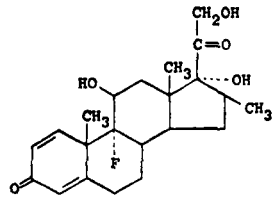
BETAMETHASONE

Therapeutic Function: Glucocorticoid

Chemical Name: 9-fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 378-44-9

Trade Name	Manufacturer	Country	Year Introduced
Celestone	Schering	U.S.	1961
Becort	Rachelle	U.S.	—
Betacortil	Pfizer	U.S.	—
Betalone	Firma	Italy	—
Betamamallet	Showa	Japan	—
Betapred	Glaxo	U.K.	—
Betasolon	Pharmax	Italy	—
Betnelan	Glaxo	U.K.	—
Betnesail	Glaxo	U.K.	—
Betnesol	Glaxo	U.K.	—
Celestan	Aesca	Austria	—
Celestene	Cetrane	France	—
Celestone	Essex	Spain	—
Cuantin	I.C.N.	Canada	—
Dermovaleas	Valeas	Italy	—
Desacort-Beta	Caber	Italy	—
Diprosone	Byk-Essex	W. Germany	—
Diprosone	Unilabo	France	—
Diprostene	Centrane	France	—
Hormezone	Tobishi	Japan	—
Linosal	Wakamoto	Japan	—
Minisone	IDI	Italy	—
No-Rheumar	Janus	Italy	—
Pertene Vita	Vita	Italy	—
Rinderon	Shionogi	Japan	—
Sanbetason	Santen	Japan	—
Sclane	Promesa	Spain	—
Unicort	Unipharm	Israel	—
Valisone	Schering	U.S.	—

Raw Materials

Betamethasone Acetate
Hydrogen Chloride

Manufacturing Process

Betamethasone acetate is converted to betamethasone by means of hydrochloric acid in a methanol-chloroform-water mixture as described in U.S. Patent 3,164,618.

References

Merck Index 1196
Kleeman & Engel p. 95
PDR p. 1610
OCDS Vol. 1 p. 198 (1977)
I.N. p. 137
REM p. 962
Amiard, G., Torelli, V. and Cerède, J.; U.S. Patent 3,104,246; September 17, 1963; assigned to Roussel-UCLAF, SA, France
Rausser, R. and Oliveto, E.P.; U.S. Patent 3,164,618; January 5, 1965; assigned to Schering Corporation

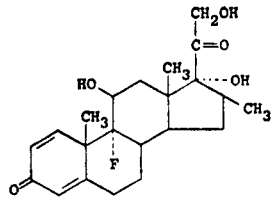
BETAMETHASONE ACETATE

Therapeutic Function: Glucocorticoid

Chemical Name: 9-fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione-21-acetate

Common Name: —

Structural Formula:



(base)

Chemical Abstracts Registry No.: 987-24-6

Trade Name	Manufacturer	Country	Year Introduced
Celestone Soluspan	Schering	U.S.	1965
Betafluorene	Lepetit	France	—
Celestone Cronodose	Essex	Italy	—

Raw Materials

17α,21-Dihydroxy-16β-methyl-4,9(11)-pregnadiene-3,20-dione 21 Acetate
N-Bromosuccinimide
Sodium Methoxide
Hydrogen Fluoride
Perchloric Acid
Acetic Anhydride
Selenium Dioxide

Manufacturing Process

The synthesis is long and complex. For brevity, only the last steps are given here. Refer to the patents cited below for full details.

Preparation of 9α-Bromo-11β,17α,21-Trihydroxy-16β-Methyl-4-Pregnene-3,20-Dione 21-Acetate: To a mixture of 620 mg of 17α,21-dihydroxy-16β-methyl-4,9(11)-pregnadiene-3,20-dione 21-acetate and 330 mg of N-bromosuccinimide in 10 ml of dioxane and 3.2 ml of water cooled to 10°C was added 1.8 ml of cold 1 M aqueous perchloric acid. The mixture was stirred at 15°C for 3 hours. Excess N-bromosuccinimide was destroyed by addition

of aqueous sodium thiosulfate and most of the dioxane was removed in vacuo. About 30 ml of water was added and crystalline bromohydrin, 9α-bromo-11β,17α,21-trihydroxy-16β-methyl-4-pregnene-3,20-dione 21-acetate, was filtered, washed with water, and dried in air.

Preparation of 9β,11β-Epoxy-17α-21-Dihydroxy-16β-Methyl-4-Pregnene-3,20-Dione 21-Acetate: To a stirred solution of 100 mg of the 9α-bromo-11β,17α,21-trihydroxy-16β-methyl-4-pregnene-3,20-dione 21-acetate in 3 ml of tetrahydrofuran and 1 ml of methanol under nitrogen was added 1.02 ml of 0.215 N methanolic sodium methoxide. After 10 minutes at 25°C, 0.2 ml of acetic acid was added and the methanol removed in vacuo. The residue was acetylated with 1.00 ml of pyridine and 0.5 ml of acetic anhydride at 60°C for 70 minutes. The mixture was taken to dryness in vacuo, water added, and the product extracted into chloroform. The residue was crystallized from ether-acetone to give pure 9β,11β-epoxy-17α,21-dihydroxy-16β-methyl-4-pregnene-3,20-dione 21-acetate.

Preparation of 9α-Fluoro-11β,17α,21-Trihydroxy-16β-Methyl-4-Pregnene-3,20-Dione 21-Acetate: To a solution of 200 mg of 9β,11β-epoxy-17α,21-dihydroxy-16β-methyl-4-pregnene 3,20-dione 21-acetate in 2 ml of chloroform and 2 ml of tetrahydrofuran in a polyethylene bottle at -60°C was added 2 ml of a 2:1 (by weight) mixture of anhydrous hydrogen fluoride and tetrahydrofuran. After 4 hours at -10°C the mixture was cooled to -60°C and cautiously added to a stirred mixture of 30 ml or 25% aqueous potassium carbonate and 25 ml of chloroform kept at -5°C. The aqueous phase was further extracted with chloroform and the latter phase washed with water and dried over magnesium sulfate. The residue on crystallization from acetone-ether gave pure 9α-fluoro-11β,17α,21-trihydroxy-16β-methyl-4-pregnene-3,20-dione 21-acetate.

Preparation of 9α-Fluoro-11β,17α,21-Trihydroxy-16β-Methyl-1,4-Pregnadiene-3,20-Dione 21-Acetate: 100 mg of 9α-fluoro-11β,17α,21-trihydroxy-16β-methyl-4-pregnene-3,20-dione 21-acetate was treated with selenium dioxide to produce the corresponding 9α-fluoro-11β, 17α,21-trihydroxy-16β-methyl-1,4-pregnadiene-3,20-dione 21-acetate. Alternately, *Bacillus sphaericus* may be utilized.

References

Merck Index 1196
Kleeman & Engel p. 97
PDR p. 1612
I.N. p. 137
REM p. 963
Taub, D., Wendler, N.L. and Slates, H.L.; U.S. Patent 3,053,865; September 11, 1962; assigned to Merck & Co., Inc.
Rausser, R. and Oliveto, E.P.; U.S. Patent 3,164,618; January 5, 1965; assigned to Schering Corporation.

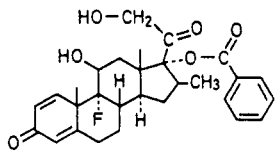
BETAMETHASONE BENZOATE

Therapeutic Function: Glucocorticoid

Chemical Name: 9-Fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione-17-benzoate

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 22298-29-9

Trade Name	Manufacturer	Country	Year Introduced
Benisone	Warner Lambert	U S.	1973
Flurobate Gel	Texas Pharm.	U.S.	1973
Beben	Parke Davis	Italy	1974
Uticort Gel	Warner Lambert	U.S.	1977
Benisone	Cooper Vision	U.S.	1979
Bebate	Warner	U.K.	–
Beben	Vister	Italy	–
Dermizol	Roux-Ocefa	Argentina	–
Euvaderm	Sasse	W. Germany	–
Parbetan	Parke Davis	W. Germany	–
Skincort	Parke Davis	W. Germany	–
Uticort	Parke Davis	U.S.	–

Raw Materials

Betamethasone
Methyl Orthobenzoate

Manufacturing Process

A mixture of 50 g of betamethasone, 50 cc of dimethylformamide, 50 cc of methyl orthobenzoate and 1.5 g of p-toluenesulfonic acid is heated for 24 hours on oil bath at 105°C while a slow stream of nitrogen is passed through the mixture and the methanol produced as a by-product of the reaction is distilled off. After addition of 2 cc of pyridine to neutralize the acid catalyst the solvent and the excess of methyl orthobenzoate are almost completely eliminated under vacuum at moderate temperature. The residue is chromatographed on a column of 1,500 g of neutral aluminum oxide. By elution with ether-petroleum ether 30 g of a crystalline mixture are obtained consisting of the epimeric mixture of 17α,21-methyl orthobenzoates. This mixture is dissolved without further purification, in 600 cc of methanol and 240 cc of methanol and 240 cc of aqueous 2N oxalic acid are added to the solution. The reaction mixture is heated at 40°-50°C on water bath, then concentrated under vacuum. The residue, crystallized from acetone-ether, gives betamethasone 17-benzoate, MP 225°-231°C.

References

Merck Index 1196
Kleeman & Engel p. 98
PDR p. 1393
DOT 10 (1) 9 (1974)
I.N. p. 137
Ercoli, A. and Gardi, R.; U.S. Patent 3,529,060; September 15, 1970; assigned to Warner-Lambert Pharmaceutical Co.

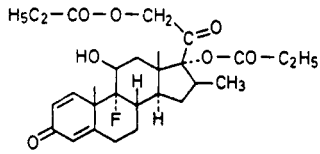
BETAMETHASONE DIPROPIONATE

Therapeutic Function: Glucocorticoid

Chemical Name: –

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 5593-20-4

Trade Name	Manufacturer	Country	Year Introduced
Betnovate	Glaxo	U.K.	1961
Bentelan	Glaxo	Italy	1962
Betnesol	Glaxo	France	1963
Betnesol	Glaxo	W. Germany	1965
Diprosone	Schering	U.S.	1975
Rinderon DP	Shionogi	Japan	1980
Diprolene	Schering	U.S.	1983
Alphatrex	Savage	U.S.	–
Beloderm	Belupo	Yugoslavia	–
Diproderm	Essex Espana	Spain	–
Diproderm	Aesca	Austria	–
Diproderm	Schering	U.S.	–
Diprogenta	Byk-Essex	W. Germany	–
Diprosalic	Unilabo	France	–
Diprosalic	Schering	U.K.	–
Diprostene	Cetrane	France	–
Lortisone	Schering	U.S.	–
Vanceril	Schering	U.S.	–

Raw Materials

9α,Fluoro-11β-hydroxy-16β-methyl-17α,21-(1'-ethyl-1'-ethoxymethylenedioxy)pregna-1,4-diene-3,20-dione
Acetic Acid
Propionyl Chloride

Manufacturing Process

A solution of 9α-fluoro-11β-hydroxy-16β-methyl-17α,21-(1'-ethyl-1'-ethoxymethylenedioxy) pregna-1,4-diene-3,20-dione (538 mg) in acetic acid (20 ml), containing 2 drops of water, was allowed to stand at room temperature for 5 hours. Dilution of the mixture with water gave a white solid (457 mg) which, after being filtered off and dried, was recrystallized from acetone to afford 9α-fluoro-11β,21-dihydroxy-16β-methyl-17α-propionyloxypregna-1,4-diene-3, 20-dione (361 mg), MP 230°–235°C.

Bethmethasone 17-propionate (812 mg) in pyridine (10 ml) was treated with propionyl chloride (0.21 ml) at 0°C for 1 hour. Dilution with water and acidification with dilute hydrochloric acid gave the crude diester. Recrystallization from acetone-petroleum ether afforded betamethasone 17,21-dipropionate (649 mg), MP 117°C (decomposition).

References

Merck Index 1196
Kleeman & Engel p. 99

PDR pp. 888, 1429, 1601, 1614, 1631
I.N. p. 138
Elks, J., May, P.J. and Weir, N.G.; U.S. Patent 3,312,590; April 4, 1967; assigned to Glaxo Laboratories, Ltd.

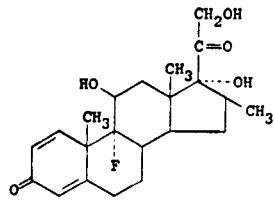
BETAMETHASONE VALERATE

Therapeutic Function: Corticosteroid

Chemical Name: 9-fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione-17-valerate

Common Name: —

Structural Formula:



(base)

Chemical Abstracts Registry No.: 33755-46-3; 38196-44-0 (Divalerate)

Trade Name	Manufacturer	Country	Year Introduced
Valisone	Schering	U.S.	1967
Beta Dival	Fardeco	Italy	1978
Beta Val	Lemmon	U.S.	1980
Cordel	Taisho	Japan	1981
Betatrex	Savage	U.S.	1983
Betacort	ICN	Canada	—
Betacorten	Trima	Israel	—
Betaderm	K-Line	Canada	—
Betnesol	Glaxo	W. Germany	—
Betnelan	Glaxo	U.K.	—
Betnevate	Daiichi	Japan	—
Celestan	Schering	W. Germany	—
Celestoderm	Cetrane	France	—
Celestoderm	Essex Espana	Spain	—
Dermosol	Iwaki	Japan	—
Dermovaleas	Valeas	Italy	—
Ecoval	Glaxo	Italy	—
Metaderm	Riva	Canada	—
Muhibeta	Nippon Shoji	Japan	—
Novobetamet	Novopharm	Canada	—
Procto-Celestan	Byk-Essex	W. Germany	—
Recto-Betnesol	Glaxo	W. Germany	—
Retenema	Glaxo	U.K.	—
Rinderon	Shionogi	Japan	—
Rolazote	Lando	Argentina	—
Stranoval	Glaxo	Italy	—

Raw Materials

Betamethasone
Methyl Orthovalerate

Manufacturing Process

The valerate is made from betamethasone as a starting material as follows: A suspension of 9α-fluoro-11β,17α,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione (betamethasone) (2 grams) in sodium dried benzene (500 ml) was distilled vigorously for a few minutes, toluene-p-sulfonic acid monohydrate (30 mg) and methyl orthovalerate (5 ml) were added and distillation was continued for 10 minutes. The mixture was then boiled under reflux for 1.5 hours after which time unreacted betamethasone alcohol (400 mg) was removed by filtration. The benzene solution was treated with solid sodium bicarbonate and a few drops of pyridine, filtered and evaporated to dryness at about 50°C. The residue, in ether, was filtered through grade III basic alumina (20 grams) to remove traces of unreacted betamethasone alcohol, the ether removed in vacuo and the residue of crude betamethasone 17,21-methyl orthovalerate was treated with acetic acid (20 ml) and a few drops of water and left overnight at room temperature.

The acetic acid solution was poured into water (100 ml) and extracted with chloroform. The chloroform extracts were washed in turn with water, saturated sodium bicarbonate solution and water, dried and evaporated in vacuo. The residual gum was triturated with ether and a white crystalline solid (1.16 grams) isolated by filtration. Recrystallization from ether (containing a small amount of acetone)-petroleum ether gave 9α-fluoro-11β,21-dihydroxy-16β-methyl-17α-valeryloxypregna-1,4-diene-3,20-dione (871 mg) as fine needles.

References

Merck Index 1196
Kleeman & Engel p. 101
PDR pp. 888, 1034, 1428, 1602, 1658
I.N. p. 138
REM p. 963
Elks, J., May, P.J. and Weir, N.G.; U.S. Patent 3,312,590; April 4, 1967; assigned to Glaxo Laboratories Limited, England

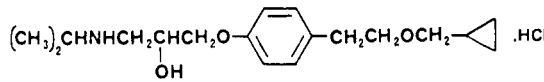
BETAXOLOL HYDROCHLORIDE

Therapeutic Function: β-Adrenergic blocking agent for cardiovascular problems

Chemical Name: 1-[4-[2-(Cyclopropylmethoxy)ethyl]phenoxy]-3-[(1-methylethyl)amino]-2-propanol hydrochloride

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 63659-18-7

Trade Name	Manufacturer	Country	Year Introduced
Kerlone	Carriere	France	1983
Kerlon	Kramer	Switz.	1983

Raw Materials

4-[2-(Cyclopropylmethoxy)ethyl] phenol
Sodium Hydroxide
Hydrogen Chloride
Epichlorohydrin
Isopropylamine

Manufacturing Process

(1) 1 g of sodium hydroxide pellets (0.025 mol) is added to a suspension of 3.8 g of 4-[2-(cyclopropylmethoxy)-ethyl] -phenol in 30 ml of water. When the solution becomes homogenous, 2.3 ml of epichlorohydrin are added and the mixture is stirred for 8 hours. It is then extracted with ether and the extract is washed with water, dried over sodium sulfate and evaporated to dryness. The compound is purified by passing it over a silica column. 2.4 g of 1-[4-[2-(cyclopropylmethoxy)ethyl] -phenoxy] -2,3-epoxy-propane are thus obtained.

(2) 4.9 g of the preceding compound (0.02 mol) are condensed with 25 ml of isopropylamine by contact for 8 hours at ambient temperature and then by heating for 48 hours at the reflux temperature. After evaporation to dryness, the compound obtained is crystallized from petroleum ether. 5 g (yield 80%) of 2-[[4-(2-cyclopropylmethoxy)-ethyl] -phenoxy] -3-isopropylamino-propan-2-ol are thus obtained, melting point 70° to 72°C.

The hydrochloride is prepared by dissolving the base in the minimum amount of acetone and adding a solution of hydrochloric acid in ether until the pH is acid. The hydrochloride which has precipitated is filtered off and is recrystallized twice from acetone, melting point 116°C.

References

Merck Index 1197
DFU 4 (12) 867 (1979)
DOT 18 (10) 552 (1982)
Manoury, P.M.J., Cavero, I.A.G., Majer, H. and Guidicelli, D.P.R.L.; U.S. Patent 4,252,984; February 24, 1981; assigned to Synthelabo

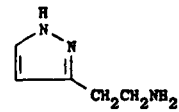
BETAZOLE

Therapeutic Function: Diagnostic aid (gastric secretion)

Chemical Name: 1H-pyrazole-3-ethanamine

Common Name: β-aminoethylpyrazole; ametazole

Structural Formula:



Chemical Abstracts Registry No.: 105-20-4; 138-92-1 (Dihydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Histalog	Lilly	U.S.	1953
Betazol	Lilly	W. Germany	–
Histimin	Shionogi	Japan	–

Raw Materials

Pyrone

Hydrazine Hydrate
Hydrogen

Manufacturing Process

A solution of 55 grams (1.1 mol) of hydrazine hydrate in 100 ml of methanol was cooled in a water bath and stirred while a solution of 48 grams (0.50 mol) of pure γ-pyrone in 100 ml of methanol was added over a period of about 15 minutes. After the addition was complete, the solution was allowed to stand at room temperature for about 1 hour, and was placed in a 1 liter hydrogenation bomb. 25 ml of liquid ammonia were added cautiously with stirring, followed by about 15 cc of Raney nickel catalyst. The bomb was charged with hydrogen to 1,800 pounds pressure, heated to 90°C and agitated. The quantity of hydrogen required to convert the hydrazone into the desired aminoethylpyrazole was taken up in about 3 hours. The bomb was cooled and opened, and the contents filtered. The filtrate was evaporated under reduced pressure to remove the methanol and the residual liquid was distilled under reduced pressure, whereby there were obtained 44.5 grams (81% yield) of 3-β-aminoethylpyrazole boiling at 118°-123°C at a pressure of 0.5 mm of Hg.

References

Merck Index 1198
Kleeman & Engel p. 102
I.N. p. 139
REM p. 1124
Jones, R.G.; U.S. Patent 2,785,177; March 12, 1957; assigned to Eli Lilly and Company

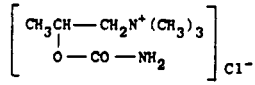
BETHANECHOL CHLORIDE

Therapeutic Function: Cholinergic

Chemical Name: 2-[(aminocarbonyl)oxy]-N,N,N-trimethyl-1-propanamium chloride

Common Name: Carbamylmethylcholine chloride

Structural Formula:



Chemical Abstracts Registry No.: 590-63-3

Trade Name	Manufacturer	Country	Year Introduced
Urecholine Cl	MSD	U.S.	1949
Urecholine Cl	MSD	Switz.	–
Duvoid	Norwich Eaton	U.S.	1978
Besacolin	Eisai	Japan	–
Bethachorol	Nichiiko	Japan	–
Mechothane	Farillon	U.K.	–
Mictone	Kenyon	U.S.	–
Mictrol	Misemer	U.S.	–
Mycholine	Glenwood	U.S.	–
Myo Hermes	Hermes	Spain	–
Myotonachol	Glenwood	U.S.	–
Myotonine	Glenwood	U.K.	–

Trade Name	Manufacturer	Country	Year Introduced
Paracholin	Kanto	Japan	–
Perista	Nissin	Japan	–
Urocarb	Hamilton	Australia	–
Urolax	Century	U.S.	–

Raw Materials

β-Methylcholine Chloride
Phosgene
Ammonia

Manufacturing Process

About 3 grams of β-methylcholine chloride are stirred at room temperature with an excess of phosgene dissolved in 50 grams of chloroform, for about 2 hours. Excess phosgene and hydrochloric acid are removed by distillation under vacuo. Additional chloroform is added to the syrup and the mixture is poured into excess ammonia dissolved in chloroform and cooled in solid carbon dioxide-acetone. The solid is filtered and extracted with hot absolute alcohol. The solid in the alcohol is precipitated with ether, filtered, and recrystallized from isopropanol. The carbaminoyl-β-methylcholine chloride obtained has a melting point of about 220°C.

References

Merck Index 1200
Kleeman & Engel p. 102
PDR pp. 830, 926, 1219, 1276
I.N. p. 139
REM p. 895
Major, R.T. and Bonnett, H.T.; U.S. Patent 2,322,375; June 22, 1943; assigned to Merck & Co., Inc.

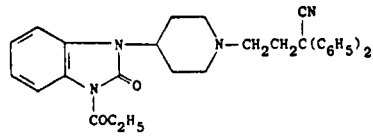
BIALAMICOL

Therapeutic Function: Antiamebic

Chemical Name: 3,3'-Bis[(diethylamino)methyl]-5,5'-di-(2-propenyl)-[1,1'-biphenyl]-4,4'-diol

Common Name: Biallylamicol

Structural Formula:



Chemical Abstracts Registry No.: 493-75-4

Trade Name	Manufacturer	Country	Year Introduced
Camoform HCl	Parke Davis	U.S.	1956

Raw Materials

Paraformaldehyde
Diethylamine
3,3'-Diallyl-4,4'-biphenol

Manufacturing Process

Paraformaldehyde (7.5 g) (0.25 mol) and 18.3 g (0.25 mol) of diethylamine are mixed in 25 cc of alcohol and warmed until a clear solution is obtained. The solution is cooled and mixed with 26.6 g (0.10 mol) of 3,3'-diallyl-4,4'-biphenol in 25 cc of alcohol. After standing several hours, the solution is warmed for one hour on the steam bath, allowing the alcohol to boil off. The residue is then taken up in ether and water, the ether layer separated and washed with 2% sodium hydroxide solution and finally with water. The washed ether solution is dried over solid potassium carbonate, and filtered. After acidifying with alcoholic hydrogen chloride, the ether is distilled off and the alcoholic residue diluted with an equal volume of acetone. The crystalline hydrochloride is filtered off, triturated with alcohol, diluted with several volumes of acetone, filtered and dried; MP 209°-210°C.

References

Merck Index 1209
I.N. p. 141
Rawlins, A.L., Holcomb, W.F., Jones, E.M., Tendick, F.H. and Burckhalter, J.H.; U.S. Patent 2,459,338; January 18, 1949; assigned to Parke, Davis & Co.

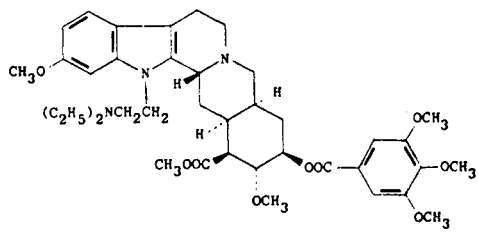
BIETASERPINE

Therapeutic Function: Antihypertensive

Chemical Name: 1-[2-(Diethylamino)ethyl]-11,17-dimethoxy-18-[(3,4,5-trimethoxybenzoyl)oxy] yohimban-16-carboxylic acid methyl ester

Common Name: 1-[2-(Diethylamino)ethyl] reserpine

Structural Formula:



Chemical Abstracts Registry No: 53-18-9

Trade Name	Manufacturer	Country	Year Introduced
Tensibar	Le Franco	France	1967
Pleiatensin	Guidotti	Italy	–
Pleiatensin	Byla	France	–

Raw Materials

Naphthalene
Diethylaminochloroethane
Sodium
Reserpine

Manufacturing Process

The first stage is to prepare the naphthyl sodium solution in the following way:

To a solution of 0.6 g naphthalene in 10 ml tetrahydrofurane, anhydrous, used as solvent, add 96 mg sodium under a nittrogen atmosphere. After a few minutes, an intensive dark green coloration develops, while the sodium dissolves. The reaction is completed after a period of time ranging between 30 and 60 minutes.

Then add to the above solution a solution of 2.42 g reserpine in 60 ml anhydrous dioxan at 50°C.

After heating for 15 minutes (which corresponds to carrying out reaction a), add 0.6 g, diethylaminochloroethane, while the mixture is kept boiling under reflux, for 6 hours. Reaction b is then completed.

Then cool the mixture and evaporate the dioxan under reduced pressure. The pasty residue is dissolved in a mixture of 50 ml benzene and 20 ml ether, and washed several times with water.

The aqueous solutions resulting from the washing are also extracted with ether, and the ether portions are added to the main ether-benzene solution.

This solution is extracted several times with 5% acetic acid, until the silico-tungstate test (an identification test for alkaloids) yields a negative result, and the acetic solutions are washed with 10 ml ether.

After combining the acetic extracts, the solution is adjusted to a pH of 9 with sodium carbonate, which precipitates the base, which is insoluble in water.

The oily suspension obtained in this way is extracted several times with chloroform. The chloroform solutions are then washed, each with 10 ml water, then they are combined and dried over anhydrous potassium carbonate.

After filtering and evaporating the solvent under reduced pressure, the pasty residue, constituted by the enriched product, is diluted with 30 ml ether and in this way 0.225 g reserpine (which has not taken part in the reaction) is isolated by filtration.

After evaporation of the ether under reduced pressure, 1.525 g of the crude resinous base is obtained, which constitutes the required product in a crude and impure condition.

This product is purified in the following way: After dissolving in 15 ml of dry benzene, the resulting solution is filtered on an alumina column, which fixes the base.

After consecutive elutions with pure benzene, and benzene containing increasing proportions of chloroform, 0.748 g of 1-diethylaminoethyl-reserpine is isolated in the form of a resin. The crystalline acid bitartrate prepared in ethyl acetate melts at 145°-150°C, with decomposition.

References

Merck Index 1217
Kleeman & Engel p. 105
I.N. p. 142
Societe Nogentaise De Produits Chimiques and Buzas, A.; British Patent 894,866; April 26, 1962

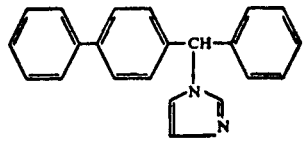
BIFONAZOLE

Therapeutic Function: Antifungal

Chemical Name: 1-[(1,1'-Biphenyl)-4-ylphenylmethyl]-1H-imidazole

Common Name: (Biphenyl-4-yl)-imidazol-1-yl-phenylmethane

Structural Formula:



Chemical Abstracts Registry No.: –

Trade Name	Manufacturer	Country	Year Introduced
Mycospor	Bayer	W. Germany	1983

Raw Materials

4-Phenylbenzophenone
Imidazole
Sodium Borohydride
Thionyl Chloride

Manufacturing Process

38.8 g (0.15 mol) of 4-phenylbenzophenone are dissolved in 200 ml of ethanol and 3 g (0.075 mol) of sodium borohydride are added. After heating for 15 hours under reflux, and allowing to cool, the reaction mixture is hydrolyzed with water containing a little hydrochloric acid. The solid thereby produced is purified by recrystallization from ethanol. 36 g (89% of theory) of (biphenyl-4-yl)-phenyl-carbinol [alternatively named as diphenyl-phenyl carbinol or α-(biphenyl-4-yl)benzylalcohol] of melting point 72°–73°C are obtained.

13.6 g (0.2 mol) of imidazole are dissolved in 150 ml of acetonitrile and 3.5 ml of thionyl chloride are added at 10°C. 13 g (0.05 mol) of (biphenyl-4-yl)-phenyl-carbinol are added to the solution of thionyl-bis-imidazole thus obtained. After standing for 15 hours at room temperature, the solvent is removed by distillation in vacuo. The residue is taken up in chloroform and the solution is washed with water. The organic phase is collected, dried over sodium sulfate and filtered and the solvent is distilled off in vacuo. The oily residue is dissolved in ethyl acetate and freed from insoluble, resinous constituents by filtration. The solvent is again distilled off in vacuo and the residue is purified by recrystallization from acetonitrile. 8.7 g (56% of theory) of (biphenyl-4-yl)-imidazol-1-yl-phenylmethane [alternatively named as diphenyl-imidazolyl-(1)-phenyl-methane or as 1-(α-biphenyl-4-ylbenzyl)imidazole] of melting point 142°C are obtained.

References

Merck Index A-3
DFU 7 (2) 87 (1982)
DOT 19 (6) 341 (1983)
I.N. p. 142
Regal, E., Draber, W., Buchel, K.H. and Plempel, M.; U.S. Patent 4,118,487; October 3, 1978; assigned to Bayer A.G.

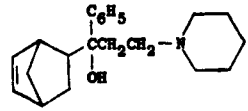
BIPERIDEN

Therapeutic Function: Antiparkinsonism

Chemical Name: α-bicyclo[2.2.1] hept-5-en-2-yl-α-phenyl-1-piperidinepropanol

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 514-65-8; 1235-82-1 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Akineton HCl	Knoll	U.S.	1959
Akineton HCl	Knoll	W. Germany	—
Akineton HCl	Knoll	Switz.	—
Akinophyl	Biosedra	France	1970
Akineton	Abbott	U.K.	—
Akineton	Dainippon	Japan	—
Akineton	Medinsa	Spain	—
Dekinet	Rafa	Israel	—
Ipsatol	Orion	Finland	—
Paraden	Yurtoglu	Turkey	—
Tasmolin	Yoshitomi	Japan	—

Raw Materials

Acetophenone
5-Chloro-2-norbornene
Hydrogen Chloride
Piperidine HCl
Magnesium
Formaldehyde

Manufacturing Process

65 grams of 3-piperidino-1-phenyl propanone-1 of the summary formula $C_{14}H_{29}ON$, produced according to Mannich's reaction by reacting acetophenone with formaldehyde and piperidine hydrochloride are dissolved in 300 cc of benzene. The resulting solution is added to an organo-magnesium solution prepared from 96 grams of [Δ5-bicyclo-(2,2,1)-heptenyl-2]-chloride (also known as 5-chloro-2-norbornene) 18.5 grams of magnesium shavings, and 300 cc of ether.

The reaction mixture is boiled for half an hour under reflux. Thereafter the ether is removed by distillation, until the inside temperature reaches 65°-70°C. The resulting benzene solution is added to 95 cc concentrated hydrochloric acid containing ice for further processing. Thereby, 3-piperidino-1-phenyl-1-[Δ5-bicyclo-(2,2,1)-heptenyl-2]-propanol-1 of the summary formula $C_{21}H_{29}ON$ is obtained. The compound melts at 101°C and its chlorohydrate has a melting point of about 238°C. The compound is difficultly soluble in water, slightly soluble in ethanol, and readily soluble in methanol.

References

Merck Index 1231
Kleeman & Engel p. 107
PDR p. 975
OCDS Vol. 1 p. 47 (1977)
DOT 18 (2) 90 (1982)
I.N. p. 144
REM pp. 928, 929
Klavehr, W.; U.S. Patent 2,789,110; April 16, 1957; assigned to Knoll AG Chemische Fabriken, Germany

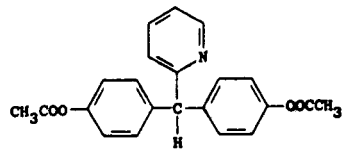
BISACODYL

Therapeutic Function: Laxative

Chemical Name: 4,4'-(2-pyridylmethylene)bisphenol diacetate

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 603-50-9

Trade Name	Manufacturer	Country	Year Introduced
Dulcolax	Boehr. Ingel.	U.S.	1958
Dulcolax	Thomae	W. Germany	—
Dulcolax	Boehr. Ingel.	Switz.	—
Contalax	Riker	France	1959
Bicol	Wampole	U.S.	1974
Biscolax	Fleet	U.S.	1975
Theralax	Beecham	U.S.	1976
Alaxa	Angelini	Italy	—
Anan	Ono	Japan	—
Bisacolax	ICN	Canada	—
Biomit	Sampo	Japan	—
Brocalax	Brocades-Steethman	Neth.	—
Cathalin	Hokoriku	Japan	—
Codilax	Pharbil	Belgium	—
Contalax	Fischer	Israel	—
Darmoletten	Omegin	W. Germany	—
Deficol	Vangard	U.S.	—
Delco-Lax	Delco	U.S.	—
Durolax	Boehr. Ingel.	W. Germany	—
Endokolat	Weiskopf	W. Germany	—
Ercolax	Erco	Denmark	—
Ethanis	Taisho	Japan	—
Eulaxan	Ferring	W. Germany	—
Evac-Q-Kwik	Adria	U.S.	—
Godalax	Pfleger	W. Germany	—
Hillcolax	Hillel	Israel	—
Ivilax	Bieffe	Italy	—
Laco	Paul Maney	Canada	—
Laksodil	Uranium	Turkey	—
Lax	Kanto	Japan	—
Laxadin	Teva	Israel	—
Laxagetten	Tempelhof	W. Germany	—
Laxanin N	Schwarzhaupt	W. Germany	—
Laxbene	Merckle	W. Germany	—
Laxematic	Kemifarma	Denmark	—
Med-Laxan	Med	W. Germany	—
Metalax	Star	Finland	—
Mormalene	Montefarmaco	Italy	—
Neodrast	Werner Schnur	W. Germany	—

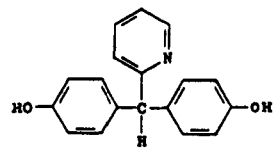
Trade Name	Manufacturer	Country	Year Introduced
Neo-Salvilax	Para-Pharma	Switz.	–
Novolax	Krka	Yugoslavia	–
Obstilax	Zirkulin	W. Germany	–
Organolax	Azuchemie	W. Germany	–
Perilax	Nordex	Norway	–
Prontolax	Streuli	Switz.	–
Pyrilax	Berlin-Chemie	E. Germany	–
Rytmil	Vicks	U.S.	–
Sanvacual	Santos	Spain	–
Satolax	Sato	Japan	–
Serax	Hameln	W. Germany	–
Stadalax	Stada	W. Germany	–
Telemin	Funai	Japan	–
Toilax	Erco	Denmark	–
Toilex	Protea	Australia	–
Ulcolax	Ulmer	U.S.	–
Vemas	Nippon Zoki	Japan	–
Vencoll	Maruko	Japan	–
Vinco	OTW	W. Germany	–

Raw Materials

α-Pyridine Aldehyde
Phenol
Acetic Anhydride

Manufacturing Process

Preparation of (4,4'-Dihydroxy-Diphenyl)-(Pyridyl-2)-Methane—



70.0 grams of α-pyridine aldehyde are fed portionwise with stirring and cooling to a mixture of 200 grams of phenol and 100 cc of concentrated sulfuric acid. The reaction mixture is allowed to stand for a while with repeated stirring, whereby it becomes syrupy, neutralized with sodium carbonate, dissolved in methanol and filtered. The filtrate is introduced into a large quantity of water and the resulting precipitate is recrystallized from a methanol/water mixture. Colorless crystals are obtained of MP 254°C. When using zinc chloride or tin tetrachloride and warming to a temperature of about 50°C, a corresponding result is obtained.

Preparation of Bisacodyl: 5 grams of (4,4'-dihydroxy-diphenyl)-(pyridyl-2)-methane are heated with 5 grams of anhydrous sodium acetate and 20 cc of acetic anhydride for three hours over a boiling waterbath. The cooled reaction mixture is poured into water, whereby after a while a colorless substance precipitates, which is filtered off with suction, washed with water and recrystallized from aqueous ethanol. Colorless bright crystals, MP 138°C are obtained.

References

Merck Index 1238
Kleeman & Engel p. 107

PDR pp. 561, 677, 879, 1569
I.N. p. 145
REM p. 800
Kottler, A. and Seeger, E.; U.S. Patent 2,764,590; September 25, 1956; assigned to Dr. Karl Thomae GmbH, Germany

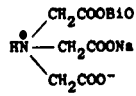
BISMUTH SODIUM TRIGLYCOLLAMATE

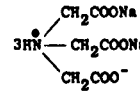
Therapeutic Function: Lupus Erythematosus Suppressant

Chemical Name: Nitrilotriacetic acid bismuth complex sodium salt

Common Name: —

Structural Formula:





Chemical Abstracts Registry No.: 5798-43-6

Trade Name	Manufacturer	Country	Year Introduced
Bistrimate	Smith, Miller & Patch	U.S.	1946

Raw Materials

Bismuth Oxide
Triglycollamic Acid
Sodium Carbonate

Manufacturing Process

A mixture of 2.33 g of bismuth oxide (Bi_2O_3), 3.71 g of anhydrous sodium carbonate, and 7.64 g of triglycollamic acid and 40 cc of water was heated at 80°C on the water bath until all was dissolved. The solution was evaporated on the water bath to a syrup. The syrup was allowed to cool, during which time partial solidification occurred. It was then triturated with 300 cc of alcohol, and the solid anhydrous salt was collected on a filter, washed with alcohol, ground fine, and dried in a vacuum desiccator. This substance has a water solubility at 25°C of 31.8% by weight. It decomposes on heating in the melting point bath.

References

Merck Index 1279
I.N. p. 147
Lehman, R.A. and Sproull, R.C.; U.S. Patent 2,348,984; May 16, 1944

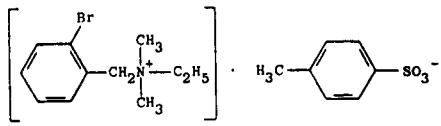
BRETYLIUM TOSYLATE

Therapeutic Function: Antiadrenergic; cardiac antiarrhythmic

Chemical Name: 2-Bromo-N-ethyl-N, N-dimethylbenzenemethanaminium 4-methylbenzene sulfonate

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 61-75-6

Trade Name	Manufacturer	Country	Year Introduced
Bretylate	Wellcome	U.K.	1973
Bretylate	Wellcome	France	1974
Bretylol	Am. Crit. Care	U.S.	1978
Critifib	Arnar-Stone	U.S.	–
Darenthin	Burroughs Wellcome	U.S.	–

Raw Materials

N-o-Bromobenzyl-N,N-dimethylamine
Ethyl-p-toluene Sulfonate

Manufacturing Process

N-o-bromobenzyl-N,N-dimethylamine (100 g) and ethyl p-toluenesulfonate (94 g) were mixed and warmed to 50°–60°C; after standing for either (*a*) a minimum of 96 hours at 15°–20°C or (*b*) a minimum of 18 hours at 50°–60°C and cooling to room temperature, a hard, crystalline mass was formed. Recrystallization of this product from acetone (2.0 ml/g of crude solid), followed by filtration and drying to 60°C gave N-o-bromobenzyl-N-ethyl-N,N-dimethylammonium p-toluenesulfonate as a white, crystalline solid, MP 97°–99°C. For this procedure it was necessary that the reactants were substantially colorless and of a high purity.

References

Merck Index 1348
PDR p. 574
OCDS Vol. 1 p. 55 (1977)
DOT 16 (10) 359 (1980)
I.N. p. 152
REM p. 860
Copp, F.C. and Stephenson, D.; U.S. Patent 3,038,004; June 5, 1962; assigned to Burroughs Wellcome & Co.

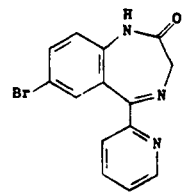
BROMAZEPAM

Therapeutic Function: Tranquilizer

Chemical Name: 7-bromo-1,3-dihydro-5-(2-pyridinyl)-2H-1,4-benzodiazepin-2-one

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 1812-30-2

Trade Name	Manufacturer	Country	Year Introduced
Lexotan	Roche	Italy	1975
Lexotan	Roche	Japan	1977
Lexotanil	Roche	W. Germany	1977
Lexotanil	Roche	Switz.	1977
Lexomil	Roche	France	1981
Lexotan	Roche	U.K.	1982
Compedium	Polifarma	Italy	—
Creosidin	Osiris	Argentina	—
Lectopam	Hoffman-La Roche	U.S.	—
Lenitin	Ikapharm	Israel	—
Lexaurin	Krka	Yugoslavia	—
Lexilium	Alkaloid	Yugoslavia	—
Normoc	Merckle	W. Germany	—

Raw Materials

2-(2-Aminobenzoyl)pyridine
Acetic Anhydride
Bromine
Hydrogen Chloride
Bromo Acetyl Bromide
Water
Ammonia

Manufacturing Process

Example: 32.8 grams of 2-(2-aminobenzoyl)-pyridine and 200 cc of acetic anhydride were stirred at room temperature for 3 hours and then permitted to stand overnight. Evaporation to dryness and digestion of the residue with 200 cc of water containing a little sodium bicarbonate to make the pH slightly alkaline gave 2-(2-acetamidobenzoyl)-pyridine as a light tan powder, which upon crystallization from methanol formed colorless crystals melting at 151°-153°C.

A solution of 8.6 cc of bromine in 100 cc of acetic acid was added slowly over a 3.5 hour period to a stirred solution of 38.5 grams of 2-(2-acetamidobenzoyl)-pyridine in 250 cc of acetic acid. The dark solution was stirred for another 3 hours, permitted to stand overnight, stirred for 1 hour with N_2 sweeping, and evaporated at diminished pressure in the hood. The gummy residue (75 grams) was treated with water and ether, made alkaline with dilute sodium bicarbonate solution, and separated. Both phases contained undissolved product which was filtered off. Additional crops were obtained by further extraction of the aqueous phase with ether and evaporation of the resulting ether solutions. All these materials were recrystallized from methanol (decolorizing carbon added) yielding 2-(2-acetamido-5-bromobenzoyl)-pyridine as yellow crystals melting at 131.5°-133°C.

20.85 grams of 2-(2-acetamido-5-bromobenzoyl)-pyridine in 250 cc of 20% hydrochloric acid in ethanol were heated to reflux for 2 hours. 100 cc of alcohol were added after one hour to maintain fluidity. The mixture stood overnight, was chilled and filtered to give 20.5 grams of colorless crystalline 2-(2-amino-5-bromobenzoyl)-pyridine hydrochloride. Digestion of this hydrochloride with 0.5 liter hot water hydrolyzed this product to the free base, 2-(2-amino-5-bromobenzoyl)-pyridine which formed yellow crystals, melting at 98°-100°C. Evaporation of the alcoholic mother liquor, water digestion of the residue, and alkalization of the water digests afforded additional crops of 2-(2-amino-5-bromobenzoyl)-pyridine.

0.145 kg of 2-(2-amino-5-bromobenzoyl)-pyridine, was dissolved in 2.0 liters of glacial acetic acid. The resultant solution was placed in a 3 liter, 3-necked, round bottom flask fitted with a stirrer, thermometer and dropping funnel. The system was protected by a drying tube filled with anhydrous calcium chloride. To the solution, with stirring at room temperature, were carefully added 46.7 ml of bromoacetyl bromide. After the addition was

completed, the stirring was continued for two hours. The mixture was then warmed to 40°C, stirred at that temperature for 1.5 hours, chilled and filtered. The residue, after being washed with glacial acetic acid, was dried in vacuo over flake potassium hydroxide to give 2-(2-bromoacetamido-5-bromobenzoyl)-pyridine hydrobromide orange crystals, MP 205°-206°C, dec.

The hydrobromide was hydrolyzed to the free base as follows: 0.119 kg of 2-(2-bromoacetamido-5-bromobenzoyl)-pyridine hydrobromide was stirred with 1.2 liters of cold water for 3.5 hours. The mixture was chilled and filtered, and the residue washed with cold water and dried to give 2-(2-bromoacetamido-5-bromobenzoyl)-pyridine, MP 101°C (sinters), 103°-106°C, dec.

93.0 grams of 2-(2-bromoacetamido-5-bromobenzoyl)-pyridine was carefully added to 0.5 liter of anhydrous ammonia in a 1 liter, 3-necked, round bottom flask equipped with stirrer and reflux condenser and cooled by a Dry Ice-acetone bath. The system was protected from moisture by a drying tube containing anhydrous calcium chloride. After stirring for 2 hours, the cooling bath was removed. The mixture was then stirred for 6 hours, during which time the ammonia gradually boiled off. 0.4 liter of water was added to the solid residue and stirring was resumed for about 2 hours. The solid was then filtered off, washed with water and dried in vacuo over potassium hydroxide flakes. The residue was dissolved on a steam bath in 1.4 liters of ethyl alcohol-acetonitrile (1:1) (decolorizing charcoal added). The solution was filtered hot and the filtrate chilled overnight. The crystalline deposit was filtered off, washed with cold ethyl alcohol and dried in vacuo over flake potassium hydroxide to give 54.2 grams. 7-Bromo-1,3-dihydro-5-(2-pyridyl)-2H-1,4-benzodiazepin-2-one, MP 238°C (sinters), 239°-240.5°, dec. Further processing of the mother liquor yielded additional product.

References

Merck Index 1357
Kleeman & Engel p. 110
DOT 9 (6) 238 (1973) & 11 (1) 31 (1975)
I.N. p. 154
REM p. 1064
Fryer, R.I., Schmidt, R.A. and Sternbach, L.H.; U.S. Patent 3,100,770; August 13, 1963; assigned to Hoffmann-LaRoche Inc.
Fryer, R.I., Schmidt, R.A. and Sternbach, L.H.; U.S. Patent 3,182,065; May 4, 1965; assigned to Hoffmann-LaRoche Inc.
Fryer, R.I., Schmidt, R.A. and Sternbach, L.H.; U.S. Patent 3,182,067; May 4, 1965; assigned to Hoffmann-LaRoche Inc.

BROMELAIN

Therapeutic Function: Antiinflammatory

Chemical Name: Complex proteolytic enzyme

Common Name: –

Structural Formula: Complex protein, molecular weight 33,000

Chemical Abstracts Registry No.: 9001-00-7

Trade Name	Manufacturer	Country	Year Introduced
Ananase	Rorer	U.S.	1962
Bromelain	Nadrol	W. Germany	1965

Trade Name	Manufacturer	Country	Year Introduced
Resolvit	Mepha	Switz.	1965
Ananase	Rorer	Italy	1965
Ananase	Rorer	U.K.	1966
Extranase	Rorer	France	1969
Bromelain	Towa Yakuhin	Japan	1981
Ananase	Pharmax	U.K.	–
Ananase	Yamanouchi	Japan	–
Bromelain	Permicutan	W. Germany	–
Dayto Anase	Dayton	U.S.	–
Inflamen	Hokoriku	Japan	–
Mexase	Ciba-Geigy	France	–
Pinase	Dainippon	Japan	–
Proteolis	Benvegna	Italy	–
Resolvit	Mepha	Switz.	–
Rogorin	Saba	Italy	–
Traumanase	Arznei Muller-Rorer	W. Germany	–

Raw Materials

Pineapple Juice
Acetone

Manufacturing Process

According to U.S. Patent 3,002,891, the following describes pilot plant production of bromelain. Stripped pineapple stumps were passed four times through a three roll sugar mill press. In the second and following passes through the press, water was added to the pulp to increase the efficiency of the extraction procedure. The crude juice was screened to remove the coarse particles. Hydrogen sulfide gas was bled into the collected juice to partially saturate it. The pH was adjusted to pH 4.8 and then the juice was centrifuged.

To 50 gallons of juice were added 30 gallons of cold acetone. The precipitate which formed was removed by centifuging in a Sharples centrifuge. This precipitate was discarded. To the supernatant liquor an additional 35 gallons of acetone was added and the precipitate was collected in a Sharples centrifuge. The wet precipitate was dropped into fresh acetone, mixed well, and then recovered by settling. The paste was then dried in a vacuum oven at a shelf temperature of 110°F. Yield: 8 pounds of enzyme per 100 gallons of juice. Activity: 4,000 MCU/g.

References

Merck Index 1360
Kleeman & Engel p. 112
PDR p. 831
I.N. p. 154
REM p. 1038
Gibian, H. and Bratfisch, G.; U.S. Patent 2,950,227; August 23, 1960; assigned to Schering AG, Germany
Heinicke, R.M.; U.S. Patent 3,002,891; October 3, 1961; assigned to Pineapple Research Institute of Hawaii

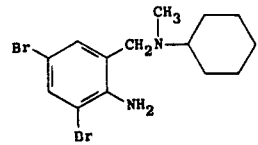
BROMHEXINE

Therapeutic Function: Expectorant, mucolytic

Chemical Name: 2-Amino-3,5-dibromo-N-cyclohexyl-N-methyl-benzenemethanamine

Common Name: N-(2-Amino-3,5-dibromobenzyl)-N-methyl-cyclohexylamine

Structural Formula:



Chemical Abstracts Registry No.: 3572-43-8; 611-75-6 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Bisolvon	Boehringer Ingel.	Switz.	1963
Bisolvon	Thomae	W. Germany	1963
Bisolvon	Boehringer Ingel.	Italy	1968
Bisolvon	Boehringer Ingel.	U.K.	1968
Bisolvon	Boehringer Ingel.	France	1969
Lebelon	Towa Yakuhin	Japan	1981
L-Customed	Roha	W. Germany	1982
Aletor	Cantabria	Spain	–
Auxit	Heyden	W. Germany	–
Bendogen	Gea	Denmark	–
Brometksin	Mulda, Yurtoglu	Turkey	–
Broncokin	Geymonat	Italy	–
Bronkese	Lennon	South Africa	–
Dakryo	Basotherm	W. Germany	–
Fulpen	Sawai	Japan	–
Mucovin	Leiras	Finland	–
Ophthosol	Winzer	W. Germany	–
Solvex	Ikapharm	Israel	–
Viscolyt	Gea	Denmark	–

Raw Materials

2-Nitrobenzyl Bromide
Cyclohexylmethylamine
Hydrazine
Bromine

Manufacturing Process

In initial steps, 2-nitrobenzylbromide and cyclohexylmethylamine are reacted and that initial product reacted with hydrazine to give N-(2-aminobenzyl)-N-methyl-cyclohexylamine.

A solution of 29.3 g of bromine in 50 cc of glacial acetic acid was slowly added dropwise to a solution of 15.9 g of N-(2-aminobenzyl)-N-methyl-cyclohexylamine, accompanied by stirring. The glacial acetic acid was decanted from the precipitate formed during the addition of the bromine solution, and the precipitate was thereafter shaken with 200 cc of 2N sodium hydroxide and 600 cc of chloroform until all of the solids went into solution. The chloroform phase was allowed to separate from the aqueous phase. The chloroform phase was decanted, evaporated to dryness and the residue was dissolved in absolute ether. The resulting solution was found to be a solution of N-(2-amino-3,5-dibromobenzyl)-N-methyl-cyclohexylamine in ethanol. Upon introducing hydrogen chloride into this solution, the hydrochloride of N-(2-amino-3,5-dibromobenzyl)-N-methyl-cyclohexylamine precipitated out. It had a melting point of 232°-235°C (decomposition).

References

Merck Index 1361

Kleeman & Engel p. 113
OCDS Vol. 2 p. 96 (1980)
I.N. p. 154
Keck, J.; U.S. Patent 3,336,308; August 15, 1967; assigned to Boehringer Ingelheim G.m.b.H.

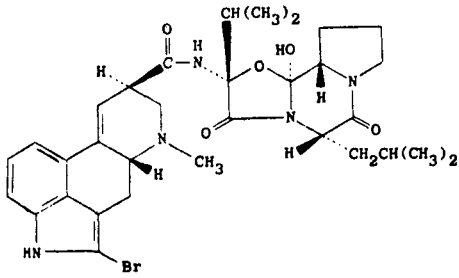
BROMOCRIPTINE

Therapeutic Function: *Lactation antagonist*

Chemical Name: 2-bromo-12'-hydroxy-2'-(1-methylethyl)-5'α-(2-methylpropyl)ergotaman-3',6',18-trione

Common Name: 2-Bromoergocryptine

Structural Formula:



Chemical Abstracts Registry No.: 25614-03-3; 22260-51-1 (Mesylate)

Trade Name	Manufacturer	Country	Year Introduced
Parlodel	Sandoz	U.K.	1975
Pravidel	Sandoz	W. Germany	1977
Parlodel	Sandoz	Switz.	1977
Parlodel	Sandoz	U.S.	1978
Parlodel	Sandoz	France	1978
Parlodel	Sandoz	Japan	1979
Parlodel	Sandoz	Italy	1979
Bromergon	Lek	Yugoslavia	—

Raw Materials

N-Bromosuccinimide
Ergocryptine

Manufacturing Process

A solution of 3.4 grams of N-bromosuccinimide in 60 cc of absolute dioxane is added dropwise in the dark, during the course of 5 minutes, to a stirred solution, heated to 60°C, of 9.2 grams of ergocryptine in 180 cc of absolute dioxane. The reaction mixture is stirred at this temperature for 70 minutes and is concentrated to a syrup-like consistency in a rotary evaporator at a bath temperature of 50°C. The reaction mixture is subsequently diluted with 300 cc of methylene chloride, is covered with a layer of about 200 cc of a 2 N sodium carbonate solution in a separating funnel and is shaken thoroughly. The aqueous phase is extracted thrice with 100 cc amounts of methylene chloride. The combined

organic phases are washed once with 50 cc of water, are dried over sodium sulfate and the solvent is removed under a vacuum.

The resulting brown foam is chromatographed on a 50-fold quantity of aluminum oxide of activity II-III with 0.2% ethanol in methylene chloride as eluant, whereby the compound indicated in the heading is eluted immediately after a secondary fraction which migrates somewhat more rapidly than the fractions containing the heading compound. The last fractions to leave the aluminum oxide contain varying amounts of starting material together with the heading compound, and may be subjected directly, as mixed fractions, to an after-bromination in accordance with the method described above. The fractions containing the pure heading compound are combined and crystallized from methyl ethyl ketone/isopropyl ether. Melting point 215°-218°C (decomp.), $[\alpha]_D^{20}$ -195° (c = 1 in methylene chloride).

References

Merck Index 1386
Kleeman & Engel p. 114
PDR p. 1589
DOT 12 (3) 87 (1976)
I.N. p. 155
REM pp. 929, 955
Fluckiger, E., Troxler, F. and Hofmann, A.; U.S. Patent 3,752,814; August 14, 1973; assigned to Sandoz Ltd., Switzerland
Fluckiger, E., Troxler, F. and Hofmann, A.; U.S. Patent 3,752,888; August 14, 1973; assigned to Sandoz Ltd., Switzerland

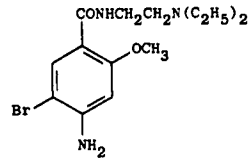
BROMOPRIDE

Therapeutic Function: Antiemetic

Chemical Name: 4-Amino-4-bromo-N-[2-(diethylamino)ethyl] -2-methoxybenzamide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 4093-35-0

Trade Name	Manufacturer	Country	Year Introduced
Praiden	Italchemi	Italy	1977
Valopride	Vita	Italy	1977
Cascapride	Cascan	W. Germany	1978
Artomey	Syncro	Argentina	–
Emepride	Roche	Switz.	–
Emoril	Roemmers	Argentina	–
Opridan	Locatelli	Italy	–
Plesium	Chiesi	Italy	–
Viaben	Schurholz	W. Germany	–

Raw Materials

Bromine
4-Aminosalicylic Acid
Dimethyl Sulfate
Acetic Anhydride
Methanol

Manufacturing Process

To 119 g (0.45 mol) of N-(2-diethylaminoethyl)-2-methoxy-4-aminobenzamide dissolved in 200 cc of acetic acid are added in the cold in small portions 69 g of acetic anhydride (0.45 mol + 50% excess). The starting material is made by esterifying 4-aminosalicylic acid with methanol, then acetylating with acetic anhydride and then methylating with dimethyl sulfate. The solution obtained is heated for 2 hours on a water bath and then boiled for 15 minutes. It is cooled at 25°C. While agitating constantly and maintaining the temperature between 25° and 30°C, there is added to the solution drop by drop 72 g of bromine dissolved in 60 cc of acetic acid. It is agitated for one hour. The mixture obtained is added to one liter of water and the base is precipitated by the addition of 30% soda. The precipitated base is extracted with 40 cc of methylene chloride. After evaporation of the solvent, the residue is boiled for two hours with 390 g of concentrated hydrochloric acid in 780 cc of water. It is cooled, diluted with one liter of water, 12 g of charcoal are added, and the mixture filtered. The base is precipitated with 30% soda. The N-(2-diethylaminoethyl)-2-methoxy-4-amino-5-bromobenzamide formed crystallizes, is centrifuged and washed with water. A yield of 85 g of base having a melting point of 129°-130°C is obtained.

To produce the dihydrochloride, the free base is dissolved in 110 cc of absolute alcohol, 9.6 g of dry hydrochloric acid dissolved in 35 cc of alcohol are added, followed by 2.8 cc of water. The dihydrochloride precipitates, is centrifuged, washed, and dried at 40°C. It was a solid white material having a melting point of 134°-135°C.

References

Merck Index 1404
Kleeman & Engel p. 115
DOT 14 (5) 193 (1978)
I.N. p. 156
Thominet, M.L.; U.S. Patents 3,177,252; April 6, 1965; 3,219,528; November 23, 1965; 3,357,978; December 12, 1967; all assigned to Societe d'Etudes Scientifiques et Industrielles de l'Ile-de-France

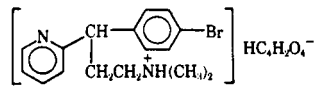
BROMPHENIRAMINE MALEATE

Therapeutic Function: Antihistaminic

Chemical Name: (4-bromophenyl)-N,N-dimethyl-2-pyridinepropanamine maleate

Common Name: Parabromdylamine

Structural Formula:



Chemical Abstracts Registry No.: 980-71-2; 86-22-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Dimetane	Robins	U.S.	1957
Dimegan	Dexo	France	1962
Symptom 3	WL/PD	U.S.	1977
Brombay	Bay	U.S.	1983
Antial	Ellem	Italy	–
Atronist	Adams	U.S.	–
Bromfed	Muro	U.S.	–
Bromphen	Schein	U.S.	–
Bromrun	Hokuriku	Japan	–
Dimetapp	Scheurich	W. Germany	–
Dimotane	Robins	U.K.	–
Drauxin	Francia	Italy	–
Dura-Tap	Dura	U.S.	–
Ebalin	Allergo Pharma	W. Germany	–
E.N.T. Syrup	Springbok	U.S.	–
Febrica	Dexo	France	–
Gammistin	IBP	Italy	–
Ilvico	Bracco	Italy	–
Ilvin	Merck	W. Germany	–
Martigene	Martinet	France	–
Nagemid Chronule	Ortscheit	W. Germany	–
Poly Histine	Bock	U.S.	–
Probahist	Legere	U.S.	–
Rupton	Dexo	France	–
Velzane	Lannett	U.S.	–

Raw Materials

Sulfuric Acid
Sodium Amide
Dimethylaminoethyl Chloride
4-Bromobenzyl Cyanide
2-Chloropyridine
Maleic Acid

Manufacturing Process

Initially, 4-bromobenzyl-cyanide is reacted with sodium amide and 2-chloropyridine to give bromophenyl-pyridyl acetonitrile. This is then reacted with sodium amide then dimethyl amino ethyl chloride to give 4-bromophenyl-dimethylaminoethyl-pyridyl acetonitrile. This intermediate is then hydrolyzed and decarboxylated to brompheniramine using 80% H_2SO_4 at 140°-150°C for 24 hours. The brompheniramine maleate may be made by reaction with maleic acid in ethanol followed by recrystallization from pentanol.

References

Merck Index 1417
Kleeman & Engel p. 116
PDR pp. 555, 674, 865, 993, 1033, 1268, 1454, 1606, 1735
OCDS Vol. 1 p. 77 (1977)
I.N. p. 157
REM p. 1126
Sperber, N., Papa, D. and Schwenk, E.; U.S. Patent 2,567,245; September 11, 1951; assigned to Schering Corporation
Sperber, N., Papa, D. and Schwenk, E.; U.S. Patent 2,676,964; April 27, 1954; assigned to Schering Corporation

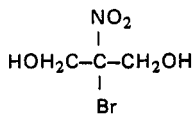
BRONOPOL

Therapeutic Function: Antiseptic

Chemical Name: 2-Bromo-2-nitropropane-1,3-diol

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 52-51-7

Trade Name	Manufacturer	Country	Year Introduced
Bronosol	Green Cross	Japan	1977
Bronopol	Boots	U.K.	–

Raw Materials

Nitromethane
Formaldehyde
Bromine

Manufacturing Process

A mixture of 441 g (3 mols) of calcium chloride dihydrate, 61 g (1 mol) of nitromethane, 163 g (2 mols) of formalin (37% formaldehyde solution) and 470 ml of water was cooled to 0°C and mixed with 5 g of calcium hydroxide while stirring. The temperature thereby rose to 30°C. As soon as the temperature had fallen again, a further 32 g of calcium hydroxide (total of 0.5 mol) were added. The mixture was then cooled to 0°C and with intensive cooling and stirring, 159.8 g (1 mol, 51 ml) of bromine were dropped in at a rate so that the temperature remained at around 0°C. After the addition was ended, the mixture was stirred for a further 2 hours, when the reaction product separated in crystalline form. The product was quickly filtered on a suction filter and the crystalline sludge obtained was taken up in 450 ml of ethylene chloride and dissolved at reflux. Then by addition of magnesium sulfate, undissolved inorganic salts were separated and the solution was slowly cooled whereby 140 g (70% yield) of 2-bromo-2-nitropropane-1,3-diol precipitated in colorless crystals melting at 123°–124°C.

References

Merck Index 1421
I.N. p. 158
Wessendorf, R.; U.S. Patents 3,658,921; April 25, 1972; and 3,711,561; January 16, 1973; both assigned to Henkel & Cie G.m.b.H.

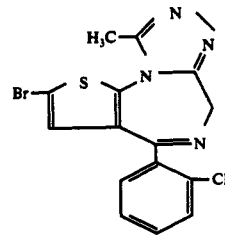
BROTIZOLAM

Therapeutic Function: Psychotropic agent

Chemical Name: 8-Bromo-6-(o-chlorophenyl)-1-methyl-4H-s-triazolo-[3,4c]-thieno-[2,3e]-1,4-diazepine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 57801-81-7

Trade Name	Manufacturer	Country	Year Introduced
Lendormin	Boehringer Ingel.	Switz.	1983
Lendorm	Boehringer Ingel.	Switz.	–

Raw Materials

7-Bromo-5-(o-chlorophenyl)-3H-[2,3e] thieno-1,4-diazepin-2-one
Phosphorus Pentasulfide
Hydrazine Hydrate

Manufacturing Process

(a) 11.5 g of 7-bromo-5-(o-chlorophenyl)-3H-[2,3e] -thieno-1,4-diazepin-2-one (see German Patent 2,221,623), were heated at 55° to 60°C with 100 cc of absolute pyridine and 6.5 g of phosphorus pentasulfide for 4 hours while stirring. The mixture was allowed to cool and was then poured into 100 cc of saturated ice-cold NaCl solution. The precipitate was collected by suction filtration, washed with water, dissolved in 100 cc of methylene chloride, the solution was dried and evaporated, and the residue was treated with a little methylene chloride. After suction filtration, 6 g of brown crystalline 7-bromo-5-(o-chlorophenyl)-3H-[2,3e]-thieno-1,4-diazepine-2-thione, melting point 214°C (decomposition) were obtained.

(b) 6.0 g of this compound were suspended in 100 cc of tetrahydrofuran, and the suspension was stirred at room temperature with 1.2 g of hydrazine hydrate for 20 minutes. After evaoration to about 10 cc, 20 cc of ether were added, and the crystals were collected by suction filtration. Yield: 5.2 g of 7-bromo-5-(o-chlorophenyl)-2-hydrazino-3H-[2,3e] -thieno-1,4-diazepine, melting point about 300°C (decomposition).

(c) 5.2 g of this compound were suspended in 50 cc of orthotriethyl acetate, and the suspension was heated to 80°C. After about 30 minutes a clear solution was first formed from which later colorless crystals separated out. The mixture was allowed to cool, and the crystals were collected by suction filtration and washed with ether. Yield: 5 g of the compound, melting point 211° to 213°C.

References

Merck Index 1423
DFU 4 (2) 85 (1979)
I.N. p. 159
Weber, K.H., Bauer, A., Danneberg, P. and Kunn, F.J.; U.S. Patent 4,094,984; June 13, 1978; assigned to Boehringer Ingelheim GmbH

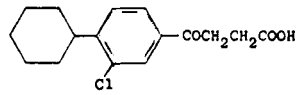
BUCLOXIC ACID

Therapeutic Function: Antiinflammatory

Chemical Name: 3-chloro-4-cyclohexyl-α-oxo-benzenebutanoic acid

Common Name: 4-(4-cyclohexyl-3-chlorophenyl)-4-oxobutyric acid

Structural Formula:



Chemical Abstracts Registry No.: 32808-51-8

Trade Name	Manufacturer	Country	Year Introduced
Esfar	Clin Midy	France	1974

Raw Materials

Phenylcyclohexane
Succinic Acid Anhydride
Chlorine

Manufacturing Process

Phenylcyclohexane and succinic acid (Bernstein Acid) anhydride are reacted in the presence of $AlCl_3$ to give 4-(4'-cyclohexylphenyl)-4-keto-n-butyric acid.

177 grams of anhydrous aluminum chloride are introduced into a 3-necked 1 liter flask. A hot solution of 144 grams of 4-(4'-cyclohexylphenyl)-4-keto-n-butyric acid in 330 ml of methylene chloride is added slowly from a dropping funnel. Slight reflux is observed during this addition. 33.2 ml of liquefied chlorine are then introduced slowly, drop by drop. This addition requires 5 hours. The solution is then poured on to 1 kg of ice containing 100 ml of concentrated hydrochloric acid. The aqueous phase is extracted twice, each time with 200 ml of methylene chloride, the organic phase is washed with water to pH 6.5 and dried and the organic solvent then evaporated. The desired acid is recrystallized from 500 ml of toluene. The yield is 64%. MP: 159°C.

References

Merck Index 1431
Kleeman & Engel p. 118
OCDS Vol. 2 p. 126 (1980)
DOT 10 (11) 294 (1974)
British Patent 1,315,542; May 2, 1973; assigned to Ets Clinbyla, France

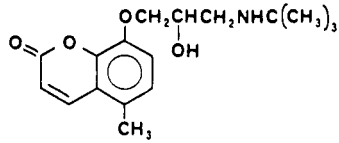
BUCUMOLOL HYDROCHLORIDE

Therapeutic Function: Beta adrenergic blocker

Chemical Name: 8-(2-Hydroxy-3-t-butylaminopropoxy)-5-methyl coumarin hydrochloride

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 58409-59-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Bucumarol	Sankyo	Japan	1982

Raw Materials

t-Butylamine
8-(2-Hydroxy-3-chloropropoxy)-5-methyl coumarin

Manufacturing Process

A mixture of 3 g of 8-(2-hydroxy-3-chloropropoxy)-5-methyl coumarin, 4.3 g of t-butylamine and 60 ml of ethanol is heated at 100°C in a sealed tube for 15 hours. The reaction mixture is concentrated under reduced pressure to dryness. The residue is recrystallized from a mixture of ethanol and ether to give 2.1 g of the desired product melting at 226° to 228°C (with decomposition).

References

Merck Index 1434
DFU 3 (9) 638 (1978)
DOT 19 (1) 10 (1983)
Sato, Y., Kobayashi, Y., Taragi, H., Kumakura, S., Nakayama, K. and Oshima, T.; U.S. Patent 3,663,570; May 16, 1972; assigned to Sankyo Co., Ltd.

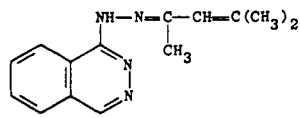
BUDRALAZINE

Therapeutic Function: Antihypertensive

Chemical Name: 1(2H)-Phthalazinone-(1,3-dimethyl-2-butenylidene)-hydrazone

Common Name: Mesityl oxide (1-phthalazinyl) hydrazone

Structural Formula:



Chemical Abstracts Registry No.: 36798-79-5

Trade Name	Manufacturer	Country	Year Introduced
Buterazine	Daiichi Seiyaku	Japan	1983

Raw Materials

1-Hydrazinophthalazine HCl
Mesityl Oxide

Manufacturing Process

A mixture of 2.0 g of 1-hydrazinophthalazine hydrochloride, 1.1 g of mesityl oxide (isopropylideneacetone) and 100 ml of ethanol, was refluxed for 3 hours. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in water. The water solution was neutral-

ized with sodium bicarbonate, salted out and the product was extracted with benzene. The benzene layer was passed through a comparatively short column of alumina and the solvent was removed. The residue was crystallized from ether to give 0.7 g of 1-(1,3-dimethyl-2-butenylidene) hydrazinophthalazine, melting point 131°-132°C.

References

Merck Index 1437
DFU 2 (12) 788 (1977)
DOT 18 (10) 553 (1982) & 19 (10) 582 (1983)
Ueno, K., Miyazaki, S. and Akashi, A.; U.S. Patent 3,840,539; October 8, 1974; assigned to Daiichi Seiyaku Co., Ltd.

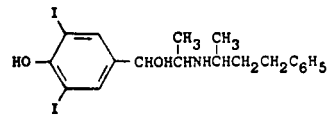
BUFENIODE

Therapeutic Function: Antihypertensive

Chemical Name: 4-hydroxy-3,5-diiodo-α-[1-[(1-methyl-3-phenylpropyl)amino] ethyl] benzyl alcohol

Common Name: Diiodobuphenine

Structural Formula:



Chemical Abstracts Registry No.: 22103-14-6

Trade Name	Manufacturer	Country	Year Introduced
Proclival	Houde	France	1970
Bufeniod	Weiskopf	W. Germany	1974
Diastal	Bayropharm	Italy	1982

Raw Materials

4-Hydroxypropiophenone
3-Butyl-1-phenylamine
Hydrogen
Benzyl Chloride
Bromide
Iodine

Manufacturing Process

Buphenine is the starting material. See under the alternative name "Nylidrin" in this publication for synthesis.

24 grams of buphenine hydrochloride are suspended in a mixture of 440 ml of 34% ammonia (specific gravity = 0.89) and 315 ml of water. 41 grams of iodine dissolved in 1,080 ml of 96% alcohol are added little by little, with good stirring. During this addition, effected in about 30 min, buphenine hydrochloride dissolves fairly rapidly, and then the diiodobuphenine precipitates out as a crystalline powder. Stirring is continued for a further hour. The precipitate is suction filtered, and then washed with water, with alcohol and with ether and is finally dried in vacuo in the exsiccator in the presence of phosphoric anhydride. Thus, about 23 grams of diiodobuphenine solvated with 1 mol of ethanol are obtained in the form of a microcrystalline white powder. MP (slow) = 185°C (dec.). MP (inst.): 212°C.

References

Merck Index 1440
Kleeman & Engel p. 119
DOT 7 (2) 52 (1971) & 11 (8) 306 (1975)
I.N.p. 161
South African Patent 680,046; January 3, 1968; assigned to Laboratoires Houde, France

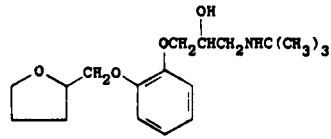
BUFETROL

Therapeutic Function: Antiarrhythmic

Chemical Name: 1-(tert-butylamino)-3-[2-[(tetrahydro-2-furanyl)methoxy] phenoxy]-2-propanol

Common Name: Bufetolol

Structural Formula:



Chemical Abstracts Registry No.: 53684-49-4; 35108-88-4 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Adobiol	Yoshitomi	Japan	1974

Raw Materials

2-(2-Tetrahydrofurfuryloxy)phenol
Epichlorohydrin
t-Butylamine

Manufacturing Process

The preparation of a similar compound in which a methoxyethoxy group replaces the tetrahydrofurfuryloxy group in Bufetrol is described in the following example. Nine grams of o-(2-methoxyethoxy)phenol is suspended in 50 milliliters of water containing 3.7 grams of potassium hydroxide, and 5.5 grams of epichlorhydrin is added thereto with stirring. The mixture is stirred at room temperature for 7 hours, and then extracted with two 50 milliliter portions of benzene. The extract is washed with water, dried over anhydrous magnesium sulfate and the benzene is distilled off to give 8.5 grams of oily 1-(2,3-epoxypropoxy)-2-(2-methoxyethoxy)benzene showing n_D^{20} = 1.5257. This compound has the methoxyethoxy group in place of the 2-tetrahydrofurfuryloxy group in Bufetrol.

To a solution of 1-(2,3-epoxypropoxy)-2-(2-tetrahydrofurfuryloxy)benzene in methanol are added tert-butylamine and water, the mixture is allowed to stand at 25°-30°C for 72 hours, and then the methanol is distilled off. The residue is dissolved in toluene and the solution is extracted twice with 5% oxalic acid. The aqueous extract is dried over potassium carbonate and concentrated to give Bufetrol.

References

Merck Index 1441

Kleeman & Engel p. 119
DOT 10 (12) 332 (1974)
I.N. p. 161
Nakanishi, M., Muro, T., Imamura, H. and Yamaguchi, N.; U.S. Patent 3,723,476; March 27, 1973; assigned to Yoshitomi Pharmaceutical Industries, Ltd., Japan

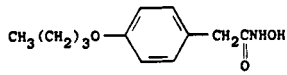
BUFEXAMAC

Therapeutic Function: Antiinflammatory, analgesic, antipyretic

Chemical Name: 4-Butoxy-N-hydroxybenzeneacetamide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 2438-72-4

Trade Name	Manufacturer	Country	Year Introduced
Parfenac	Lederle	U.K.	1973
Feximac Cream	Nicholas	U.K.	1973
Parfenac	Lederle	France	1974
Parfenac	Cyanamid	Italy	1975
Parfenac	Cyanamid	W. Germany	1976
Parfenac	Opopharma	Switz.	1976
Anderm	Lederle-Takeda	Japan	1977
Droxan	Continental Pharma	Belgium	–
Droxarol	Continental Pharma	W. Germany	–
Flogocid	Continental Pharma	–	–
Malipuran	Scheurich	W. Germany	–
Norfemac	Nordic	Canada	–
Paraderm	Continental Pharma	Belgium	–
Viafen	Zyma	Switz.	–

Raw Materials

p-Hydroxyacetophenone
Sulfur
Sodium Hydroxide
Hydroxylamine HCl
Butyl Bromide
Morpholine
Ethanol

Manufacturing Process

(1) 136 g of p-hydroxyacetophenone, 140 g of butyl bromide, 152 g of potassium carbonate, 17 g of potassium iodide and 275 cc of ethanol are mixed and then refluxed for 48 hours. The reaction mixture is cooled, diluted with water, then extracted with ether. The ethereal phase is washed with a 10% sodium hydroxide solution, then with water, followed by drying, ether is evaporated and the product distilled under reduced pressure. 168 g of p-butyloxy-acetophenone are obtained with yield of 87% (160°-162°C at 11 mm Hg).

(2) 192 g of p-butyloxyacetophenone, 42 g of sulfur and 130 g of morpholine are mixed and then refluxed for 14 hours. The resulting solution is poured into water and stirred until crystallization of the sulfurated complex. The latter is filtered, washed with water and dried. Production: 270 g (88% yield).

(3) 200 g of sodium hydroxide are dissolved in 1,500 cc of ethanol and then 293 g of the thus-obtained sulfurated complex are added. The mixture is refluxed overnight. The mixture is distilled to separate the maximum of the alcohol and then diluted with water. The resulting solution is acidified with hydrochloric acid, and extracted with ether. The ethereal phase is washed with water, followed by extraction with a 10% sodium carbonate solution. The carbonated solution is acidified with 10% hydrochloric acid, and the resulting precipitate of p-n-butyloxyphenylacetic acid is filtered and dried. 100 g of this product are obtained (70% yield).

(4) 208 g of p-n-butyloxyphenylacetic acid, 368 g of ethanol and 18 cc of sulfuric acid are refluxed for 5 hours. The mixture is diluted with water, after which it is extracted with ether. The ethereal phase is successively washed with water, then with carbonate, and again with water, following which it is dried and distilled to remove solvent. The ester is then distilled at a reduced pressure. 200 g of ethyl p-butyloxyphenylacetate are thus obtained with yield of 61% (186°C at 8 mm Hg).

(5) 7 g of hydroxylamine hydrochloride are dissolved in 100 cc of methanol. A solution of 5 g of sodium in 150 cc of methanol is added and the salt precipitate is separated by filtration. 22 g of ethyl p-n-butyloxyphenylacetate are added to the filtrate and the mixture is refluxed for 1 hour. The mixture is cooled and acidified with 20% hydrochloric acid. 14.7 g of p-n-butyloxyphenylacetohydroxamic acid are thus obtained with yield of 71% (melting point: 153°-155°C).

References

Merck Index 1442
Kleeman & Engel p. 120
DOT 12 (11) 435 (1976)
I.N. p. 161
Buu-Hoi, N.P., Lambelin, G., Lepoivre, C., Gillet, C. and Thiriaux, J.; U.S. Patent 3,479,396; November 18, 1969; assigned to Madan A.D.

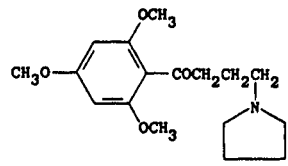
BUFLOMEDIL

Therapeutic Function: Vasodilator (peripheral)

Chemical Name: 4-(1-Pyrrolidinyl)-1-(2,4,6-trimethoxyphenyl)-1-butanone

Common Name: —

Structural Formula:



(base)

Chemical Abstracts Registry No.: 55837-25-7; 35543-24-9 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Fonzylane	Lafon	France	1976
Loftyl	Abbott	Italy	1981
Bufedil	Abbott	W. Germany	1982
Loftyl	Abbott	Switz.	1983

Trade Name	Manufacturer	Country	Year Introduced
Buflan	Pierrel	Italy	–
Irrodan	Biomedica Foscama	Italy	–

Raw Materials

4-Chlorobutyronitrile
Pyrrolidine
1,3,5-Trimethoxybenzene

Manufacturing Process

Introduce 33.6 g (0.2 mol) of 1,3,5-trimethoxybenzene and 100 ml of chlorobenzene into a 500 ml three-neck flask with stirrer, hydrochloric acid bubbler and condenser. Stir to dissolve and add 27.7 g of 4-pyrrolidinobutyronitrile (from 4-chlorobutyronitrile and pyrrolidine). Cool to about 15°-20°C and bubble hydrochloric acid gas in for 4 hours. Cool to about 5°C and add 200 cm^3 of water. Stir. Decant the aqueous layer, wash again with 150 cm^3 of water. Combine the aqueous layers, drive off the traces of chlorobenzene by distilling 150 cm^3 of water, and heat under reflux for one hour. Cool and render alkaline by means of 60 ml of sodium hydroxide solution of 36° Baume. Extract twice with 100 ml of ether. Wash the ether with 100 ml of water. Dry the ether over sodium sulfate and slowly run in 50 ml of 5 N hydrogen chloride solution in ether, at the boil. Cool in ice. Filter, wash with ether and dry in a vacuum oven. 33.6 g of crude product are obtained. Recrystallize from 200 ml of isopropanol in the presence of 3 SA carbon black. Filter. Wash and dry in a vacuum oven.

26.9 g of a white, crystalline water-soluble powder are obtained. Yield: 39.2%. Instantaneous melting point: 192°-193°C.

References

Merck Index 1443
Kleeman & Engel p. 121
DOT 11 (9) 339 (1975)
I.N. p. 161
Lafon, L; U.S. Patent 3,895,030; July 15, 1975; assigned to Orsymonde

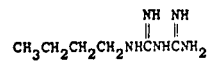
BUFORMIN HCl

Therapeutic Function: Antidiabetic

Chemical Name: N-Butylimidodicarbonimidic diamide

Common Name: Butyldiguanide

Structural Formula:



(base)

Chemical Abstracts Registry No.: 692-13-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Silubin	Protochemie	Switz.	–
Sindiatil	Bayer	Italy	1979
Adebit	Chinoin	Hungary	–

Trade Name	Manufacturer	Country	Year Introduced
Andere	Toyama	Japan	–
Biforon	Meiji	Japan	–
Bigunal	Nikken	Japan	–
Bufonamin	Kaken Drug	Japan	–
Bulbonin	Sankyo	Japan	–
Dibetos	Kodama	Japan	–
Gliporai	Grossmann	Mexico	–
Insulamin	Iwaki	Japan	–
Panformin	Shionogi	Japan	–
Ziavetine	Teikoku Kagaku	Japan	–

Raw Materials

n-Butylamine HCl
Dicyandiamide

Manufacturing Process

105.6 g of n-butylamine hydrochloride and 79.3 g of dicyandiamide were ground intimately and mixed. The mixture was heated by means of an oil bath, gradually with stirring, and after thirty minutes when the internal temperature had reached 150°C, an exothermic reaction ensued with internal pressure rising to 178°C. The reaction mixture was removed from the oil bath until the internal temperature had fallen to 150°C and then heating was resumed at 150°C for one hour. The cooled fusion mixture was dissolved in 3 liters of acetonitrile and on cooling n-butyl-biguanide hydrochloride precipitated.

References

Merck Index 1445
OCDS Vol. 1 p. 221 (1977); 2, 21 (1980)
I.N. p. 162
Shapiro, S.L.; U.S. Patent 2,961,377; November 22, 1960; assigned to U.S. Vitamin & Pharmaceutical Corp.

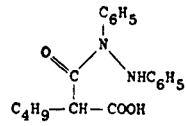
BUMADIZON

Therapeutic Function: Analgesic, antipyretic, antirheumatic

Chemical Name: butylpropanedioic acid mono-(1,2-diphenylhydrazide)

Common Name: Butylmalonic acid diphenylhydrazide

Structural Formula:



Chemical Abstracts Registry No.: 3583-64-0

Trade Name	Manufacturer	Country	Year Introduced
Eumotol	Byk-Gulden	W. Germany	1972
Eumotol	Iromedica	Switz.	1972

Trade Name	Manufacturer	Country	Year Introduced
Eumotol	Valpan	France	1976
Eumotol	Byk-Gulden	Italy	1976
Dibilan	Byk-Gulden	—	—
Rheumatol	Tosse	W. Germany	—

Raw Materials

Dicyclohexylcarbodiimide
n-Butyl Malonic Acid Ethyl Ester
Hydrazobenzene

Manufacturing Process

(a) A solution of 22.4 grams of dicyclohexylcarbodiimide in 120 ml of absolute tetrahydrofuran is added dropwise at 5°-10°C in an atmosphere of nitrogen to a solution of 20 grams of n-butyl malonic acid monoethyl ester and 19.6 grams of freshly recrystallized hydrazobenzene in 320 ml of anhydrous tetrahydrofuran. The mixture is then stirred for 15 hr at 25°C in an atmosphere of nitrogen, then the precipitated dicyclohexyl urea is filtered off and the filtrate, after the addition of 3 drops of glacial acetic acid, is evaporated to dryness in vacuo. The residue is dissolved in 1 liter of ether, the ethereal solution is extracted twice with 2 N potassium bicarbonate solution and twice with 2 N hydrochloric acid, whereupon it is washed with water until the washing water is neutral. The ethereal solution is dried over sodium sulfate and concentrated in vacuo. The residue is fractionally distilled under high vacuum whereupon the ester is obtained as a yellow oil. BP 170°C at 0.05 torr vacuum. Crystals which melt at 63°-65°C are obtained from cyclohexane.

(b) A suspension of 7.1 grams of the ester obtained according to (a) in 40 ml of aqueous 0.5 N sodium hydroxide solution is refluxed for 24 hours in an atmosphere of nitrogen. The solution is filtered and traces of hydrazobenzene are removed by extraction with ether. The aqueous solution is made acid to Congo paper at 10°C with concentrated hydrochloric acid, the oil which separates is dissolved in 40 ml of ethyl acetate, the ethyl acetate solution is isolated, and washed neutral with water. The solution is then extracted twice with 36 ml of 0.5 N sodium bicarbonate solution each time.

The separate extracts are made acid to Congo paper with concentrated HCl, extracted with ethyl acetate, the extracts are washed neutral with a little water, dried and concentrated under vacuum. The colorless oil which remains is recrystallized twice from ether/petroleum ether, whereupon n-butyl malonic acid-N,N'-diphenylhydrazide is obtained in the form of short needles which melt at 116°-118°C.

References

Merck Index 1451
Kleeman & Engel p. 121
DOT 9 (1) 14 (1973)
I.N. p. 162
Pfister, R., Sallmann, A. and Hammerschmidt, W.; U.S. Patent 3,455,999; July 16, 1969; assigned to Geigy Chemical Corporation

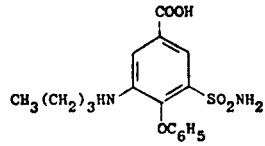
BUMETANIDE

Therapeutic Function: Diuretic

Chemical Name: 3-(aminosulfonyl)-5-(butylamino)-4-phenoxybenzoic acid

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 28395-03-1

Trade Name	Manufacturer	Country	Year Introduced
Burinex	Leo	U.K.	1973
Fordiuran	Thomae	W. Germany	1976
Lunetoron	Sankyo	Japan	1976
Burinex	Sigmatau	Italy	1977
Lixil	Leo	France	1978
Fontego	Polifarma	Italy	1979
Bumex	Hoffmann La Roche	U.S.	1983
Aquazone	Prodes	Spain	—
Butinat	Gerardo Ramon	Argentina	—
Cambiex	Bernabo	Argentina	—
Farmadiuril	Alter	Spain	—
Poliurene	Lepetit	—	—
Primex	Medica	Finland	—
Salurex	Byk Gulden	—	—
Salurin	Yurtoglu	Turkey	—
Segurex	Ricar	Argentina	—
Yurinex	Hemofarm	Yugoslavia	—

Raw Materials

4-Chloro-3-nitro-5 Sulfamyl Benzoic Acid
Sodium Bicarbonate
Hydrogen
n-Butanol
Phenol

Manufacturing Process

Preparation of 3-Nitro-4-Phenoxy-5-Sulfamylbenzoic Acid: A mixture of 4-chloro-3-nitro-5-sulfamylbenzoic acid (140 grams), phenol (100 grams), sodium hydrogencarbonate (170 grams), and water (1,000 ml) was heated to 85°C while stirring and kept at this temperature for 16 hours. After cooling to 4°C, the precipitated sodium salt of 3-nitro-4-phenoxy-5-sulfamylbenzoic acid was filtered off and washed with ice water. The sodium salt was dissolved in boiling water (3,000 ml), and the 3-nitro-4-phenoxy-5-sulfamylbenzoic acid was precipitated by addition of 4 N hydrochloric acid. After cooling, the acid was isolated by suction and dried. The melting point was 255°-256°C.

Preparation of 3-Amino-4-Phenoxy-5-Sulfamylbenzoic Acid: A suspension of 3-nitro-4-phenoxy-5-sulfamylbenzoic acid (20 grams) in water (100 ml) was adjusted to pH 8 by addition of 1 N lithium hydroxide. The resulting solution was hydrogenated at room temperature and 1.1 atmospheres hydrogen pressure after addition of Pd on carbon catalyst (0.6 grams catalyst containing 10% Pd). After the hydrogen uptake had become negligible, the catalyst was removed by filtration, and the 3-amino-4-phenoxy-5-sulfamylbenzoic acid was precipitated from the filtrate by addition of 4 N hydrochloric acid to pH 2.5. After recrystallization from aqueous ethanol and drying, the melting point was 255°-256°C.

Preparation of 3-n-Butylamino-4-Phenoxy-5-Sulfamylbenzoic Acid: To a suspension of 3-amino-4-phenoxy-5-sulfamylbenzoic acid (10 grams) in n-butanol (200 ml), concentrated sulfuric acid (2 ml) was added while stirring. The reaction mixture was heated under reflux under conditions in which the water formed during the reaction could be removed. When, after dilution with n-butanol, the NMR-spectrum of a sample of the reaction mix-

ture showed at the two doublets of the aromatic protons in ring A that the butyl-3-amino-4-phenoxy-5-sulfamylbenzoate formed as an intermediate was more than 90% converted to the corresponding 3-n-butylaminobenzoate, 2 N sodium hydroxide (200 ml) was added and the boiling was continued for 45 minutes. After the saponification, the reaction mixture was neutralized to pH 8 by addition of concentrated hydrochloric acid.

By cooling, the sodium salt of 3-n-butylamino-4-phenoxy-5-sulfamylbenzoic acid precipitated. It was filtered off and recrystallized from water (100 ml). The sodium salt, crystallizing with 3 molecules of water, was then dissolved in boiling water (200 ml), 1 N hydrochloric acid was added to pH 2.5, and after cooling the precipitated 3-n-butylamino-4-phenoxy-5-sulfamylbenzoic acid was collected by filtration. After recrystallization from aqueous ethanol and drying, the pure compounds were obtained with melting point 230°-231°C.

References

Merck Index 1452
Kleeman & Engel p. 121
PDR p. 1479
OCDS Vol. 2 p. 87 (1980)
DOT 8 (6) 238 (1972) & 9 (11) 449 (1973)
I.N. p. 162
Felt, P.W.; U.S. Patent 3,634,583; January 11, 1972; assigned to Lovens Kemiske Fabrik Produktionsaktieselskab, Denmark

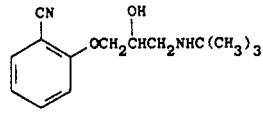
BUNITROLOL

Therapeutic Function: Antianginal

Chemical Name: 2-[3-[(1,1-Dimethylethyl)amino]-2-hydroxypropoxy]-benzonitrile

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 34915-68-9

Trade Name	Manufacturer	Country	Year Introduced
Stresson	Boehringer Ingel.	W. Germany	1976
Betriol	Boehringer Ingel.	Italy	1981
Betrilol	Boehringer Ingel.	Japan	1983
Betrilol	Tanabe Seiyaku	Japan	1983

Raw Materials

Epichlorohydrin
2-Cyanophenol
t-Butylamine

Manufacturing Process

Epichlorohydrin and 2-cyanophenol are first reacted to give 1-(2-cyanophenoxy)-2,3-epoxypropane.

15 g (0.085 mol) of 1-(2-cyanophenoxy)-2,3-epoxy propane were dissolved in 100 ml of ethanol and 18.6 g (0.255 mol) of t-butylamine were added thereto. After standing for 1 hour at room temperature, the solution was heated at 60°–70°C for 2 hours after which the volatile constituents were distilled off in vacuo. The residue was digested with dilute HCl, and the insoluble constituents were vacuum filtered off. Then the filtrate was made alkaline with NaOH and the precipitating base was taken up in ether. After the ether solution had been dried over $MgSO_4$, the ether was distilled off and the residue was dissolved in ethanol and by addition of ethereal HCl, the hydrochloride was precipitated therefrom in crystalline form which after recrystallization from ethanol with an addition of ether gave 9.8 g of 1-(2-cyanophenoxy)-2-hydroxy-3-t-butylamino propane hydrochloride having a melting point of 163°–165°C.

References

Merck Index 1457
DFU 1 (5) 210 (1976)
Kleeman & Engel p. 123
OCDS Vol. 2 pp. 106, 110 (1980)
DOT 13 (1) 15 (1977)
I.N. p. 163
Koppe, H., Engelhardt, A. and Zelle, K.; U.S. Patents 3,541,130; November 17, 1970; 3,940,489; February 24, 1976; and 3,961,071; June 1, 1976; all assigned to Boehringer Ingelheim GmbH

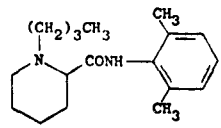
BUPIVACAINE

Therapeutic Function: Local anesthetic

Chemical Name: dl-1-butyl-2',6'-pipecoloxylidide

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 2180-92-9; 18010-40-7 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Carbostesin	Astra	W. Germany	1967
Carbostesin	Globopharm	Switz.	1967
Marcain	Duncan Flockhart	U.K.	1968
Marcain	Yoshitomi	Japan	1969
Marcaina	Pierrel	Italy	1971
Marcaine	Winthrop-Breon	U.S.	1973
Marcaine	Cook-Waite	U.S.	—
Sensorcaine	Astra	U.S.	1981
Bupivan	Abbott	U.S.	—
Meaverin	Woelm Pharma	W. Germany	—

Raw Materials

2,6-Dimethylaniline
Nitrosyl Chloride
Formic Acid
Diethyl Malonate
Zinc Powder
n-Butylbromide

Manufacturing Process

121 parts by weight of 2,6-xylidine are heated with 400 parts of diethylmalonate at 160°C for 1 hour, and the alcohol formed by the reaction is allowed to distill off. Thereafter the reaction mass is cooled to 80°C, and 500 parts of alcohol are added. After cooling the dixylidide is sucked off, and the alcohol solution with malonic ester monoxylidide is poured into 2,000 parts of water. The monoxylidide precipitates, is filtered off and washed with water, and recrystallized in diluted alcohol. Nitrosation thereafter takes place by dissolving the dried monoxylidide in chloroform and by introducing nitrosyl chloride at 0°C until the nitrosation is completed. The isonitrosomalonic ester xylidide is filtered off and dried. Thereafter the reduction takes place with zinc powder and formic acid at 90°-100°C.

The formic acid is distilled off, and the remainder dissolved in warm benzene and washed with a bicarbonate solution to a neutral reaction. After the benzene has been distilled off, the aminomalonic ester xylidide is obtained. This is treated with an equal quantity of sodium ethylate and boiled with twice the theoretical quantity of tetramethylene bromide in absolute alcohol.

After 6 hours of boiling, the sodium bromide formed is separated, and the mixture is steam-distilled in order to remove the excess of tetramethylene bromide. The remaining oil, which mainly consists of delta-bromobutylaminomalonic ester xylidide is separated from the water and boiled with 3 parts of concentrated hydrochloric acid for 3 hours. Thereafter carbon-filtering and evaporation to dryness under vacuum takes place. The residue is dissolved in water, and the pH adjusted with sodium hydroxide to 5.5. The solution is extracted twice with ether, and the water is made strongly alkaline with sodium hydroxide.

The oil precipitates and is crystallized after a time. The crystals are separated and dried under vacuum. The pipecolyl-2,6-xylidide produced is alkylated by boiling for 10-20 hours with 0.6 part n-butylbromide in an n-butanol solution in the presence of 0.5 part potassium carbonate. The potassium carbonate is filtered off and the butanol is distilled off in vacuum. The residue is dissolved in diluted hydrochloric acid and carbon treated, after which the base is precipitated with sodium hydroxide in the form of white crystals, which are filtered off and washed with water. The base obtained, which consists of N-n-butyl-pipecolyl-2,6-xylidide is sufficiently pure for the production of salts.

References

Merck Index 1462
Kleeman & Engel p. 124
PDR pp. 596, 825, 1915
OCDS Vol. 1 p. 17 (1977)
DOT 3 (3) 88 (1967)
I.N. p. 164
REM p. 1050
Thuresson, B. and Egnér, B.P.H.; U.S. Patent 2,792,399; May 14, 1957; assigned to AB Bofors, Sweden
Thuresson, B. and Pettersson, B.G.; U.S. Patent 2,955,111; October 4, 1960; assigned to AB Bofors, Sweden

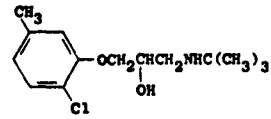
BUPRANOLOL

Therapeutic Function: Antiarrhythmic

Chemical Name: 1-(tert-butylamino)-3-[(6-chloro-m-tolyl)oxy]-2-propanol

Common Name: Bupranol

Structural Formula:



Chemical Abstracts Registry No.: 14556-46-8; 15146-80-8 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Betadrenol	Pharma-Schwarz	W. Germany	1969
Betadrenol	Adrosanol	Switz.	1969
Betadran	Logeais	France	1972
Looser (Lucer)	Kaken	Japan	1974
Panimit	Nattermann	W. Germany	–
Ophtorenin	Dr. Winzer	W. Germany	–

Raw Materials

Epichlorohydrin
2-Chloro-5-methylphenol
t-Butylamine

Manufacturing Process

A mixture of 16.3 g of (2-chloro-5-methylphenyl)glycidic ether (from epichlorohydrin and 2-chloro-5-methylphenol) and 6.2 g of t-butylamine in 50 ml of ethanol is heated at reflux for 6 hours. The solvent is removed, the residue is washed with water and then extracted with benzene. The dried extract is evaporated to give 1-t-butylamino-3-(2-chloro-5-methylphenoxy)-2-propanol. Treatment of the free base in benzene solution with dry hydrogen chloride yields the hydrochloride salt.

References

Merck Index 1463
Kleeman & Engel p. 125
I.N. p. 164
Kunz, W., Jacobi, H., Koch, C. and Geus, R.J.; U.S. Patent 3,309,406; March 14, 1967

BUSULFAN

Therapeutic Function: Antineoplastic

Chemical Name: 1,4-butanediol dimethanesulfonate

Common Name: –

Structural Formula: $CH_3SO_2O(CH_2)_4OSO_2CH_3$

Chemical Abstracts Registry No.: 55-98-1

Trade Name	Manufacturer	Country	Year Introduced
Myleran	Burroughs Wellcome	U.S.	1954
Misulban	Techni-Pharma	France	1955
Myleran	Wellcome	Switz.	1955
Myleran	Wellcome	W. Germany	1955

Trade Name	Manufacturer	Country	Year Introduced
Mablin	Takeda	Japan	–
Mielucin	Farmasimes	Spain	–
Myeleukon	Arzneimittelwerk Dresden	E. Germany	–
Mylecytan	Spofa	Czechoslovakia	–
Sulfabutin	–	–	–

Raw Materials

1,4-Butanediol
Methane Sulfonyl Chloride

Manufacturing Process

3.6 grams of redistilled 1,4-butanediol were dissolved in 10 ml of pyridine and the solution was cooled in ice and water. 9.6 grams of redistilled methane-sulfonyl-chloride were added dropwise at such a rate that the temperature did not rise above 20°C. The solution was then allowed to stand at room temperature for 30 minutes, during which time the temperature rose to 60°C. A thick precipitate of pyridine hydrochloride was formed.

The mass was cooled in ice water and was treated with 30 ml of ice cold water. On agitation, a white crystalline precipitate was formed. This was filtered off and washed well with ice cold water and allowed to drain on the pump. It weighed 7.8 grams and had a melting point of 100°C. 3.5 grams of the material were recrystallized from acetone and ether to give small white needles, having a melting point of 106°-107°C, unchanged by further recrystallization.

References

Merck Index 1470
Kleeman & Engel p. 125
PDR p. 754
I.N. p. 165
REM p. 1144
Timmis, G.M.; U.S. Patent 2,917,432; December 15, 1959; assigned to Burroughs Wellcome & Co., Inc.

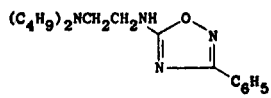
BUTALAMINE HYDROCHLORIDE

Therapeutic Function: Peripheral vasodilator

Chemical Name: N,N-dibutyl-N'-(3-phenyl-1,2,4-oxadiazol-5-yl)-1,2-ethanediamine hydrochloride

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 22131-35-7 (Base); 28875-47-0 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Surheme	Aron	France	1969

Trade Name	Manufacturer	Country	Year Introduced
Surheme	Spemsa	Italy	1974
Adrevil	Zyma-Blaes	W. Germany	1975
Oxadilene	Leurquin	France	—
Surem	Cepa	Spain	—

Raw Materials

Benzaldehyde
Chlorine
Dibutylaminoethyl Chloride
Hydroxylamine
Cyanamid
Sodium Amide

Manufacturing Process

Benzaldehyde and hydroxylamine may be reacted, the product chlorinated and then reacted with cyanamid to give 5-amino-3-phenyl-1,2,4-oxadiazole.

32 grams of 3-phenyl-5-amino-1,2,4-oxadiazole dissolved in about 150 ml of anhydrous benzene, 7.8 grams of sodium amide are added and the reaction mixture heated at the boiling point with stirring for 2 hours. A solution of 38.3 grams of dibutylaminoethyl chloride in benzene is then added and the mixture heated to boiling under reflux for four hours. The sodium chloride is separated as previously described, the benzene removed by vacuum distillation and 56 grams of 3-phenyl-5-(dibutylaminoethylamino)-1,2,4-oxadiazole is obtained in the form of an oil which is then converted directly to the crystalline hydrochloride. This is accomplished by dissolving the oil in ethanol and adding the stoichiometric equivalent of anhydrous ethyl ether saturated with gaseous hydrogen chloride. The recrystallized salt is found to have a melting point of 145°C.

References

Merck Index 1477
Kleeman & Engel p. 126
I.N. p. 166
Aron-Samuel, J.M.D. and Sterne, J.J.; U.S. Patent 3,338,899; August 29, 1967

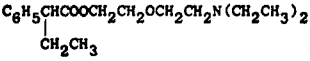
BUTAMIRATE CITRATE

Therapeutic Function: Antitussive

Chemical Name: α-ethylbenzeneacetic acid 2-[2-(diethylamino)ethoxy] ethyl ester citrate

Common Name: Butamyrate

Structural Formula:



(base)

Chemical Abstracts Registry No.: 18109-81-4; 18109-80-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Sinecod	Hommel	Switz.	1967
Sinecod	Karlspharma	W. Germany	1967
Sinecod	Bonomelli	Italy	1969
Acodeen	Hommel	Switz.	—
Acodfen	Klimitschek	Austria	—
Codesin-F	Hommel	Switz.	—

Trade Name	Manufacturer	Country	Year Introduced
Intussin	Spofa	Czechoslovakia	–
Sincoden	Hommel	Switz.	–
Sincodix	Beta	Argentina	–
Sinecod	Abello	Spain	–
Pertix-Hommel	Hommel	W. Germany	–

Raw Materials

α-Phenyl Butyric Acid Chloride
Diethylaminoethoxyethanol
Citric Acid

Manufacturing Process

18.2 grams of α-phenylbutyric acid chloride are dissolved in 25 ml of toluene. To this solution, there is slowly added a solution of 16.1 grams of diethylaminoethoxyethanol in 25 ml of toluene, the reaction mixture thereby becoming hot. It is then heated for 8 hr under reflux. The reaction mixture, after cooling, is carefully poured onto 75 grams of ice and made alkaline with dilute ammonia. After thorough shaking of the solution, the toluene layer is removed and washed until neutral with water. The toluene solution is treated with carbon and dried over sodium sulfate. The toluene is distilled off from the filtered solution.

The residue is α-phenylbutyric acid diethylaminoethoxyethyl ester. The basic ester is purified by distillation in a high vacuum. 10 grams of ester are added to a solution of 7 grams of citric acid in 30 ml of warm acetone. After standing for some time, the citrate of the ester crystallizes out. After suction filtration and washing with acetone the ester citrate is recrystallized from acetone. The melting point of the citrate is 75°C.

References

Merck Index 1481
Kleeman & Engel p. 127
OCDS Vol. 2 p. 76 (1980)
DOT 9 (7) 280 (1973)
I.N. p. 166
Heusser, J.; U.S. Patent 3,349,114; October 24, 1967; assigned to Hommel AG, Switzerland

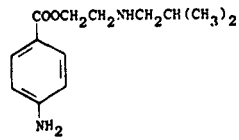
BUTETHAMINE

Therapeutic Function: Local anesthetic

Chemical Name: 2-[(2-Methylpropyl)amino] ethanol 4-aminobenzoate

Common Name: Ibylcaine

Structural Formula:



Chemical Abstracts Registry No.: 2090-89-3; 553-68-4 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Monocaine	Novocol	U.S.	1941
Dentocaine	Amer. Chem.	U.S.	–

Raw Materials

Isobutylaminoethanol
p-Nitrobenzoyl Chloride
Tin Metal
Hydrochloric Acid

Manufacturing Process

The preparation of the normal butyl analog is as follows:

10 g of isobutylaminoethanol, 16 g of p-nitrobenzoyl chloride and 5 g of sodium hydroxide in 175 cc of water were allowed to react. The temperature was maintained between 30°–40°C during reaction. The reaction mixture was extracted with ether, the ether evaporated, and the resultant oil washed with water to remove any unreacted secondary amino alcohol and then dried. The yield was 21 g or 91% of theory. The compound responded positively when tested for the presence of the amine configuration and also the nitro group. The yellow viscous oil which was formed was isobutylaminoethyl p-nitrobenzoate. 20 g of this latter material was directly reduced with 15 g of tin and 50 cc of concentrated hydrochloric acid. The temperature of the reduction was controlled by addition from time to time of small quantities of cold water to maintain the temperature at or near 70°C. When the reaction was completed 150 cc of sodium hydroxide was added and the solution then cooled to 15°C. The oil which gradually formed combined with undissolved tin to form a pasty mass which soon settled. The supernatant liquid was decanted and the residue washed two or three times with water to remove all traces of alkali. The oily mass, freed from most of its water, was then extracted with ether and filtered. The filtrate was evaporated to dryness and the yield of the base obtained was 13 g or 73.5% of theory. In order to get the melting point of the base, the monohydrochloride was first formed and purified, then the hydrochloride was dissolved in water and just neutralized with ammonia water. The colorless oil formed soon crystallized into a white solid, which after filtration and air drying, had a melting point of 74°–74.5°C. The hydrochloride was made when the oily base was dissolved in propyl alcohol and the calculated quantity of aqueous hydrochloric acid added to form the monohydrochloride of this compound. After repeated recrystallizations, a white needle crystal was formed which had a melting point at 146°C.

References

Merck Index 1492
Kleeman & Engel p. 128
DOT 15 (7) 368 (1979)
I.N. p. 168
Goldberg, S.D.; U.S. Patent 2,139,818; December 13, 1938; assigned to Novocol Chemical Mfg. Co., Inc.

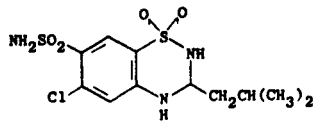
BUTHIAZIDE

Therapeutic Function: Diuretic; antihypertensive

Chemical Name: 6-Chloro-3,4-dihydro-3-(2-methylpropyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide

Common Name: Thiabutazide; butizide; isobutylhydrochlorothiazide

Structural Formula:



Chemical Abstracts Registry No.: 2043-38-1

Trade Name	Manufacturer	Country	Year Introduced
Saltucin	Boehringer Mannheim	W. Germany	1961
Eunephran	Servier	France	–
Intensain	Boehringer-Mannheim	W. Germany	–
Modenol	Boehringer-Mannheim	W. Germany	–
Sembrina	Boehringer-Mannheim	W. Germany	–

Raw Materials

3-Chloraniline
Chlorosulfonic Acid
Ammonia
Isovaleraldehyde

Manufacturing Process

Chlorsulfonic acid and 3-chloroaniline react to give an intermediate which when treated with ammonia yields 5-chloro-2,4-disulfamylaniline.

20 g of 5-chloro-2,4-disulfamylaniline in 15 cc of diethyleneglycol-dimethyl ether with 0.9 g of isovaleraldehyde are reacted in the presence of 0.5 cc of a saturated solution of hydrochloric acid in ethyl acetate at 80°-90°C. The reaction mixture is concentrated under reduced pressure, an oily product precipitates on the addition of water, the latter is decanted and ethanol added to the remaining oil. 3-Isobutyl-6-chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide crystallizes and, after recrystallization from dimethylformamide and water, melts at 241°-245°C.

References

Merck Index 1494
Kleeman & Engel p. 129
DOT 14 (3) 119 (1978)
I.N. p. 169
Ciba, Ltd.; British Patents 861,367; February 22, 1961 and 885,078; December 20, 1961

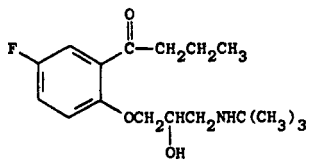
BUTOFILOLOL

Therapeutic Function: Beta blocker

Chemical Name: 1-[2-[3-[(1,1-Dimethylethyl)amino]-2-hydroxypropoxy]-5-fluorophenyl]-1-butanone

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 64552-17-6

Trade Name	Manufacturer	Country	Year Introduced
Cafide	Clin Midy	France	1982

Raw Materials

5-Fluorosalicylaldehyde
1-Chloro-2-hydroxy-3-t-butylaminopropane
Propyl Magnesium Bromide
Sodium Hydride
Hydrogen Chloride

Manufacturing Process

(a) 5-Chloromethyl-3-tert-butyl-2-(2-hydroxy-5-fluorophenyl)oxazolidine: 5-Fluorosalicylaldehyde (1.4 g, 0.01 mol) is dissolved in anhydrous benzene (20 ml) in the presence of a crystal of p-toluenesulfonic acid in a Dean-Stark apparatus. 1-Chloro-2-hydroxy-3-tert-butylaminopropane (2.08 g, approximately 1 equivalent, purity 75%) is then added within a period of 10 hours in portions of 250 mg at a time at the reflux temperature of benzene and the mixture is allowed to stand overnight. An insoluble substance is precipitated on addition of ether after which the solution is filtered, concentrated and distilled. A fraction is obtained having a boiling point of 118°-123°C/10^{-3} mm of mercury. A mixture of 1.03 g (yield 43%) of isomeric oxazolidines is obtained which solidifies. This is crystallized once from hexane. Melting point 75°-78°C.

(b) 8-Aza-4,9-dioxa-11-fluoro-8-tert-butyl-2,3-benzobicyclo[4.2.1] octane: The product of the previous stage (620 mg) is dissolved in anhydrous dimethylformamide (10 ml) and two quantities each of 300 mg of 50% sodium hydride is added within 2 hours. The mixture is then left for 24 hours at 25°C while being stirred mechanically and is then heated for 2 minutes on a water bath (80°-90°C). The mixture is poured into water, the product extracted with ether, the ethereal extract dried over anhydrous sodium sulfate and the organic phase then concentrated and filtered through a short column of activated alumina. A mixture of light petroleum and diethyl ether (75:25) is used to elute 186 mg of pure product from the column. Melting point 85°-86°C (after recrystallization from diisopropyl ether).

(c) 1-(2-Formyl-4-fluorophenoxy)-2-hydroxy-3-tert-butylaminopropane: The compound obtained as described above (50 mg) is dissolved in a solution of 1 N hydrochloric acid (0.5 ml). The mixture is then heated on a water bath (80°-90°C) for several hours. After complete hydrolysis, which requires approximately 8 hours, the mixture is poured into an excess of water which has been basified, the solid base thus formed is extracted with ether, dried and recrystallized from diisopropyl ether. Melting point 103°-105°C.

(d) 1-[2-(1-Hydroxybutyl)-4-fluorophenoxy]-2-hydroxy-3-tert-butylaminopropane: To a solution of propylmagnesium bromide prepared from 195 mg (8.1 X 10^{-3} mol) of magnesium, 1.08 g (8.1 X 10^{-3} mol) of bromopropane and a crystal of iodine in 10 ml of anhydrous diethyl ether under nitrogen is added a solution of the previously prepared aldehyde (197 mg, 0.73 X 10^{-3} mol) in 4 ml of an ether/tetrahydrofuran mixture (1:3 by volume) and the mixture is heated to reflux for 70 minutes. The mixture is poured into water, extracted with diethyl ether, dried over anhydrous sodium sulfate and 208 mg of an oil which is homogeneous, as shown by thin-layer chromatography, is isolated.

(e) CM 6805 (Butofilolol): The previously prepared base (200 mg, 0.66 X 10^{-3} mol) is dissolved in purified acetone (8 ml). A drop of sulfuric acid solution (prepared from 35 ml of concentrated sulfuric acid and 65 ml of water) is added and the mixture heated on a water bath for 1 minute. When the solution has cooled to 5° to 10°C a solution of chromic acid (66 mg, 1 equivalent) dissolved in 2 ml of the same acid solution is quickly added and the resulting mixture is stirred while cold. The mixture is then poured into a saturated solution of sodium carbonate, the acetone is evaporated under reduced pressure on a water bath, and the organic phase is extracted with diethyl ether. After drying and evaporating the solvent

an oil is obtained (172 mg) all of which solidifies. Recrystallization is carried out from diisopropyl ether. 122 mg of CM 6805 is obtained (yield 61%). Melting point 88°-89°C.

References

Merck Index 1500
DFU 7 (2) 96 (1982)
DOT 18 (10) 551 (1982) & 19 (2) 112 (1983)
I.N. p. 169
Demarne, H.; U.S. Patent 4,252,825; February 24, 1981; assigned to C.M. Industries.

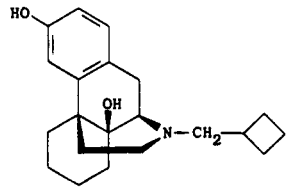
BUTORPHANOL

Therapeutic Function: Analgesic, antitussive

Chemical Name: N-Cyclobutylmethyl-3,14-dihydroxymorphinan

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 42408-82-2

Trade Name	Manufacturer	Country	Year Introduced
Stadol	Bristol-Myers	U.S.	1978
Stadol	Bristol-Myers	U.K.	1980
Moradol	Galenika	Yugoslavia	–

Raw Materials

N-Cyclobutylmethyl-14-hydroxy-3-methoxymorphinan
Hydrogen Bromide

Manufacturing Process

A mixture of 1.0 g (2.58 mmols) of N-cyclobutylmethyl-14-hydroxy-3-methoxymorphinan and 10 ml of 48% HBr was refluxed, under a nitrogen atmosphere, during five minutes. After cooling, the reaction mixture was diluted with water and made basic with aqueous ammonium hydroxide. The aquous basic mixture was extracted with chloroform and the combined chloroform extracts were dried over anhyrous sodium sulfate. After evaporation of the solvent, the residual oil (730 mg) was taken up in dry ether and the resulting solution filtered through celite-charcoal. The filtrate was treated with a saturated solution of hydrogen chloride in dry ether. The hydrochloride salt thus obtained was collected by filtration and recrystallized from a methanol-acetone mixture to yield 565 mg (56.5%) of Butorphanol hydrochloride crystals melting at 272°-274°C (decomposition).

References

Merck Index 1503

DFU 2 (4) 231 (1977) & 3 (5) 330 (1978)
Kleeman & Engel p. 129
PDR p. 713
OCDS Vol. 2 p. 325 (1980)
DOT 14 (5) 197 (1978)
I.N. p. 170
REM p. 1107
Monkovic, I. and Conway, T.T.; U.S. Patent 3,775,414; November 27, 1973; Monkovic, I., Wong, H. and Lim, G.; U.S. Patent 3,980,641; September 14, 1976; Pachter, I.J., Belleau, B.R. and Monkovic, I.; U.S. Patent 3,819,635; June 25, 1974; and Lim, G. and Hooper, J.W.; U.S. Patent 4,017,497; April 12, 1977; all assigned to Bristol-Myers Company

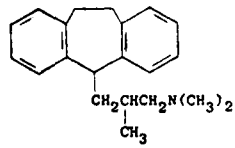
BUTRIPTYLINE

Therapeutic Function: Antidepressant

Chemical Name: (±)-10,11-dihydro-N,N,β-trimethyl-5H-dibenzo[a,d] cycloheptene-5-propanamine

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 35941-65-2; 5585-73-9 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Evadyne	Ayerst	U.K.	1975
Evadene	Ayerst	Italy	1976
Centrolyse	Ayerst	—	—
Evasidol	Arcana	Austria	—

Raw Materials

Dibenzo[a,e] cycloheptadiene
Sodium Hydride
2-Methyl-3-dimethylaminopropyl Chloride

Manufacturing Process

A solution of dibenzo[a,e] cycloheptadiene in anhydrous xylene is added in a dropwise fashion with stirring to a suspension of sodium hydride in refluxing anhydrous xylene. The mixture is heated at reflux for two hours with continual agitation and there is then added dropwise a solution of 2-methyl-3-dimethylaminopropyl chloride in an equal volume of xylene. The mixture is then heated for fifteen hours, after which time it is cooled and decomposed by the cautious addition of ice water. The layers are separated and the aqueous layer extracted with ether. The combined organic layers are next extracted with 10% hydrochloric acid and the acidic extracts then rendered alkaline by the addition of ammonium hydroxide. The precipitated oil is extracted three times with chloroform. The chloroform extracts are dried and concentrated in vacuo, the residue being distilled to yield the product.

References

Merck Index 1506

Kleeman & Engel p. 131
OCDS Vol. 1 p. 151 (1977)
DOT 9 (6) 219 (1973) & 10 (7) 235 (1974)
I.N. p. 170
Villani, F.J.; U.S. Patent 3,409,640; November 5, 1968; assigned to Schering Corporation

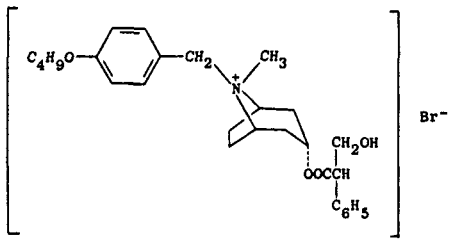
BUTROPIUM BROMIDE

Therapeutic Function: Antispasmodic

Chemical Name: [3(S)-endo]-8-[(4-butoxyphenyl)methyl]-3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-azoniabicyclo[3.2.1] octane bromide

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 29025-14-7

Trade Name	Manufacturer	Country	Year Introduced
Coliopan	Eisai	Japan	1974

Raw Materials

Hyoscyamin
Butoxybenzyl Bromide

Manufacturing Process

To 100 ml of an isopropanol solution containing 11.8 grams of hyoscyamine base were added drop by drop with stirring 10 ml of an isopropanol solution containing 11 grams of p-n-butoxybenzyl bromide. After a while, the reaction mixture had a turbid appearance followed by separation of white crystals.

After stirring for 5 hours at room temperature, the crystals were recovered by filtration, which were then recrystallized from 120 ml of isopropanol. There was obtained 15.8 grams of white needles having the melting point of 158°-160°C.

References

Merck Index 1507
Kleeman & Engel p. 131
OCDS Vol. 2 p. 308 (1980)
DOT 10 (11) 292 (1974)
I.N. p. 170
Tanaka, S. and Hasimoto, K.; U.S. Patent 3,696,110; October 3, 1972; assigned to Eisai, KK, Japan