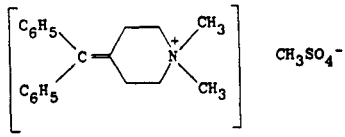
DIPHEMANIL METHYLSULFATE

Therapeutic Function: Antispasmodic

Chemical Name: 4-(diphenylmethylene)-1,1-dimethylpiperidinium methyl sulfate

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 62-97-5

Trade Name	Manufacturer	Country	Year Introduced
Prantal	Schering	U.S.	1952
Prantal	Unicet	France	1958
Demotil	Pharmacia	Sweden	—
Prentol	Essex Espana	Spain	—

Raw Materials

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

Manufacturing Process

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

(B) Preparation of Diphenyl-(N-Methyl-4-Piperidylidene)Methane: The carbinol can be dehydrated with 60% sulfuric acid. In general, to one part of the carbinol there is added 10 parts of 60% sulfuric acid. The mixture after heating for 6 hours is poured onto cracked ice, the solution made alkaline with dilute sodium hydroxide and the oily basic layer extracted with ether. The ether extracts after washing with water are dried over sodium sulfate, and after removing the ether, the residue is distilled in vacuo, MP 52°-53°C.

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

References

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

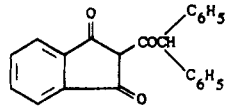
DIPHENADIONE

Therapeutic Function: Anticoagulant

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

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

Structural Formula:



Chemical Abstracts Registry No.: 82-66-6

Trade Name	Manufacturer	Country	Year Introduced
Dipaxin	Upjohn	U.S.	1955
Didandin	Boots	–	–

Raw Materials

Dimethyl phthalate
Diphenylacetone
Sodium
Methanol

Manufacturing Process

A solution of sodium methoxide was prepared by adding 2.76 grams (0.12 mol) of sodium to 50 ml of absolute methanol and gently warming the mixture to effect complete solution of the sodium. To this was added 300 milliliters of dry benzene with vigorous stirring, whereafter excess methanol was removed by concentrating the mixture to a volume of about 100 ml. To the resulting sodium methoxide suspension was added a solution of 19.4 grams (0.1 mol) of dimethyl phthalate in 200 ml of dry benzene. The mixture was heated to boiling and a solution of 21 grams (0.1 mol) of diphenylacetone in 200 ml of dry benzene was added dropwise thereto. During addition approximately 200 ml of liquid, which consisted of benzene together with methanol formed during the course of the reaction, was distilled from the reaction mixture. After addition of the diphenylacetone, the mixture was heated under reflux for about 6 hours, cooled and stirred vigorously with 200 ml of 5% sodium hydroxide solution.

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

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

References

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

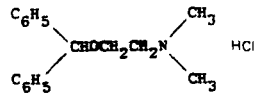
DIPHENHYDRAMINE HYDROCHLORIDE

Therapeutic Function: Antihistaminic

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

Common Name: Benzhydramine hydrochloride

Structural Formula:



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

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

Trade Name	Manufacturer	Country	Year Introduced
Kendiphen	Key	U.S.	–
Lensen	Geneva	U.S.	–
Mandrax	I.S.H.	France	–
Medidryl	Medica	Finland	–
Nautamine	Delagrange	France	–
Niramine	Rachelle	U.S.	–
Noctomin	Medichemie	Switz.	–
Phentamine	Restan	S. Africa	–
Pheramin	Kanoldt	W. Germany	–
Prodryl	Progress	U.S.	–
Restamin	Kowa	Japan	–
Reston	Kowa	Japan	–
Serundal D	Woelm	W. Germany	–
Somenox	Cooper	Switz.	–
Valdrene	Vale	U.S.	–
Vilbin	Felbena	Switz.	–
Ziradryl	Parke Davis	U.S.	–

Raw Materials

β-Dimethylaminoethanol
Diphenylmethane
Sodium carbonate
Bromine

Manufacturing Process

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

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

(b) 490 parts β-dimethylaminoethanol and 530 parts of anhydrous sodium carbonate are heated to 110°C with stirring. The addition of the benzene-benzhydryl bromide mixture is then begun. The temperature is raised to 120°-125°C. As reaction takes place carbon dioxide is evolved, the addition requires 1½ hours. The mixture is kept at 125°C for 5 hours additional time. After cooling, 3,000 parts of water is added and the mixture stirred until the inorganic salts are dissolved. The mixture is transferred to a large separatory funnel and 1,500 parts of ether added. The ether solution is washed several times with water and then the ether layer extracted with 1 to 4 hydrochloric acid. The acid solution is treated with 30 parts of Darco and 30 parts Filter-Cel and filtered.

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

References

Merck Index 3320
Kleeman & Engel p. 327

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

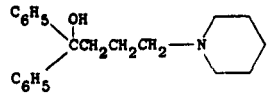
DIPHENIDOL

Therapeutic Function: Antinauseant

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

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 972-02-1

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

Raw Materials

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

Manufacturing Process

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

References

Merck Index 3323
Kleeman & Engel p. 300
PDR p. 1731
OCDS Vol. 1 p. 45 (1977)
DOT 3 (1) 32 (1967)
I.N. p. 323
REM p. 808
Miescher, K. and Marxer, A.; U.S. Patent 2,411,664; November 26, 1946; assigned to Ciba Pharmaceutical Products, Inc.

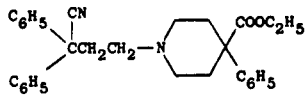
DIPHENOXYLATE HYDROCHLORIDE

Therapeutic Function: Antidiarrheal

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

Common Name: —

Structural Formula:



(base)

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

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

Raw Materials

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

Manufacturing Process

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

References

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

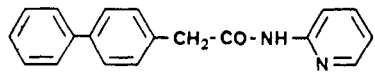
DIPHENPYRAMIDE

Therapeutic Function: Antiinflammatory

Chemical Name: 2-(Diphenylacetylamino)-pyridine

Common Name: Difenpiramide

Structural Formula:



Chemical Abstracts Registry No.: 51484-40-3

Trade Name	Manufacturer	Country	Year Introduced
Difenax	Zambeletti	Italy	1977

Raw Materials

Diphenylacetic acid chloride
2-Aminopyridine

Manufacturing Process

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

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

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

References

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

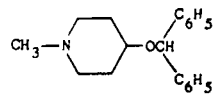
DIPHENYLPYRALINE HYDROCHLORIDE

Therapeutic Function: Antihistaminic

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

Common Name: —

Structural Formula:



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

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

Raw Materials

1-Methyl-4-piperidinol
Benzhydryl bromide
Hydrogen chloride

Manufacturing Process

A mixture of 46 grams of 1-methyl-4-piperidinol (0.4 mol), 49.4 grams of benzhydryl bromide (0.2 mol) and 100 ml of xylene was refluxed for approximately 24 hours. The reaction mixture separated into two phases with the upper phase containing the desired

ether compound dissolved in xylene. The lower phase consisted of the hydrobromide salt of the excess 1-methyl-4-piperidinol. The upper phase was separated from the lower phase and the desired benzhydryl ether recovered in the crude state by distilling off the xylene under reduced pressure.

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

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

References

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

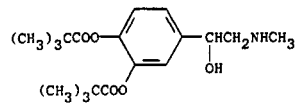
DIPIVEFRIN

Therapeutic Function: Adrenergic (Ophthalmic)

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

Common Name: Dipivalyl epinephrine

Structural Formula:



Chemical Abstracts Registry No.: 52365-63-6

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

Raw Materials

α-Chloro-3',4'-dihydroxyacetophenone
Methylamine
Pivaloyl chloride
Hydrogen

Manufacturing Process

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

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

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

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

References

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

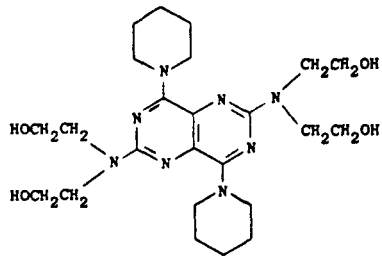
DIPYRIDAMOLE

Therapeutic Function: Coronary vasodilator

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

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 58-32-2

Trade Name	Manufacturer	Country	Year Introduced
Persantine	Boehr./Ingel.	U.S.	1961
Natyl	Nativelle	France	1961
Persantin	Boehr./Ingel.	U.K.	1961
Persantin	Thomae	W. Germany	1966
Agilease	Isei	Japan	—
Anginal	Yamanouchi	Japan	—
Atlantin	Dojin	Japan	—
Cardoxin	Rafa	Israel	—
Cleridium	Millot	France	—
Coribon	Radiumpharma	Italy	—
Coronamole	Nichiiko	Japan	—
Coronarine	Negma	France	—
Corosan	Saita	Italy	—
Coroxin	Malesci	Italy	—
Curantyl	Arzneimittelwerk Dresden	E. Germany	—
Dipyrida	Schurholz	W. Germany	—
Drisentin	Drifa	Turkey	—
Functiocardon	Krewel	W. Germany	—
Gulliostin	Taiyo	Japan	—
Isephanine	Kanto	Japan	—
Justpertin	Horita	Japan	—
Padicor	Padil	Italy	—
Penselin	Sawai	Japan	—
Peridamol	Lab. Franc. Therap.	France	—
Perkod	Generod	France	—
Permilitin	Zensei	Japan	—
Piroan	Towa	Japan	—
Prandiol	Botto	France	—
Protangix	Lefrancq	France	—
Royalcor	Morgan	Italy	—
Santhimon	Santen	Japan	—
Stenocor	Chemipharma	Italy	—
Stimolcardio	Phanthox & Burck.	Italy	—
Tinol	Teikoku	Japan	—
Trancocard	Benvegna	Italy	—
Trombostaz	Yurtoglo	Turkey	—
Viscor	Italsuisse	Italy	—

Raw Materials

Urea
Nitric acid
Acetoacetic ester
Hydrogen

Potassium cyanate	Diethanolamine
Phosphorus oxychloride	Piperidine

Manufacturing Process

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

References

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

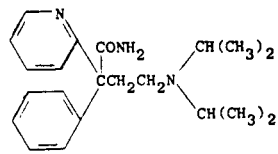
DISOPYRAMIDE PHOSPHATE

Therapeutic Function: Antiarrhythmia

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

Common Name: –

Structural Formula:



(base)

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

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

Raw Materials

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

Manufacturing Process

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

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

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

References

Merck Index 3378
Kleeman & Engel p. 332
PDR pp. 673, 830, 993, 1691
OCDS Vol. 2 p. 81 (1980) & 3, 41 (1984)
DOT 6 (6) 213 (1970)
I.N. p. 352
REM p. 858
Cusic, J.W. and Sause, H.W.; U.S. Patent 3,225,054; December 21, 1965; assigned to G.D. Searle & Co.

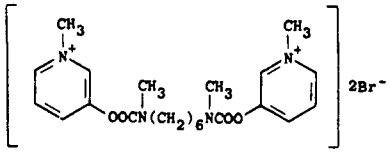
DISTIGMINE BROMIDE

Therapeutic Function: Cholinesterase inhibitor

Chemical Name: 3,3'-[1,6-Hexanediylbis[(methylimino)carbonyl]oxy]bis-[1-methylpyridinium] dibromide

Common Name: Hexamarium bromide

Structural Formula:



Chemical Abstracts Registry No.: 15876-67-2

Trade Name	Manufacturer	Country	Year Introduced
Ubretid	Hormonchemie	W. Germany	1966
Ubretid	Berk	U.K.	–
Ubretid	Lentia	W. Germany	–
Ubretid	Torii	Japan	–

Raw Materials

3-Oxypyridine
Sodium
Methanol
Hexamethylene-bis-(N-methyl carbamic acid chloride)
Methyl bromide

Manufacturing Process

2 parts of sodium are dissolved in 24 parts of methanol and to the solution of sodium methylate formed 8.25 parts of 3-oxypyridine and 90 parts of xylene (mixture of isomers) are added. Then the mixture is distilled in an atmosphere of nitrogen as protecting gas until the boiling point of xylene is reached and the methanol is completely removed. The remainder is brought together with a solution of 11.7 parts of hexamethylene-bis-(N-methyl carbamic acid chloride) in 45 parts of xylene and maintained 4 hours at a temperature of 80°C under vigorous stirring.

After having been cooled it is washed three times in water, three times in a 5% solution of caustic soda, and then another three times in water. The solution in xylene is dried over sodium sulfate and the xylene is completely distilled off in vacuo. Thus 11.0 parts of hexamethylene-bis-(N-methyl carbamic acid-3-pyridyl ester) are obtained.

7.3 parts of hexamethylene-bis-(N-methyl carbamic acid-3-pyridyl ester) are dissolved in 120 parts of acetone, then 22 parts of methyl bromide are added and the mixture is left to stand at room temperature until the reaction is finished, whereby crystals are precipitated. The reaction product after being drawn off and dried (9.9 parts) can be purified by dissolving in acetic acid and precipitating with methyl ethyl ketone. The hexamethylene-bis-(N-methyl carbamic acid-3-pyridyl ester bromomethylate) has a micro melting point between 147°C and 150°C.

References

Merck Index 3380
Kleeman & Engel p. 332
I.N. p. 353
Schmid, O.; U.S. Patent 2,789,981; April 23, 1957; assigned to Oesterreichische Stickstoffwerke A.G. (Austria)

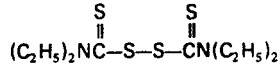
DISULFIRAM

Therapeutic Function: Alcohol deterrent

Chemical Name: Tetraethylthioperoxydicarbonic diamide

Common Name: Tetraethyl thiuram disulfide

Structural Formula:



Chemical Abstracts Registry No.: 97-77-8

Trade Name	Manufacturer	Country	Year Introduced
Esperal	Millot Solac	France	1950
Antabuse	Ayerst	U.S.	1951
Abstenil	Sintesina	Argentina	–
Abstinyl	Pharmacia	Sweden	–
Antabus	Tosse	W. Germany	–
Antabuse	Ethnor	Australia	–
Antabuse	Crinos	Italy	–
Antabuse D	Tokyo Tanabe	Japan	–
Antietil	Italfarmaco	Italy	–
Antivitium	Reder	Spain	–
Aversan	A.F.I.	Norway	–
Nocbin	Tokyo Tanabe	Japan	–
Ro-Sulfiram	Robinson	U.S.	–
Tetidis	Krka	Yugoslavia	–

Raw Materials

Diethyl amine
Sodium hydroxide
Carbon bisulfide
Hydrogen peroxide

Manufacturing Process

Disulfiram may be made by the reaction of diethyl amine with carbon disulfide in the presence of sodium hydroxide. The $(C_2H_5)_2NCSSNa$ intermediate is oxidatively coupled using hydrogen peroxide to give disulfiram.

References

Merck Index 3382
Kleeman & Engel p. 333
PDR pp. 611, 830, 1606
OCDS Vol. 1 p. 223 (1977)
DOT 10 (9) 324 (1974)
I.N. p. 353
REM p. 1070
Adams, H.S. and Meuser, L.; U.S. Patent 1,782,111; November 18, 1930; assigned to The Naugatuck Chemical Company
Bailey, G.C.; U.S. Patent 1,796,977; March 17, 1931; assigned to The Roessler & Hasslacher Chemical Company

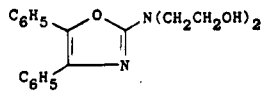
DITAZOL

Therapeutic Function: Antiinflammatory

Chemical Name: 2,2'-[(4,5-diphenyl-2-oxazolyl)imino]diethanol

Common Name: Diethamphenazol

Structural Formula:



Chemical Abstracts Registry No.: 18471-20-0

Trade Name	Manufacturer	Country	Year Introduced
Ageroplas	Serona	Italy	1973

Raw Materials

2-Chloro-4,5-diphenyl oxazole
Diethanolamine

Manufacturing Process

A solution of 5.1 grams 2-chloro-4,5-diphenyl-oxazole, 6.3 grams diethanolamine and 50 ml absolute ethanol was refluxed for 4 hours. The solvent was stripped at 1 mm and the oily residue was added at 60°C to 100 ml 50% ethanol; by cooling the hydro-alcoholic solution, 4.5 grams of 2-bis(β-hydroxyethyl)amino-4,5-diphenyl-oxazole was obtained (yield, 69.5%). The product crystallized from ethyl ether + petroleum ether, with a MP of 96° to 98°C.

References

Merck Index 3386
DOT 10 (4) 135 (1974)
I.N. p. 354
Marchetti, E.; U.S. Patent 3,557,135; January 19, 1971; assigned to Istituto Farmacologico Serono SpA, Italy

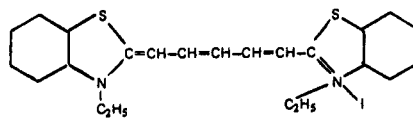
DITHIAZANINE IODIDE

Therapeutic Function: Anthelmintic

Chemical Name: 3-Ethyl-2-[5-[3-ethyl-2-(3H)-benzothiazolinylidene]-1,3-pentadienyl]benzothiazolium iodide

Common Name: 3,3'-Diethylthiacarbocyanine iodide

Structural Formula:



Chemical Abstracts Registry No.: 514-73-8

Trade Name	Manufacturer	Country	Year Introduced
Delvex	Lilly	U.S.	1958
Abminthic	Pfizer	U.S.	1959

Trade Name	Manufacturer	Country	Year Introduced
Dilombrin	Pfizer	—	—
D.I.M.	Mediphar	Congo	—
Elmizin	Bouty	Italy	—
Nectocyd	Pfizer	—	—
Ossiurene	A.M.S.A.	Italy	—
Partel	Lilly	—	—
Telmid	Lilly	—	—

Raw Materials

1-Methylbenzthiazole ethiodide
β-Ethyl thioacrolein diethyl acetal

Manufacturing Process

3.05 g of 1-methylbenzthiazole ethiodide, 1.11 g of β-ethyl thio acrolein diethyl acetal and 15 cc of pyridine were mixed and boiled gently under reflux for 15 minutes. The reaction mixture was then poured into an aqueous solution of potassium iodide. The dye was precipitated and was filtered off, and washed with ethyl alcohol and ether. Recrystallization from methyl alcohol solution yielded the dye as green needles. Melting point 248°C with decomposition.

References

Merck Index 3388
OCDS Vol. 1 p. 327 (1977)
I.N. p. 354
Kendall, J.D. and Edwards, H.D.; U.S. Patent 2,412,815; December 17, 1946; assigned to Ilford, Ltd.

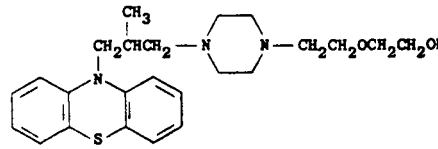
DIXYRAZINE

Therapeutic Function: Tranquilizer

Chemical Name: 2-[2-[4-[2-methyl-3-(10H-phenothiazin-10-yl)propyl]-1-piperazinyl]ethoxy]-ethanol

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 2470-73-7

Trade Name	Manufacturer	Country	Year Introduced
Esucos	UCB Chemie	W. Germany	1962
Esucos	UCB	Italy	1962
Esucos	UCB	France	1964
Esocalm	Assia	Israel	—
Roscal	Rosco	Denmark	—

Raw Materials

Phenothiazine
Sodium amide
1-Chloro-2-methyl-3-bromopropane
1-[2-(2-Hydroxyethoxy)ethyl] piperazine

Manufacturing Process

To a suspension of sodamide in liquid ammonia and made from sodium in liquid ammonia, there is added fractionally and with stirring phenothiazine. After an hour there is added thereto, while maintaining the stirring, 1-chloro-2-methyl-3-bromopropane, then 700 cc of toluene. The ammonia is then driven off and heating under reflux is carried out for one hour.

After cooling, water is added and the solution then decanted. The toluene phase is then evaporated in vacuo to constant weight. The residue is constituted of 10-(2-methyl-3-chloro-propyl)-phenothiazine containing a certain quantity of phenothiazine which has not reacted. As this product is not readily soluble in petroleum ether, it is possible to eliminate it by extraction by means of this solvent.

By operating in this manner 10-(2-methyl-3-chloro-propyl)phenothiazine is obtained. A mixture of 10-(2-methyl-3-chloro-propyl)phenothiazine and 1-[2-(2-hydroxyethoxy)ethyl] piperazine is then heated at 110°-120°C for 20 hours. After cooling, the reaction product is dissolved in 200 cc of benzene and the solution washed several times with water.

The benzene phase is then extracted by dilute hydrochloric acid. The acid aqueous phase is decanted, it is made distinctly alkaline and then extracted with benzene. The benzene extract is dried and evaporated in vacuo. The condensation product could not be crystallized. It may be converted into the dihydrochloride which, after recrystallization from isopropanol, melts at 192°C.

References

Merck Index 3403
Kleeman & Engel p. 334
OCDS Vol. 1 p. 384 (1977)
I.N. p. 356
Morren, H.; British Patent 861,420; February 22, 1961

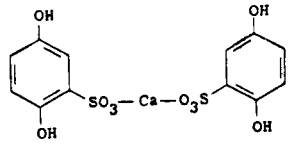
DOBESILATE CALCIUM

Therapeutic Function: Vasodilator

Chemical Name: 2,5-dihydroxybenzenesulfonic acid calcium salt

Common Name: Hydroquinone calcium sulfonate

Structural Formula:



Chemical Abstracts Registry No.: 20123-80-2

Trade Name	Manufacturer	Country	Year Introduced
Doxium	Carrion	France	1971
Dexium	Delalande	W. Germany	1971
Doxium	Delalande	Italy	1973
Dobesiphar	Farmila	Italy	–
Doxi-OM	O.M.	Switz.	–
Doxytrex	O.M.	Switz.	–
Romiven	Roche	–	–

Raw Materials

1,4-Benzoquinone
Calcium bisulfite

Manufacturing Process

To an ether solution of 108 grams 1,4-benzoquinone, maintained below 0°C, one adds an also very cold solution of 102 grams of pure calcium bisulfite as a 50% solution in distilled water. The addition is made carefully so as to maintain a very low temperature (0° to 4°C) in the vessel, and under stirring so as to mix the water and ether phase.

At the end of the addition, an almost colorless ether layer swims on the surface of the strongly colored water layer. After removal of the ether layer, the water layer is concentrated to dryness under vacuum and a stream of an inert gas. An earthy precipitate is formed, which after recrystallization yields 100 grams of hydroquinone calcium sulfonate, which decomposes without melting above 250°C.

The product consists of very small crystals having a powdery aspect and a pink color which deepens on contact with air. This product is very soluble in water and alcohol, and insoluble in ether.

References

Merck Index 3406
Kleeman & Engel p. 135
I.N. p. 356
Esteve-Subirana, A.; U.S. Patent 3,509,207; April 28, 1970; assigned to Laboratories Om Societe Anonyme, Switzerland

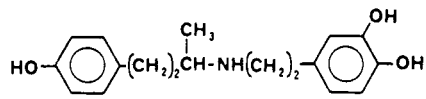
DOBUTAMINE

Therapeutic Function: Cardiotonic

Chemical Name: 3,4-Dihydroxy-N-[3-(4-hydroxyphenyl)-1-methylpropyl]-β-phenethylamine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 34368-04-2; 52663-81-4 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Dobutrex	Lilly	U.K.	1977
Dobutrex	Lilly	U.S.	1978
Dobutrex	Lilly	W. Germany	1978
Dobutrex	Shionogi	Japan	1982
Dobutrex	Lilly	Italy	1983
Dobuject	Leiras	Finland	—
Inotrex	Lilly	—	—

Raw Materials

4-(p-Methoxyphenyl)-3-buten-2-one
Homoveratrylamine
Acetic acid
Hydrogen
Hydrogen bromide
Hydrogen chloride

Manufacturing Process

In a stainless steel hydrogenation bottle were placed 17.6 g (0.1 mol) of 4-(p-methoxyphenyl)-3-buten-2-one, 80 ml of ethyl acetate, and 1 g of Raney nickel catalyst. The hydrogenation bottle was attached to a Paar low-pressure hydrogenation apparatus and the solution was hydrogenated under an initial hydrogen pressure of 50 psi. The hydrogenation was carried out at room temperature and after about 12 hours one equivalent of hydrogen had been absorbed. The catalyst was filtered from the reduction mixture and 18.1 g (0.1 mol) of homoveratrylamine were added to the reduction mixture.

To the reduction mixture was then added 3.5 g of 5% palladium on carbon catalyst and the mixture was hydrogenated under a hydrogen pressure of 50 psi at room temperature for 12 hours. The catalyst was removed by filtration and the filtrate was evaporated to a small volume. The concentrated filtrate was dissolved in diethyl ether and the ethereal solution was saturated with anhydrous hydrogen chloride. The reduction product, 3,4-dimethoxy-N-[3-4-methoxyphenyl)-1-methyl-n-propyl] phenethylamine was precipitated as the hydrochloride salt. The salt was filtered and recrystallized from ethanol melting at about 147°C to 149°C.

To a solution of 101.2 g of the trimethoxy secondary amine, obtained as described above, in 3,060 ml of glacial acetic acid was added 1,225 ml of 48% hydrobromic acid and the reaction mixture heated at the reflux temperature for 4 hours. The reaction mixture was then cooled and evaporated to a small volume. The crystalline residue which formed was filtered and dried in vacuo. The dried crystalline residue was then triturated with ethyl acetate and re-dried to yield 97.3 g of crude crystalline material. The crude product was dissolved in 970 ml of warm water to obtain a yellow solution. To the solution was added successively by dropwise addition 75 ml of 1 N and 75 ml of 2 N hydrochloric acid. Following the dropwise addition, the solution was allowed to stir with ice cooling. The impurities which precipitated were removed by filtration through a gauze filter. Concentrated hydrochloric acid was then added dropwise. When approximately 50 to 75 ml of the concentrated acid had been added with ice bath cooling a pale yellow oil precipitated along with a while solid precipitate. With continued stirring of the cold solution, the pale yellow oil crystallized.

The cold solution was then allowed to stand overnight and all crystalline material filtered through a sintered glass filter. The filtrate was treated with an additional 300 ml of concentrated hydrochloric acid to yield a heavy white precipitate. The precipitate was filtered, dried and combined with the initial precipitate obtained as described above. The combined precipitated product, 3,4-dihydroxy-N-[3-(4-hydroxyphenyl)-1-methyl-n-propyl-β-phenethylamine hydrochloride, had a melting point of about 184°C to 186°C after recrystallization from boiling 4 N hydrochloric acid.

References

Merck Index 3407
DFU 2 (9) 579 (1977)
Kleeman & Engel p. 334

PDR p. 1047
OCDS Vol. 2 p. 53 (1980)
DOT 14 (10) 433 (1978)
I.N. p. 357
REM p. 882
Tuttle, R.R. and Mills, J.; U.S. Patent 3,987,200; October 19, 1976; assigned to Eli Lilly & Co.

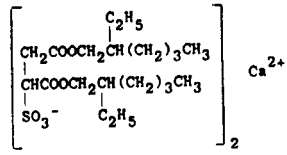
DOCUSATE CALCIUM

Therapeutic Function: Stool softener

Chemical Name: Sulfobutanedioic acid 1,4-bis(2-ethylhexyl)ester calcium salt

Common Name: Dioctyl calcium sulfosuccinate

Structural Formula:



Chemical Abstracts Registry No.: 128-49-4

Trade Name	Manufacturer	Country	Year Introduced
Surfak	Hoechst	U.S.	1959
Regutol	Schering	U.S.	1981
Doxidan	Hoechst	—	—
Dioctocal	Schein	U.S.	—

Raw Materials

Dioctyl sodium sulfosuccinate
Calcium chloride

Manufacturing Process

88 g of dioctyl sodium sulfosuccinate is first dissolved in 100 cc of isopropanol and 25 g of calcium chloride is dissolved in 50 cc of methanol. The solutions are then mixed and stirred for about 3 hours and then cooled with ice. The sodium chloride which precipitates in the cool mixture is removed by filtration and most of the alcohol is evaporated from the resulting filtrate with heat. The liquid remaining is poured into 88 cc of water, and the resulting precipitate washed with water until free of chloride ion. The washed calcium salt is then dried.

References

Merck Index 3408
PDR pp. 938, 945, 1606
I.N. p. 357
REM p. 805
Klotz, L.J.; U.S. Patent 3,035,973; May 22, 1962; assigned to Lloyd Brothers, Inc.

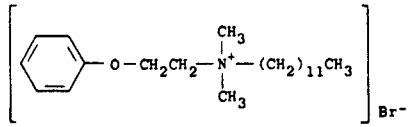
DOMIPHEN BROMIDE

Therapeutic Function: Topical antiinfective

Chemical Name: N,N-Dimethyl-N-(2-phenoxyethyl)-1-dodecanaminium bromide

Common Name: Phenododecinium bromide

Structural Formula:



Chemical Abstracts Registry No.: 538-71-6

Trade Name	Manufacturer	Country	Year Introduced
Bradosol	Ciba	U.S.	1958
Bradex-Vioform	Ciba	W. Germany	–
Brado	Ciba-Geigy-Takeda	Japan	–
Bradoral	Ciba	Italy	–
Neo-Bradoral	Ciba	Switz.	–
Oradol	Ciba-Geigy-Takeda	Japan	–

Raw Materials

β-Phenoxyethyl dimethylamine
Dodecyl bromide

Manufacturing Process

7 parts of β-phenoxyethyl-dimethylamine are heated for 2 hours on the boiling water-bath with 11 parts of dodecyl bromide. A good yield of β-phenoxy-ethyl-dimethyl-dodecyl-ammonium bromide is obtained which, after recrystallization from acetone, melts at 112°C. It is a white crystalline powder which dissolves easily in water to give a neutral reaction.

References

Merck Index 3424
Kleeman & Engel p. 335
I.N. p.. 359
Hartmann, M. and Bosshard, W.; U.S. Patent 2,581,336; January 8, 1952; assigned to Ciba Pharmaceutical Products, Inc.

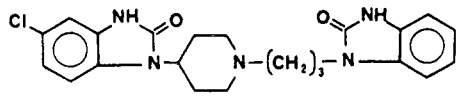
DOMPERIDONE

Therapeutic Function: Antiemetic

Chemical Name: 5-Chloro-1-[1-[3-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)-propyl] 4-piperidinyl] -1,3-dihydro-2H-benzimidazol-2-one

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 57808-66-9

Trade Name	Manufacturer	Country	Year Introduced
Motilium	Cilag	Switz.	1979
Motilium	Janssen	W. Germany	1979
Motilium	Janssen	Italy	1981
Motilium	Janssen	U.K.	1982
Nauselin	Kyowa Hakko	Japan	1982
Motilium	Janssen-Le Brun	France	1983
Euciton	Roux-Ocefa	Argentina	—
Moperidona	Sidus	Argentina	—

Raw Materials

1-(3-Chloropropyl)-1,3-dihydro-2H-benzimidazol-2-one
5-Chloro-1,3-dihydro-1-(4-piperidinyl)-2H-benzimidazol-2-one

Manufacturing Process

A mixture of 2.3 parts of 1-(3-chloropropyl)-1,3-dihydro-2H-benzimidazol-2-one, 2.5 parts of 5-chloro-1,3-dihydro-1-(4-piperidinyl)-2H-benzimidazol-2-one, 3.2 parts of sodium carbonate, 0.1 part of potassium iodide and 80 parts of 4-methyl-2-pentanone is stirred and refluxed for 24 hours. The reaction mixture is cooled to room temperature and water is added. The undissolved product is filtered off and purified by column chromatography over silica gel using a mixture of trichloromethane and 10% methanol as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from 4-methyl-2-pentanone. The product is filtered off and recrystallized from a mixture of N,N-dimethylformamide and water, yielding 1.3 parts (30%) of 5-chloro-1-[1-[3-(1,3-dihydro-2-oxo-2H-benzimidazol-1-yl)propyl]-4-piperidinyl]-1,3-dihydro-2H-benzimidazol-2-one; MP 242.5°C.

References

Merck Index 3425
DFU 2 (10) 661 (1977)
Kleeman & Engel p. 335
OCDS Vol. 3 p. 174 (1984)
DOT 17 (1) 19 (1981)
I.N. p. 360
Vanderberk, J., Kennis, L.E.J., Van der Aa, M.J.M.C. and Van Heertum, A.H.M.T.; U.S. Patents 4,066,772; January 3, 1978; 4,110,333; August 29, 1978; 4,126,687; November 21, 1978; 4,126,688; November 21, 1978; 4,160,836; July 10, 1979 and 4,175,129; November 20, 1979; all assigned to Janssen Pharmaceutica NV (Belgium)

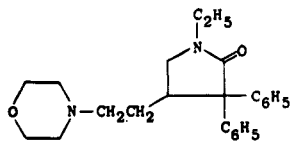
DOXAPRAM HYDROCHLORIDE

Therapeutic Function: Respiratory stimulant

Chemical Name: 1-ethyl-4-(2-morpholinoethyl)-3,3-diphenyl-2-pyrrolidinone hydrochloride monohydrate

Common Name: —

Structural Formula:



(base)

Chemical Abstracts Registry No.: 7081-53-0; 309-29-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Dopram	Robins	U.S.	1965
Doxapril	Farmalabor	Italy	1967
Dopram	Martinet	France	1969
Dopram	Robins	U.K.	1971
Dopram	Kissei	Japan	1976
Dopram	Brenner	W. Germany	1977
Stimulexin	Robins	U.S.	—

Raw Materials

Diphenylacetonitrile
1-Ethyl-3-chloropyrrolidine
Morpholine
Sodium amide
Sulfuric acid
Hydrogen chloride

Manufacturing Process

(A) Preparation of α-(1-Ethyl-3-Pyrrolidyl)-α,α-Diphenylacetonitrile: A suspension of the sodium salt of diphenylacetonitrile was formed by the dropwise addition at 50°C of 193 grams (1.0 mol) of diphenylacetonitrile to a stirred suspension of 43 grams (1.1 mols) of sodium amide in 1 liter of dry toluene. After addition was complete, the mixture was refluxed for 4 hours and then, to the refluxing mixture, 1.0 mol of 1-ethyl-3-chloropyrrolidine was added at a rapid dropwise rate with continuous stirring. After addition was complete, stirring and refluxing were continued for 3 hours. The mixture was then cooled and extracted with one normal hydrochloric acid. The aqueous layer together with an oil layer were separated, made basic with dilute sodium hydroxide, and extracted with ether. The ethereal solution was dried over sodium sulfate and concentrated and the residue was distilled in vacuo. The material crystallized from a 4:1 ethanol-water mixture.

(B) Preparation of 4-(β-Chloroethyl)-3,3-Diphenyl-1-Ethyl-2-Pyrrolidinone: A solution of α,α-diphenyl-α-(1-ethyl-3-pyrrolidyl)-acetonitrile in 70% sulfuric acid was heated at 130°-140°C for 48 hours, poured onto ice, made basic with sodium hydroxide, and extracted with chloroform. The chloroform solution was acidified with hydrogen chloride gas, dried over sodium sulfate and concentrated. The residue was refluxed in 500 ml of thionyl chloride for 3 hours; the resulting solution was concentrated in vacuo; and the residue was crystallized from isopropyl ether.

(C) Preparation of Doxapram Hydrochloride [3,3-Diphenyl-1-Ethyl-4-(2-Morpholino-Ethyl)-2-Pyrrolidinone Hydrochloride Monohydrate]: A solution of 25 grams (0.076 mol) of 4-(2-chloroethyl)-3,3-diphenyl-1-ethyl-2-pyrrolidinone and 13.3 grams (0.153 mol) of morpholine in 500 ml of absolute ethanol was heated at 95°-120°C for 21 hours in a closed system and concentrated in vacuo. The residue was dissolved in 300 ml of two normal hydrochloric acid and extracted with 150 ml of ethyl acetate. A solid crystallized (13 g) during the extraction and was removed by filtration. MP 217°-219°C. The acid extracts were made basic with sodium hydroxide and extracted with ether, and the ether solution was concentrated in vacuo and the residue was suspended in six normal hydrochloric acid. Additional crystalline product formed and was recrystallized from two normal hydrochloric acid. Yield, 10 grams; MP 217°-219°C. Total yield, 23 grams (70%).

References

Merck Index 3433
Kleeman & Engel p. 337
PDR p. 1456
OCDS Vol. 2 p. 236 (1980)
DOT 2 (2) 55 (1966)
I.N. p. 362
REM p. 867

Lunsford, C.D. and Cale, A.D. Jr.; U.S. Patent 3,192,230; June 29, 1965; assigned to A.H. Robins Company, Inc.

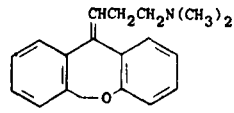
DOXEPIN HYDROCHLORIDE

Therapeutic Function: Tranquilizer

Chemical Name: N,N-dimethyl-3-dibenz[b,e]oxepin-11-(6H)-ylidene-1-propanamine hydrochloride

Common Name: —

Structural Formula:



(base)

Chemical Abstracts Registry No.: 1229-29-4; 1668-19-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Sinequan	Pfizer	U.S.	1969
Sinequan	Pfizer	U.K.	1969
Aponal	Boehr./Mann.	W. Germany	1970
Sinequan	Pfizer	W. Germany	1970
Sinequan	Pfizer	Italy	1971
Sinequan	Pfizer	France	1971
Adapin	Pennwalt	U.S.	1973
Doksapan	Eczacibasi	Turkey	—
Dolat	Yurtoglu	Turkey	—
Doxal	Orion	Finland	—
Doxedyn	Medica	Finland	—
Gilex	Ikapharm	Israel	—
Novoxapin	Ester	Spain	—
Quitaxon	Phartec	France	—
Toruan	Boehr./Mann.	—	—

Raw Materials

1,3-Dibromopropane
Dimethylamine
6,11-Dihydrodibenz-(b,e)oxepin-11-one
Triphenyl phosphine
Hydrogen bromide
Butyl lithium

Manufacturing Process

(A) Preparation of 3-Bromopropyltriphenylphosphonium Bromide: Triphenylphosphine, 1.0 kg, and 770 grams of 1,3-dibromopropane are dissolved in 2.0 liters of xylene and the solution is stirred under a nitrogen atmosphere at 130°C. After 20 hours the mixture is cooled, and the crystalline product, which precipitates, is collected and washed with 20 liters of benzene. After drying in vacuo the product weighs 1,578 grams, MP 229°-230°C; titration for bromide ion: Found, 17.1%; calculated, 17.2%.

(B) Preparation of 3-Dimethylaminopropyltriphenylphosphonium Bromide Hydrobromide: A solution of 595 grams of anhydrous dimethylamine and 1,358 grams of 3-bromopropyl-

triphenylphosphonium bromide in 4 liters of ethanol is warmed to 70°C until solution is complete and the solution then is allowed to stand at room temperature for 20 hours. Volatile components are removed by distillation in a vacuum and the residue is suspended in 2.0 liters of ethanol and is redistilled to remove excess amine. The residue is dissolved in 3.0 liters of warm ethanol and gaseous hydrogen bromide is passed into the solution until the mixture is acidic. After filtration the solution is concentrated to a volume of 3.0 liters, is cooled, whereupon the product precipitates, and the precipitate is collected; it weighs 1,265 grams, MP 274°-281°C. Recrystallization from ethanol raises the MP to 280.5°-282.5°C. Bromide ion titration: Found, 31.2%; calculated 31.3%.

(C) Preparation of Doxepin: 1,530 grams of the product from step (B) is suspended in 4.5 liters dry tetrahydrofuran and 6.0 mols of butyl lithium in heptane is added during 1 hour. After an additional 30 minutes, 483 grams of 6,11-dihydrodibenz-(b,e)oxepin-11-one, prepared as described in Belgian Patent 641,498, is added to the deep red solution and the reaction was maintained at reflux for 10 hours. Water, 500 ml, is added at room temperature and the solvent is removed in vacuo. The crude residue is treated with 10% hydrochloric acid until acidic (pH 2) and then 1.5 liters benzene is added. After stirring, the mixture separates into 3 phases (an insoluble hydrochloride salt product phase, an aqueous phase and an organic phase).

The benzene layer is removed by decantation and the remaining mixture is rendered basic with 10% sodium hydroxide solution and is extracted with three 1,500 ml portions of benzene. The benzene extracts are washed, then dried with anhydrous sodium sulfate and concentrated in a vacuum leaving a residue of 1,530 grams, gas and thin layer chromatography analysis show this to be a cis/trans mixture (approx. 4:1) of 11-dimethylaminopropylidene-6,11-dihydrodibenz-(b,e)oxepin (90% yield). This mixture has substantially more activity pharmacologically than the cis/trans mixture obtained by the Grignard route disclosed in the Belgian Patent 641,498. This base is then converted to the hydrochloride with HCl.

References

Merck Index 3434
Kleeman & Engel p. 338
PDR pp. 1397, 1530
OCDS Vol. 1 p. 404 (1977)
DOT 6 (2) 53 (1970)
I.N. p. 362
REM p. 1094
Chas. Pfizer & Co., Inc.; British Patent 1,085,406; October 4, 1967
Bloom, B.M. and Tretter, J.R.; U.S. Patent 3,420,851; January 7, 1969; assigned to Chas. Pfizer & Co., Inc.
Stach, K.; U.S. Patent 3,438,981; April 15, 1969; assigned to C.F. Boehringer & Soehne GmbH (Germany)

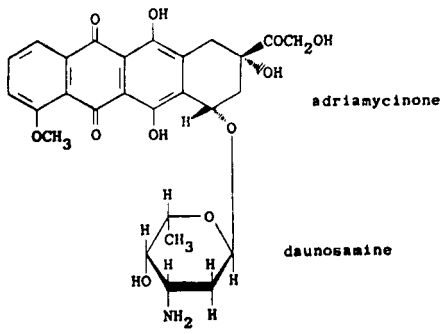
DOXORUBICIN

Therapeutic Function: Cancer chemotherapy

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

Common Name: 14-Hydroxydaunomycin

Structural Formula:



Chemical Abstracts Registry No.: 23214-92-8; 25316-40-9 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Adriblastina	Farmitalia	Italy	1971
Adriamycin	Farmitalia	U.K.	1971
Adriblastina	Farmitalia	W. Germany	1972
Adriablastine	Roger Bellon	France	1974
Adriacin	Kyowa Hakko	Japan	1974
Adriamycin	Adria	U.S.	1974

Raw Materials

Glucose
Bacterium *Streptomyces peucetius var. caesius*

Manufacturing Process

Two 300 ml Erlenmeyer flasks, each containing 60 ml of the following culture medium for the vegetative phase, were prepared: peptone 0.6%; dry yeast 0.3%; hydrated calcium carbonate 0.2%; magnesium sulfate 0.01%; the pH after sterilization was 7.2. Sterilization has been effected by heating in autoclave to 120°C for 20 minutes. Each flask was inoculated with a quantity of mycelium of the mutant F.I.106 (the new strain thus obtained has been given the code F.I.106 of the Farmitalia microbiological collection and has been called *Streptomyces peucetius* var. *caesius*) corresponding to ⅛ of a suspension in sterile water of the mycelium of a 10 day old culture grown in a big test tube on the following medium: saccharose 2%; dry yeast 0.1%; bipotassium phosphate 0.2%; sodium nitrate 0.2%; magnesium sulfate 0.2%; agar 2%; tap water up to 100%. The flasks were then incubated at 28°C for 48 hours on a rotary shaker with a stroke of 30 mm at 220 rpm.

2 ml of a vegetative medium thus grown were used to inoculate 300 ml Erlenmeyer flasks with 60 ml of the following medium for the productive phase: glucose 6%; dry yeast 2.5%; sodium chloride 0.2%; bipotassium phosphate 0.1%; calcium carbonate 0.2%; magnesium sulfate 0.01%; ferrous sulfate 0.001%; zinc sulfate 0.001%; copper sulfate 0.001%; tap water to 100%. The glucose was previously sterilized separately at 110°C for 20 minutes. The resulting pH was 7. This was sterilized at 120°C for 20 minutes and incubated at 28°C under the same conditions by stirring, as for the vegetative media.

The maximum concentration of the antibiotic was reached on the 6th day of fermentation. The quantity of adriamycin produced at this time corresponds to a concentration of 15 μg/ml.

References

Merck Index 3435
Kleeman & Engel p. 338

PDR p. 557
DOT 8 (4) 132 (1972) & 16 (5) 170 (1980)
I.N. p. 362
REM p. 1149
Arcamone, F., Cassinelli, G., di Marco, A. and Gaetani, M.; U.S. Patent 3,590,028; June 29, 1971; assigned to Societa Farmaceutici Italia, Italy
Smith, T.H., Fujiwara, A.N., Henry, D.W. and Lee, W.W.; U.S. Patent 4,012,448; March 15, 1977; assigned to Stanford Research Institute
Arcamone, F., di Marco, A. and Penco, S.; U.S. Patents 4,058,519; November 15, 1977; and 4,098,798; July 4, 1978; both assigned to Societa Farmaceutici Italia S.p.A. (Italy)

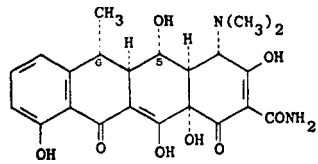
DOXYCYCLINE

Therapeutic Function: Antibiotic

Chemical Name: 4αS-(dimethylamino)-1,4,4aα,5,5aα,6,11,12a-octahydro-3,5α,10,12,12aα-pentahydroxy-6α-methyl-1,11-dioxo-2-naphthacenecarboxamide

Common Name: 6-deoxy-5-oxytetracycline

Structural Formula:



Chemical Abstracts Registry No.: 564-25-0

Trade Name	Manufacturer	Country	Year Introduced
Cyclidox	Protea	Australia	–
Doxitard	Mack	W. Germany	–
Doxy	Wolff	W. Germany	–
Doxy 200	Engelhard	W. Germany	–
Doxylin	A.L.	Norway	–
Doxy-Puren	Klinge	W. Germany	–
Doxyremed	Remed Econerica	W. Germany	–
Dumoxin	Dumex	Denmark	–
Dura Doxal	Durachemie	W. Germany	–
Geobiotico	Asia	Spain	–
Hiramicin	Pliva	Yugoslavia	–
Liviatin	Juste	Spain	–
Medomycin	Medica	Finland	–
Mespatin	Merckle	W. Germany	–
Novelciclina	Lifasa	Spain	–
Tenutan	Chinoin	Hungary	–

Raw Materials

Methacycline
Hydrogen

Manufacturing Process

Hydrogen was introduced into a standard hydrogenation vessel containing 10 grams 6-deoxy-6-demethyl-6-methylene-5-oxytetracycline hydrochloride (methacycline), 150 ml methanol and 5 grams 5% rhodium on carbon. The pressure was maintained at 50 psi while agitating at room temperature for 24 hours. The catalyst was then filtered off, the cake washed with methanol and the combined filtrates were evaporated to dryness. The dry solids were slurried in ether, filtered and the cake dried. The resulting solids exhibited a bioactivity of 1,345 units per mg versus *K. pneumoniae.*

Water (35 ml) was employed to dissolve 8.5 grams of the above product and the pH was adjusted to 6.0 with triethylamine, sufficient dimethyl formamide being added to maintain the solids in solution. Cellulose powder (2 kg) was slurried in water-saturated ethyl acetate and packed into a tower of about 3½ inches diameter, to a height of 3 ft. The product solution was then chromatographed over this column, developing with about 12 liters water-saturated ethyl acetate. The first product fraction to come from the tower yielded 1.85 grams 6-epi-6-deoxy-5-oxytetracycline. The next fraction contained 2.0 grams of 6-deoxy-6-demethyl-6-methylene-5-oxytetracycline. The third fraction yielded 0.8 grams 6-deoxy-5-oxytetracycline.

References

Merck Index 3436
Kleeman & Engel p. 339
PDR p. 1424
DOT 3 (3) 114 (1967) & 4 (3) 102 (1968)
I.N. p. 363
REM p. 1205
Blackwood, R.K., Rennhard, H.H., Beereboom, J.J. and Stephens, C.R. Jr.; U.S. Patent 3,200,149; August 10, 1965; assigned to Chas. Pfizer & Co., Inc.

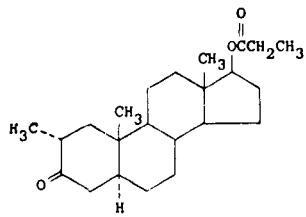
DROMOSTANOLONE PROPIONATE

Therapeutic Function: Cancer chemotherapy

Chemical Name: 2α-methyl-17β-(1-oxopropoxy)-5α-androstan-3-one

Common Name: 2-methyldihydrotestosterone propionate

Structural Formula:



Chemical Abstracts Registry No.: 521-12-0; 58-19-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Drolban	Lilly	U.S.	1961
Masterone	Recordati	Italy	1962
Masterid	Gruenenthal	W. Germany	1969

Trade Name	Manufacturer	Country	Year Introduced
Permastril	Cassenne	France	1969
Masteril	Syntex	U.K.	—
Mastisol	Shionogi	Japan	—
Metormon	I.F.L.	Spain	—

Raw Materials

Dihydrotestosterone
Sodium hydride
Ethyl formate
Propionic anhydride

Manufacturing Process

A suspension of 10 grams of dihydrotestosterone in 500 cc of anhydrous benzene free of thiophene was mixed with 10cc of ethyl formate and 3 grams of sodium hydride and the mixture was stirred for 5 hours under an atmosphere of nitrogen and at a temperature of approximately 25°C. The resulting suspension was filtered, the resulting mixture of the sodium salt of the hydroxymethylene compound and the excess of sodium hydride was washed with benzene and dried. This mixture was slowly added to a vigorously stirred solution of 20 cc of concentrated hydrochloric acid in 500 cc of water, and the stirring was continued for 30 minutes at the end of which the precipitate was collected and well washed with distilled water. After drying in vacuo, there was obtained 9.7 grams of 2-hydroxymethylene-dihydrotestosterone.

A mixture of 1 gram of 2-hydroxymethylene-dihydrotestosterone, 10 cc of pyridine and 2 cc of propionic anhydride was allowed to react at room temperature for 16 hours and then poured into water. The resulting suspension was heated for 1 hour on the steam bath to hydrolyze the excess of propionic anhydride, cooled and extracted with methylene dichloride. The extract was consecutively washed with dilute hydrochloric acid, sodium bicarbonate solution and water, dried over anhydrous sodium sulfate and evaporated to dryness under vacuum. There was thus obtained the dipropionate of 2-hydroxymethylene-dihydrotestosterone which was treated with hydrogen, in methanol solution.

When the uptake of hydrogen ceased, the catalyst was filtered and the solution was evaporated to dryness under vacuum. The residue was dissolved in a mixture of benzene-hexane, transferred to a chromatographic column with neutral alumina and the product was eluted with mixtures of benzene-hexane, gradually increasing the proportion of benzene in the mixture. Crystallization of the eluates from acetone-hexane yielded the propionate of 2α-methyldihydrotestosterone.

References

Merck Index 3443
Kleeman & Engel p. 342
OCDS Vol. 1 p. 173 (1977)
I.N. p. 366
REM p. 998
Ringold, H.J. and Rosenkranz, G.; U.S. Patent 2,908,693; October 13, 1959; assigned to Syntex SA, Mexico
Ringold, H.J. and Rosenkranz, G.; U.S. Patent 3,118,915; January 21, 1964; assigned to Syntex Corporation, Panama

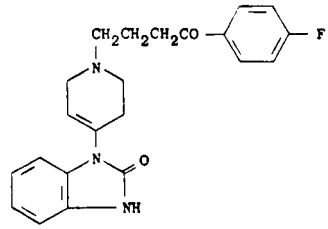
DROPERIDOL

Therapeutic Function: Tranquilizer

Chemical Name: 1-[1-[4-(4-fluorophenyl)-4-oxobutyl]-1,2,3,6-tetrahydro-4-pyridinyl]-1,3-dihydro-2H-benzimidazol-2-one

Common Name: Dehydrobenzperidol

Structural Formula:



Chemical Abstracts Registry No.: 548-73-2

Trade Name	Manufacturer	Country	Year Introduced
Dehydrobenzperidol	Janssen	W. Germany	1963
Sintodian	Carlo Erba	Italy	1965
Droleptan	Janssen	U.K.	1965
Droleptan	Janssen	France	1966
Inapsine	Mc Neil	U.S.	1970
Thalamonal	Sankyo	Japan	1972
Dridol	Leo	Sweden	—
Halkan	Thekan	France	—
Leptofen	Erba	Italy	—
Neurolidol	Abic	Israel	—

Raw Materials

γ-Chloro-4-fluorobutyrophenone
1-(1,2,3,6-Tetrahydro-4-pyridyl)-2-benzimidazolinone

Manufacturing Process

A mixture of 10 parts of γ-chloro-4-fluorobutyrophenone, 5.5 parts of 1-(1,2,3,6-tetrahydro-4-pyridyl)-2-benzimidazolinone, 4 parts of sodium carbonate, and 0.1 part of potassium iodide in 176 parts of 4-methyl-2-pentanone is stirred and refluxed for 64 hours. The cooled reaction mixture is filtered and the solvent is evaporated from the filtrate to leave an oily residue which is dissolved in toluene. The toluene solution is filtered and the solvent is evaporated. The resultant residue is recrystallized from a mixture of 32 parts of ethyl acetate and 32 parts of diisopropyl ether to give 1-[1-[(4-fluorobenzoyl)propyl]-1,2,3,6-tetrahydro-4-pyridyl]-2-benzimidazolinone hydrate melting at about 145°-146.5°C.

References

Merck Index 3444
Kleeman & Engel p. 341
PDR p. 954
OCDS Vol. 1 p. 308 (1977)
DOT 9 (6) 235 (1973)
I.N. p. 365
REM p. 1087
Janssen, P.A.J. and Gardocki, J.F.; U.S. Patent 3,141,823; July 21, 1964; assigned to Research Laboratorium Dr. C. Janssen NV, Belgium
Janssen, P.A.J.; U.S. Patent 3,161,645; December 15, 1964; assigned to Research Laboratorium Dr. C. Janssen NV, Belgium

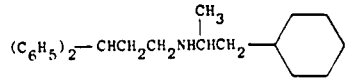
DROPRENILAMINE HCl

Therapeutic Function: Coronary vasodilator

Chemical Name: N-(2-Cyclohexyl-1-methylethyl)-γ-phenylbenzene-propanamine

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 57653-27-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Valcor	Maggioni	Italy	1979

Raw Materials

3,3-Diphenylpropylamine
Cyclohexylacetone
Hydrogen

Manufacturing Process

The flask of a Parr hydrogenation apparatus was charged with 10.5 g of 3,3-diphenylpropylamine, 7.7 g of cyclohexylacetone, 50 ml methanol and 150 mg of platinum dioxide. Hydrogen at a pressure of 3 atmospheres was introduced and the mixture stirred. Upon absorption of the theoretical amount of hydrogen, stirring is discontinued, the catalyst is filtered off and the solution is evaporated to dryness. The residue is taken up with ether and the hydrochloride is precipitated with HCl in alcoholic solution. The product, as collected on a filter and washed with ether, is recrystallized from isopropanol. Yield: 17 g (92.5% of theory). MP: 175°C to 177°C.

References

Merck Index 3445
DFU 2 (11) 720 (1977)
OCDS Vol. 3 p. 47 (1984)
I.N. p. 366
Carissimi, M., Ravenna, F. and Picciola, G.; British Patent 1,461,240; January 13, 1977; assigned to Maggioni & Co. S.p.A. (Italy)

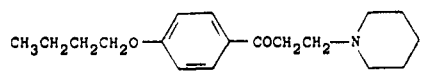
DYCLONINE HYDROCHLORIDE

Therapeutic Function: Topical anesthetic

Chemical Name: 1-(4-butoxyphenyl)-3-(1-piperidinyl)-1-propanone hydrochloride

Common Name: —

Structural Formula:



(base)

Chemical Abstracts Registry No.: 536-43-6; 586-60-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Dyclone	Dow	U.S.	1956
Resolve	Merrell Dow	U.S.	1980
Epicain Ace	S.S. Pharm.	Japan	—
Epirocain	Eisai	—	—

Raw Materials

p-n-Butoxyacetophenone
Piperidine hydrochloride
Paraformaldehyde
Hydrogen chloride

Manufacturing Process

A mixture of 17.6 grams of p-n-butoxyacetophenone, 12.1 grams of piperidine hydrochloride, 4.5 grams paraformaldehyde, 0.25 cc concentrated hydrochloric acid, 52.5 cc nitroethane, 7.5 cc of 95% ethanol, and 15 cc of toluene was boiled under reflux for one hour, removing water formed in the reaction by means of a condensate trap. The mixture was then cooled. The crystals which formed were collected by filtration, washed with anhydrous ether and recrystallized from methyl ethyl ketone. The crystals thus obtained, which melted at 174°-175°C, were shown by analysis to be 4-n-butoxy-beta-piperidinopropiophenone hydrochloride.

References

Merck Index 3459
Kleeman & Engel p. 343
PDR p. 592
I.N. p. 369
REM p. 1056
Bockstahler, E.R.; U.S. Patent 2,771,391; November 20, 1956; assigned to Allied Laboratories, Inc.
Florestano, H.J., Jeffries, S.F., Osborne, C.E. and Bahler, M.E.; U.S. Patent 2,868,689; January 13, 1959; assigned to Allied Laboratories, Inc.

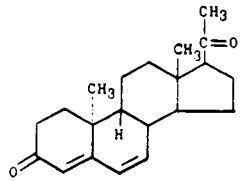
DYDROGESTERONE

Therapeutic Function: Progestin

Chemical Name: 9β,10α-pregna-4,6-diene-3,20-dione

Common Name: 10α-isopregnenone; 6-dehydro-retro-progesterone

Structural Formula:



Chemical Abstracts Registry No.: 152-62-5

Trade Name	Manufacturer	Country	Year Introduced
Duphaston	Duphar	U.K.	1961
Duphaston	Duphar	France	1962
Duphaston	Philips Roxane	U.S.	1962
Dufaston	I.S.M.	Italy	1963
Duphaston	Thomae Duphar	W. Germany	1966
Gynorest	Mead Johnson	U.S.	1968
Duphaston	Ethnor	Australia	—
Terolut	Ferrosan	Denmark	—

Raw Materials

Retroprogesterone
Chloranil

Manufacturing Process

A solution of 7.5 grams of retroprogesterone in 500 ml of freshly distilled tertiary butyl alcohol was refluxed with 12.75 grams of finely powdered chloranil, while stirring, for 5 hours in a nitrogen atmosphere. After cooling, 2 liters of water were added and extraction was performed three times with 200 ml of methylene dichloride. The combined extracts were then diluted with 1 liter of petroleum ether (40°-60°C) washed successively with 100 ml of diluted Na_2SO_4, four times with 75 ml of 1 N NaOH, and then water to neutral reaction.

By drying this solution on Na_2SO_4 and evaporating to dryness (last part in vacuo) 3.7 grams of crystalline residue was obtained. This residue was then dissolved in benzene. Filtration in benzene filtered through 35 grams of alumina (according to Brockmann was done and then the alumina was eluted with benzene. Evaporation of the benzene yielded 3.11 grams of crystalline residue. By crystallization with 15 ml of acetone at room temperature (at lower temperatures a by-product crystallized out) 900 mg of crystals, with a melting point of 165°-170°C were obtained. Transfer of the acetone mother liquor into a mixture of ethanol and hexane yielded 1.7 grams of a solid substance with a melting point of 130° to 145°C. This solid was then recrystallized with acetone at room temperature, yielding 600 mg of a solid with a melting point of 166° to 171°C. The two fairly pure fractions (600 mg and 900 mg) yielded, after crystallization with a mixture of acetone and hexane, finally 1.0 gram of 6-dehydroretroprogesterone, melting point 169° to 170°C. From the mother liquors an additional fraction of 0.44 gram with a melting point of 168° to 169°C was obtained.

References

Merck Index 3460
Kleeman & Engel p. 343
I.N. p. 369
Reerink, E.H., Westerhof, P. and Scholer, H.F.L.; U.S. Patent 3,198,792; August 3, 1965; assigned to North American Philips Company, Inc.

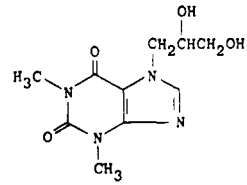
DYPHYLLINE

Therapeutic Function: Smooth muscle relaxant

Chemical Name: 7-(2,3-Dihydroxypropyl)-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione

Common Name: (1,2-Dihydroxy-3-propyl)theophylline; diprophylline

Structural Formula:



Chemical Abstracts Registry No.: 479-18-5

Trade Name	Manufacturer	Country	Year Introduced
Neothylline	Lemmon	U.S.	1948
Neutraphylline	Houde	France	1949
Droxine La	Dermik	U.S.	1979
Diprophyline	Wakodo Seiyaku	Japan	1981
Oxystat	Hyrex	U.S.	1983
AFI-Phyllin	A.F.I.	Norway	–
Aristophyllin	Kwizda	Austria	–
Astamasit	Showa	Japan	–
Asthmolysin	Kade	W. Germany	–
Astrophyllin	Astra	–	–
Austrophyllin	Petrasch	Austria	–
Coeurophylline	Barlow Cote	Canada	–
Corphyllin	Nippon Shinyaku	Japan	–
Difilina	Liade	Spain	–
Dilor	Savage	U.S.	–
Diasthmol	Trima	Israel	–
Dyflex	Econo-Rx	U.S.	–
Diurophylline	Monal	France	–
Dihydrophylline	Tokyo Hosei	Japan	–
Lufyllin	Mallinckrodt	U.S.	–
Neophyllin-M	Eisai	Japan	–
Neospect	Lemmon	U.S.	–
Neothylline	Lemmon	U.S.	–
Neo-Vasophylline	Katwijk	Neth.	–
Prophyllen	Streuli	Switz.	–
Protophylline	Rougier	Canada	–
Rominophyllin	Grelan	Japan	–
Silbephylline	Berk	U.K.	–
Sintofillina	Sintetica	Switz.	–
Solufyllin	Pharmacia	Sweden	–
Theourin	Kanto	Japan	–
Thefylan	Pharmacia	Sweden	–

Raw Materials

Theophylline
Sodium hydroxide
1-Chloro-2,3-dihydroxypropane

Manufacturing Process

180 grams of theophylline is dissolved in 500 cc of boiling water. To this solution is added 40 grams of sodium hydroxide or 56 grams of potassium hydroxide slowly and with constant stirring.

When solution is complete, 120 grams of 1-chloro-2,3-dihydroxypropane is slowly added. The thus provided mixture is brought to boiling and heating is continued until a temperature of 110°C is reached.

The resultant liquid is evaporated under reduced pressure to remove all traces of water. The resulting syrupy liquid is allowed to stand with occasional stirring until crystallization takes place. The compound is purified by recrystallization from alcohol. The product melts at 155°-157°C.

References

Merck Index 3465
Kleeman & Engel p. 329
PDR pp. 1603, 1877
I.N. p. 350
REM p. 872
Jones, J.W. and Maney, P.V.; U.S. Patent 2,575,344; November 20, 1951; assigned to the State of Iowa