S. Patent 3,109,843; November 5, 1963; assigned to Hoffmann-La Roche Inc.
Reeder, E. and Sternbach, L.H.; U.S. Patent 3,136,815; June 9, 1964; assigned to Hoffmann-La Roche Inc.
Reeder, E. and Sternbach, L.H.; U.S. Patent 3,371,085; February 27, 1968; assigned to Hoffmann-La Roche Inc.

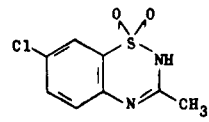
DIAZOXIDE

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 Hanburys	U.K.	1970
Hyperstat	Schering	U.S.	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	U.S.	—

Raw Materials

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

Manufacturing Process

One route is described in U.S. 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. Sus-

pend 50 grams of 2-benzylthio-4-chloro-nitrobenzene 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 1.5 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 U.S. 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 & Engel p. 290
PDR pp. 1130, 1630
OCDS Vol. 1 p. 355 (1977) & 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.; U.S. Patent 2,986,573; May 30, 1961; assigned to Schering Corporation
Topliss, J.G., Sperber, N. and Rubin, A.A.; U.S. Patent 3,345,365; October 3, 1967; assigned to Schering Corporation

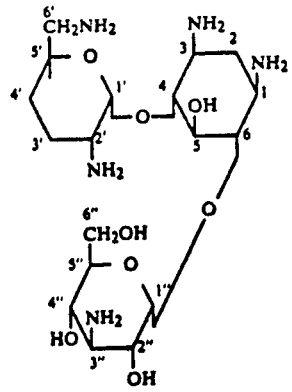
DIBEKACIN

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 Erba	Italy	1980
Ioacine	Bristol	France	1981
Decabicin	Lefa	Spain	—
Debekacyl	Meiji	Japan	—
Duramycin	Pfizer-Roerig	—	—
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., U.S.A.) 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'-enokanamycin 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 1.5 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 & Engel p. 290
DOT 12 (5) 211 (1976)
I.N. p. 311
Umezawa, H., Umezawa, S. and Tsuchiya, T.; U.S. Patent 4,169,939; October 2, 1979; assigned to Zaidan Hojin Biselbutsu Kagaku Kenkyu Kai (Japan)

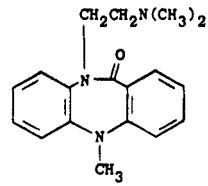
DIBENZEPIN HYDROCHLORIDE

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:



(base)

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	U.K.	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/0.01 mm 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 & Engel p. 291
OCDS Vol. 1 p. 405 (1977) & 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.; U.S. Patent 3,419,547; December 31, 1968; assigned to Dr. A. Wander, S.A. (Switzerland)

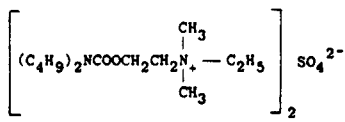
DIBUTOLINE SULFATE

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	U.S.	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 re-

sulting 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.; U.S. Patent 2,432,049; December 2, 1947

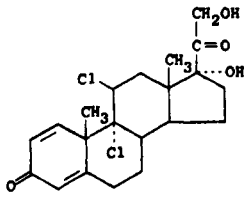
DICHLORISONE ACETATE

Therapeutic Function: Topical 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	U.S.	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 & Engel p. 292
OCDS Vol. 1 p. 203 (1977)
I.N. p. 314
Gould, D.H., Reimann, H. and Finckenor, L.E.; U.S. Patent 2,894,963; July 14, 1959; assigned to Schering Corp.

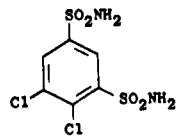
DICHLORPHENAMIDE

Therapeutic Function: Carbonic anhydrase inhibitor; glaucoma treatment

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	U.S.	1958
Oratrol	Alcon	U.S.	1960
Diclofenamid	Mann	W. Germany	1976
Antidrasi	I.S.F.	Italy	–
Barastonin	Santen	Japan	–
Fenamide	Farmigea	Italy	–
Glajust	Hotta	Japan	–

Trade Name	Manufacturer	Country	Year Introduced
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
Phosphorus pentachloride
O-Chlorophenol
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 & Engel p. 294
PDR p. 1155
OCDS Vol. 1 p. 133 (1977)
I.N. p. 316
REM p. 936
Schultz, E.M.; U.S. Patent 2,835,702; May 20, 1958; assigned to Merck & Co., Inc.

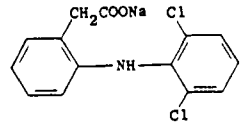
DICLOFENAC SODIUM

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	U.K.	1978
Adefuronic	Taiyo	Japan	—
Blesin	Sawai	Japan	—
Dichronic	Toyo	Japan	—
Docell	Nippon Kayaku	Japan	—
Irinatolon	Tatumi	Japan	—
Kriplex	Alfa Farm.	Italy	—
Neriodin	Teikoku	Japan	—
Shignol	Taisho	Japan	—
Sofarin	Nippon Chemiphar	Japan	—
Sorelmon	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 U.S. Patent 3,558,690.

References

Merck Index 3066
Kleeman & Engel p. 293
OCDS Vol. 2 p. 70 (1980)
DOT 9 (9) 369 (1973) & 11 (3) 106 (1975)
I.N. p. 316

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

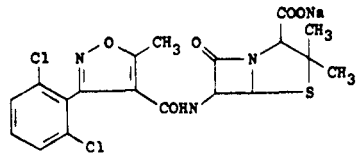
DICLOXACILLIN SODIUM

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.