B

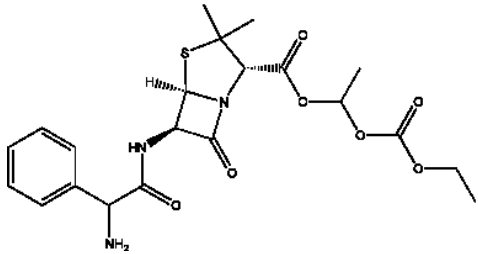
BACAMPICILLIN

Therapeutic Function: Antibacterial

Chemical Name: 6-[(Aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylic acid 1-[(ethoxycarbonyl)oxy]-ethyl ester

Common Name: 1'-Ethoxycarbonyloxyethyl 6-(D-α-aminophenylacetamido) penicillinate

Structural Formula:



Chemical Abstracts Registry No.: 50972-17-3; 37661-08-8 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Penglobe	Astra	W. Germany	1977
Bacacil	Pfizer	Switz.	1978
Penglobe	Lematte/Boinot	France	1978
Bacacil	Pfizer	Italy	1980
Ambaxin	Upjohn	UK	1981
Spectrobid	Pfizer	US	1981
Bacacil	Pfizer Taito	Japan	1981
Penglobe	Yoshitomi	Japan	1981
Bamaxin	Upjohn	Canada	1982
Ambacamp	Upjohn	W. Germany	-
Bacampicin	Upjohn	-	-
Velbacil	Pfizer	-	-

Raw Materials

Sodium 6-(D-α-azidophenylacetamido)penicillinate
α-Chlorodiethyl carbonate
Sodium bicarbonate
Hydrogen
Palladium on carbon

Manufacturing Process

1'-Ethoxycarbonyloxyethyl 6-(D-α-azidophenylacetamido)penicillinate (98 g) was prepared from sodium 6-(D-α-azidophenylacetamido)penicillinate (397 g, 1 mol), α-chlorodiethylcarbonate (458 g, 3 mols) and sodium bicarbonate (504 g, 6 mols). The product showed strong IR absorption at 2090 cm^{-1} and 1780-1750 cm^{-1} showing the presence of azido group and β-lactam and ester carbonyls.

It was dissolved in ethyl acetate (700 ml) and hydrogenated at ambient conditions over a palladium (5%)on carbon catalyst (18 g). The catalyst was removed by filtration and washed with ethyl acetate. The combined filtrates were extracted with water at pH 2.5 by addition of dilute hydrochloric acid. Lyophilization of the aqueous phase gave the hydrochloride of 1'-ethoxycarbonyloxyethyl 6-(D-α-aminophenylacetarnido)penicillinate (94 g), MP 171°-176°C.

References

Merck Index 933
Kleeman and Engel p. 69
PDR p. 1531
OCDS Vol. 3 p. 204 (1984)
DOT 11 (11) 428 (1975) and 13 (10) 415 (1977)
I.N.p.113
REM p. 1200
Ekstrom, B.A. and Sjoberg, B.O.H.; US Patents 3,873,521; March 25, 1975;and 3,939,270; February 17, 1976; both assigned to Astra Lakemedal A.B.

BACITRACIN

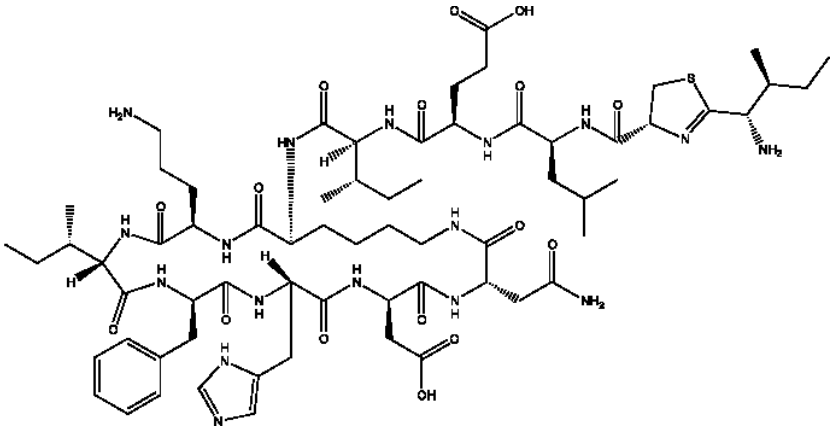
Therapeutic Function: Antibacterial

Chemical Name: Complex polypeptide mixture containing predominantly bacitracin A

Common Name: -

Chemical Abstracts Registry No.: 1405-87-4; 21373-17-1 (Bacitracin A)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Baciguent	Upjohn	US	1948
Topitracin	Comm. Solvents	US	1948
Bacitracine	Novopharm	Switz.	-
Bacitracine	Djamant	France	1953
Bacitracin	Kayaku	Japan	-
Bacitracin	Upjohn	US	-
Batrax	Gewo	W. Germany	-
Cicatrin	Calmic	UK	-
Cicatrex	Wellcome	W. Germany	-
Enterostop	Schiapparelli	Italy	-
Fortracin	A.L.	US	-
Hydroderm	Merck Sharp and Dohme	UK	-
Medicrucin	Medice	W. Germany	-
Nebacetin	Byk Gulden	W. Germany	-
Neobacrin	Glaxo	UK	-
Neo-Caf	Francia	Italy	-
Neo-Polycin	Dow	US	-
Neosporin	Burroughs-Wellcome	US	-
Orobicin	Fulton	Italy	-
Polybactrin	Calmic	UK	-
Polybactrin	Wellcome	W. Germany	-
Polycin	Dow	US	-
Polyfax	Wellcome	UK	-
Polysporin	Burroughs-Wellcome	US	-
Rikospray	Riker	UK	-
Topitracin	Reed Carnrick	US	-

Raw Materials

Bacillus subtilis
Nutrient medium

Manufacturing Process

The early patent, US Patent 2,498,165 first disclosed bacitracin and described a process for preparing bacitracin, comprising cultivating Bacillus subtilis Tracy I in a nutritive medium, at substantially pH 7 and 37°C, for more than three days, extracting the antibiotic from the resulting medium with a low molecular weight alcohol, concentrating the resulting alcoholic solution in vacuo, acidifying the resulting concentrate, extracting the antibiotic from the resulting solution, and precipitating the antibiotic from the resulting solution, with a precipitating agent for the antibiotic, selected from the group consisting of Reinecke's salt, phosphotungstic acid, phosphomolybdic acid, molybdic acid, picric acid, ammonium rhodanilate, and azobenzene-p-sulfonicacid.

A subsequent patent, US Patent 2,828,246 described a commercial process for bacitracin production. A 1,230 gallon portion of a medium containing 10% soybean oil meal, 2.50% starch and 0.50% calcium carbonate having a pH of 7.0 was inoculated with a culture of bacitracin-producing bacteria of the Bacillus subtilis group and the inoculated medium incubated for a period of 24 hours with aeration such that the superficial air velocity was 12.1. An assay of the nutrient medium following the fermentation revealed a yield of bacitracin amounting to 323 units/ml. This was more than twice the yields previously obtained.

Then, a patent, US Patent 2,834,711 described the purification of bacitracin. In this process for purifying bacitracin, the steps comprise adding a water-soluble zinc salt to a partially purified aqueous solution of bacitracin, adjusting the pH to from 5 to 9, recovering the precipitate which forms, dissolving the precipitate in water at a pH not substantially in excess of 4, and removing the zinc ion by passing the aqueous solution through a cation exchange resin and drying the resulting solution to obtain dry solid bacitracin.

Another patent, US Patent 2,915,432describes a process of recovering and concentrating bacitracin from aqueous filtered fermentation broth containing on the order of 3% protein-aceous solids which comprises intimately contacting the broth with a synthetic organic cation exchange resin having as its functional groups nuclear sulfonic acids and having a crosslinkage of the order of 1 to 2%, with the resin being in the hydrogen form, and eluting the adsorbed bacitracin from the resin with a weak base.

Bacitracin recovery is described in US Patents 3,795,663 and 4,101,539.

References

Merck Index 937
Kleeman and Engel p.70
PDR p.888
I.N. p.113
REM p.1201

Chaiet, L. and Cochrane, T.J., Jr.; US Patent 2,915,432; December 1, 1959; assigned to Merck and Co., Inc.
Johnson,R.A. and Meleney, F.L.; US Patent 2,498,165; February 21, 1950; assigned to US Secretary of War
Freaney, T.E. and Allen, L.P.; US Patent 2,828,246; March 25, 1958; assigned to Commercial Solvents Corporation
Zinn, E. and Chornock, F.W.; US Patent 2,834,711; May 13, 1958; assigned to Commercial Solvents Corporation
Miescher, G.M.; US Patent 3,795,663; March 5, 1974; assigned to Commercial Solvents Corp.
Kindraka,J.A. and Gallagher, J.B.; US Patent 4,101,539; July 18, 1978; assigned to IMC Chemical Group, Inc.

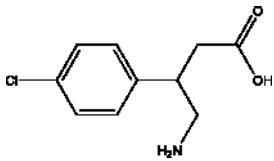
BACLOFEN

Therapeutic Function: Muscle relaxant

Chemical Name: γ-Amino-β-(p-chlorophenyl)butyric acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 1134-47-0

Trade Name	Manufacturer	Country	Year Introduced
Lioresal	Ciba Geigy	Switz.	1971
Lioresal	Ciba Geigy	W. Germany	1972
Lioresal	Ciba Geigy	UK	1974
Lioresal	Ciba Geigy	France	1974
Lioresal	Ciba Geigy	US	1977
Lioresal	Ciba Geigy	Japan	1979
Lioresal	Ciba Geigy	Japan	1979
Gabalon	Daiichi	Japan	-
Baclon	Medica	Finland	-
Spastin	Yurtoglu	Turkey	-

Raw Materials

β-(p-Chlorophenyl)glutaric Acid Imide
Sodium hydroxide
Bromine

Manufacturing Process

42.45 g of β-(p-chlorophenyl)glutaric acid imide are stirred into a solution of 8.32 g of sodium hydroxide in 200 ml of water. The mixture is heated for 10 minutes at 50°C, and the solution thus formed is cooled to 10° to 15°C. At this temperature there are then added dropwise a solution of 40.9 g of sodium hydroxide in 200 ml of water and then, in the course of 20 minutes, 38.8 g of bromine. When all has been dropped in, the batch is stirred for 8 hours at 20° to 25°C. The reaction solution is then cautiously adjusted with concentrated hydrochloric acid to pH 7, whereupon finely crystalline γ-amino-β-(p-chlorophenyl)butyric acid settles out. To purify it, it is recrystallized from water. Melting point is 206°to 208°C.

References

Merck Index 939
Kleeman and Engel p.71
PDR p.894
OCDS Vol.2 p.121 (1980)
DOT 8 (2) 49 (1972)
I.N. p.114
REM p.925
Keberle, H., Faigle, J.W. and Wilhelm, M.; US Patent 3,471,548; October 7, 1969; assigned to Ciba Corporation
Keberle, H., Faigle, J.W. and Wilhelm, M.; US Patent 3,634,428; January 11, 1972; assigned to Ciba Corporation

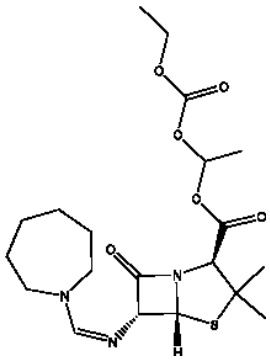
BACMECILLINAM

Therapeutic Function: Antibiotic

Chemical Name: 4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-(((hexahydro-1H-azepin-1-yl)methylene)amino)-3,3-dimethyl-7-oxo-, 1-((ethoxycarbonyl)oxy)ethyl ester, (2S-(2α,5α,6β))-

Common Name: Bacmecillinam; KW-1100

Structural Formula:



Chemical Abstracts Registry No.: 50846-45-2

Trade Name	Manufacturer	Country	Year Introduced
Bacmecillinam	ZYF Pharm Chemical	-	-
Bacmecillinam	LHA CHEMPHARMA CO. LTD.	-	-

Raw Materials

1-Hexamethyleneiminocarboxaldehyde dimethylacetate
Triethylamine
1'-Ethoxycarbonyloxyethyl 6-aminopenicillanate

Manufacturing Process

1-Hexamethyleneiminocarboxaldehyde dimethylacetate (3.1 g) in chloroform (50 ml) was added dropwise at -30°C to a solution of 1'-ethoxycarbonyloxyethyl 6-aminopenicillanate (5.0 g) and triethylamine (1.9 ml) in chloroform (150 ml) during 15 min. Then, the temperature is allowed to rise to 0°C during 30 min, and the mixture is stirred at 0°C for another 60 min. Water (120 ml) is added, and stirring is continued for 10 min. The water phase is separated and the organic layer is washed with water and stripped. There was obtained 5.0 g of the 1'-ethoxycarbonyloxy-ethyl 6-(hexahydro-1H-azepin-l-yl) methyleneaminopenicillanate.

References

Bamberg P. et al.; US Patent No. 4,089,963; May 16, 1978; Assigned: Astra Pharmaceutical Products, Inc., Framingham, Mass.

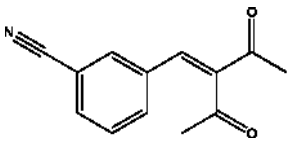
BALAZIPONE

Therapeutic Function: Immunomodulator

Chemical Name: 3-(2-Acetyl-3-oxo-1-butenyl)benzonitrile

Common Name: Balazipone; OR-1364

Structural Formula:



Chemical Abstracts Registry No.: 137109-71-8

Trade Name	Manufacturer	Country	Year Introduced
Balazipone	Orion	-	-

Raw Materials

3-Cyanbenzaldehyde
Acetic acid
2,4-Pentanedione
Piperidine

Manufacturing Process

A mixture containing 3-cyanbenzaldehyde, 2,4-pentanedione, piperidine and acetic acid in toluene was refluxed for some hours. After standing over night at room temperature the crystals were filtered and washed with toluene and dried. There was obtained the 3-[(2-cyanophenyl)methylene]-2,4-pentanedione.

References

Backstrom R.J.; EU Patent No. 0,440,324 A2; August 7, 1991

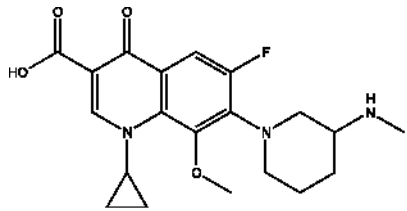
BALOFLOXACIN

Therapeutic Function: Antibacterial

Chemical Name: 3-Quinolinecarboxylic acid, 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-(methylamino)-1-piperidinyl)-4-oxo-

Common Name: Balfloxacin; Balofloxacin

Structural Formula:



Chemical Abstracts Registry No.: 127294-70-6

Trade Name	Manufacturer	Country	Year Introduced
Balofloxacin	Hangzhou Greenda Chemical Co., Ltd.	-	-
Balofloxacin	Shanghai Acychem Trade Co, Ltd.	-	-

Raw Materials

Ethyl 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate
3-Acetamidopiperidine

Dimethyl sulfoxide
Sodium methoxide
Triethylamine

Manufacturing Process

(1) A mixture of ethyl 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (933 mg), 3-acetamidopiperidine (710 mg), triethylamine (400 mg) and dimethylsulfoxide (10 ml) was heated at 100°C for 2 hours with stirring. Thereafter the mixture was cooled down and ice water was added thereto. The resulting mixture was extracted with chloroform and the chloroform layer was washed with water three times before being dried over anhydrous sodium sulfate. Removal of the solvent in vacuum followed by purification by silica gel column chromatography (chloroform-ethanol) gave ethyl 7-(3-acetamidopiperidin-1-yl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo quinoline-3-carboxylate (930 mg). Re-crystallization from ethanol-ether afforded a colorless crystalline substance (MP: 217°-218°C).

(2) Ethyl 7-(3-acetamidopiperidin-1-yl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylate obtained from the foregoing step:

(a) (433 mg) of above product was dissolved in 6 N hydrochloric acid (5 ml) and heated at 100°C. for 2.5 hours with stirring. After the removal of the solvent in vacuum, methanol was added to the residue and the insoluble materials were filtered off. Removal of the solvent followed by purification by silica gel column chromatography (chloroform-methanol) gave hydrochloride of 7-(3-aminopiperidin-1-yl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (colorless, crystalline-powder). MP: color change at about 272°C; decomposition at about 280°C.

(b) A mixture of 7-(3-acetamidopiperidin-1-yl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (4.05 g), sodium methoxide (2.16 g) and N,N-dimethylformamide (120 ml) was stirred for 2 hours at 100°-140°C. The reaction mixture was concentrated in vacuum and water was added to the residue. The mixture was neutralized with 1 N hydrochloric acid and the neutralized mixture was then concentrated in vacuum. Purification of the concentrated mixture by silica gel column chromatography (chloroform-methanol) gave 7-(3-acetamidopiperidin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid. MP: 248°-250°C.

(c) 7-(3-Acetamidopiperidin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid (1.25 g) above obtained was suspended in 6 N hydrochloric acid (30 ml) and ethanol (5 ml) and heated at 100°C for 3 hours. Then the reaction mixture was concentrated in vacuum and the residue was purified by silica gel column chromatography (chloroform:methanol:ammonium hydroxide=100:30:5) to afford 7-(3-aminopiperidin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid. MP: 176°-177°C.

References

Nagano, Hiroyuki (Saitama, JP); Yokota, Takeshi (Chiba, JP); Katoh, Yasuyuki; US Patent No. 5,051,509; September 24, 1991; Assigned to Chugai Seiyaku Kabushiki Kaisha (Tokyo, JP)

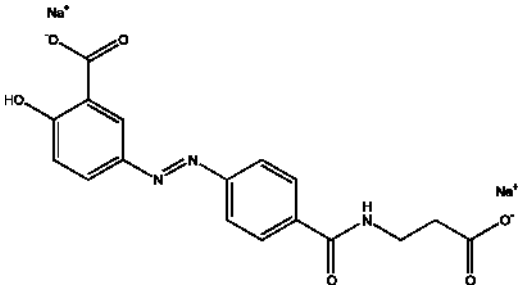
BALSALAZIDE DISODIUM SALT

Therapeutic Function: Antiinflammatory

Chemical Name: Benzoic acid, 5-((4-(((2-carboxyethyl)amino)carbonyl) phenyl)azo)-2-hydroxy-, (E)-, disodium salt

Common Name: Balsalazide sodium; Balsalazine disodium

Structural Formula:



Chemical Abstracts Registry No.: 213594-60-6; 80573-04-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Colazal	Salix Pharmaceuticals, Inc.	USA	-
Colazide	Shire Pharmaceuticals	-	-

Raw Materials

4-Nitrobenzoyl chloride
Palladium on charcoal
Salicylic acid
Alanine, β-
Sodium nitrite

Manufacturing Process

125 g finely powdered 4-nitrobenzoyl chloride were added portionwise, while stirring, to a solution of 70 g β-alanine in 500 ml water containing 65 g sodium hydroxide and cooled to 5°C. The reaction mixture was stirred for 3 hours and then added to a mixture of ice and hydrochloric acid. The precipitate obtained was filtered off, washed with water and dried by suction. After crystallisation of the dried product from hot acetone, there were obtained 130 g 4-nitrobenzoyl-β-alanine; M.P. 164°-166°C.

A suspension of 15 g finely powdered 4-nitrobenzoyl-β-alanine in 200 ml ethanol was stirred in an atmosphere of hydrogen in the presence of 1 g of palladium-charcoal (5%), while cooling gently. When the absorption of hydrogen had ceased, the reaction mixture was filtered and the filtrate concentrated to a small volume. Upon adding diethyl ether and cooling 4-aminobenzoyl-β-alanine was obtained. The yield was 11.5 g; M.P. 156°-158°C.

8.8 g 4-aminobenzoyl-β-alanine were triturated with 12 ml hydrochloric acid and the paste obtained was dissolved in 100 ml water. The solution was cooled to -5°C and a solution of 3 g sodium nitrite in 20 ml water, cooled to 0°C, was added dropwise, while stirring. The diazotised solution was left for 1 hour at 0°C and was then added dropwise at -5°C to a solution of 6 g salicylic acid in 70 ml water containing 3.6 g sodium hydroxide and 7 g sodium carbonate. The final reaction mixture was adjusted to a pH of about 8, stirred for 2 to 3 hours and added to a mixture of dilute hydrochloric acid and ice. The precipitate obtained was filtered off, washed with water and suction dried. Crystallisation from hot ethanol gave 11.9 g 5-[(2-carboxy-ethylcarbamoyl)-phenylazo]-2-hydroxy-benzoic acid; M.P. 254°-255°C.

10.7 g of the free acid were dissolved in 300 ml warm ethanol and treated with a solution of 2.4 g sodium hydroxide in 25 ml ethanol. The precipitate obtained was filtered off, washed with ethanol and diethyl ether and dried in a vacuum at 50°C to give 11.5 g of the disodium salt of 5-[(2-carboxy-ethylcarbamoyl)-phenylazo]-2-hydroxy-benzoic acid; M.P. >350°C.

References

Chan R.P.K.; US Patent No. 4,412,992; Nov. 1, 1983; Assigned to Biorex Laboratories Limited, England

Lednicer D., The organic chemistry of drug synthesis, V. 6, p.49, 1999, John Wiley and Sons, Inc.

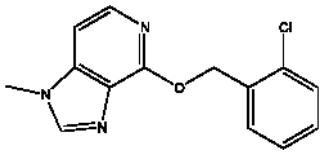
BAMALUZOLE

Therapeutic Function: Anticonvulsant

Chemical Name: 4-[(2-Chlorophenyl)methoxy]-1-methyl-1H-imidazo[4,5-c]pyridine

Common Name: Bamaluzole

Structural Formula:



Chemical Abstracts Registry No.: 87034-87-5

Trade Name	Manufacturer	Country	Year Introduced
Bamaluzole	Onbio Inc.	-	-

Raw Materials

1-Chlorophenyl-2-methanol
4-Methylamino-3-nitropyridine
Formic acid
Acetic anhydride
Sodium hydride
Hydrogen chloride
Tin(II) chloride

Manufacturing Process

1-Chlorophenyl-2-methanol is dissolved in dimethylformamide; NaH is added and the mixture is stirred at 20°C for 1 h. After a solution of 4-chloro-1-methyl-1H-imidazo[4,5-c]pyridine [melting point 132°-134°C; obtainable by reaction of 4-methylamino-3-nitropyridine with HCl/$SnCl_2$ to give 3-amino-2-chloro-4-methylaminopyridine (melting point 170°-173°C) and reaction with HCOOH/acetic anhydride] in dimethylformamide has been added, the mixture is stirred at 90°-95°C for 15 h. The mixture is evaporated and the residue is worked up in the customary manner to give 4-o-chlorobenzyloxy-1-methyl-1H-imidazo[4,5-c]pyridine, melting point 132°-135°C (crystallize from ethyl acetate-tetrahydofuran).

References

Irmscher K. et al.; US Patent No. 4,654,350; March 31, 1987; Assigned: Merck Patent Gesellschaft Mit Beschrankter Haftung, Darmstadt, Fed. Rep. of Germany

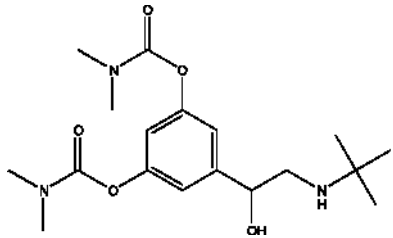
BAMBUTEROL

Therapeutic Function: Anti-asthmatic

Chemical Name: 5-(2-(tert-Butylamino)-1-hydroxyethyl)-m-phenylene bis(dimethylcarbamate)

Common Name: Bambuterol; Terbutaline bis(dimethylcarbamate)

Structural Formula:



Chemical Abstracts Registry No.: 81732-65-2

Trade Name	Manufacturer	Country	Year Introduced
Bambuterol	Paranova	-	-
Bambec	AstraZeneca	-	-
Oxeol	Orifarm	-	-
Oxeol	AstraZeneca	-	-
Bambuterol	King Sun Chemical and Pharmaceutical Co., Ltd.	-	-

Raw Materials

Palladium on carbon
Bromine
N-Benzyl-t-butylamine
3,5-Dihydroxyacetophenone
N,N-Dimethylcarbamoyl chloride
Benzyl chloride

Manufacturing Process

Preparation of 1-[bis-(3',5'-N,N-dimethylcarbamoyloxy)phenyl]-2-N-t-butylaminoethanol hydrochloride:

A solution of 78 g of bis-3',5'-(N,N-dimethylcarbamoyloxy)-2-(N-benzyl-t-butyl)aminoacetophenone in 300 ml of ethanol was hydrogenated in a Parr equipment in the presence of 25 ml of benzyl chloride and 3.5 g of 10% Pd/C. The hydrogenation time was 24 hrs at a pressure of 345 KPa (50 psig) and a temperature of 50°C. The catalyst was filtered off, and the filtrate was evaporated to dryness. The residue was dissolved in isopropanol, filtered, and to the filtrate was added diethylether to precipitate the title compound. The identity of the title product obtained was confirmed with NMR. Yield: 46.5 g. The bis-3',5'-(N,N-dimethylcarbamoyloxy)-2-(N-benzyl-t-butyl)aminoacetophenone which was used as starting material was prepared as follows:

(1a). Bis-3,5-(N-N-dimethylcarbamoyloxy)acetophenone:

To a solution of 152 g of 3,5-dihydroxyacetophenone in 700 ml dry pyridine was added 280 ml of N,N-dimethylcarbamoyl chloride. The mixture was stirred for 18 hrs at 60°-70°C. After evaporation in vacuum the residue was treated with a mixture of diethylether and water. The water phase was extracted with diethylether, whereafter the combined diethylether phases were washed with water, and dried over $MgSO_4$. After evaporation, the residue was recrystallized from isopropylalcohol-petroleum ether b.p. 40°-60°C. The identity of the product was confirmed with NMR. Yield: 180.4 g.

(1b). Bis-3',5'-(N,N-dimethylcarbamoyloxy)-2-bromoacetophenone:

To a solution of 180 g of bis-3,5-(N,N-dimethylcarbamoyloxy)acetophenone obtained in step 1a in 700 ml of dioxane was added dropwise a solution of 31 ml of bromine in 200 ml of dioxane. The mixture was stirred at 35°C for 1 hr. The residue obtained after evaporation in vacuum was recrystallized from isopropylalcohol-petroleum ether b.p. 40°-60°C. The identity of the product was confirmed with NMR. Yield: 174 g.

(1c). Bis-3',5'-(N,N-dimethylcarbamoyloxy)-2-(N-benzyl-t-butyl)aminoacetophenone:

To a solution of 5.6 g of the bromoacetophenone obtained in step 1b in 75 ml of acetone was added a solution of 4.9 g of N-benzyl-t-butylamine in 30 ml of acetone. The mixture was refluxed under stirring for 18 hrs, filtered, and evaporated in vacuum. The residue was dissolved in diethyl ether, petroleum ether b.p. 61°-70°C was added, and the yellow precipitate formed filtered off. After washing with water followed by a 1:1 mixture of isopropylalcohol-petroleum ether white crystals were obtained. The identity of the product was confirmed with NMR. Yield: 4.6 g.

References

Torsten Olsson O. A.; US Patent No. 4,419,364; December 6, 1983; Assigned to aktiebolaget Draco, Lund Sweden

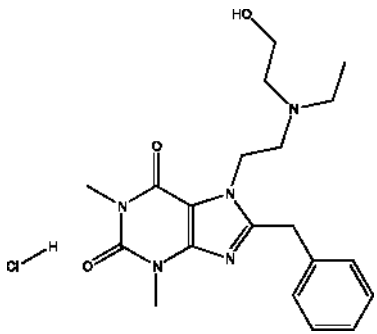
BAMIFYLLINE HYDROCHLORIDE

Therapeutic Function: Bronchodilator, Coronary vasodilator

Chemical Name: 7-[2-[Ethyl(2-hydroxyethyl)amino]ethyl]-3,7-dihydro-1,3-dimethyl-8-(phenylmethyl)-1H-purine-2,6-dione monohydrochloride

Common Name: Bamifylline hydrochloride; Benzetamophylline; Bamiphylline hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 2016-63-9 (Base); 20684-06-4

Trade Name	Manufacturer	Country	Year Introduced
Bamifylline hydrochloride	ZYF Pharm Chemical	-	-
Bamifix	Farmalab	-	-
Trentadil	Laboratoires Evans Medical	-	-

Trade Name	Manufacturer	Country	Year Introduced
Airest	Caber	-	-
Bamifix	Chiesi Farmaceutici spa	-	-
Bamifix BB	Chiesi Farmaceutici spa	-	-
Briofil	TEOFARMA	-	-
Bamifylline hydrochloride	Laboratoires Evans Medical	-	-

Raw Materials

8-Benzyltheophilline
Sodium carbonate
N-Ethylethanolamine
Hydrochloric acid

Manufacturing Process

A mixture of 100 kg of 8-benzyltheophilline, 36 L of N-ethylethanolamine, 300 L of 1,2-dichlorethane and 71 kg of sodium carbonate was refluxed for 24 hours. Then 36 L of N-ethylethanolamine was added and the reaction mixture was refluxed. After cooling to the mixture was added the water and hydrochloric acid. The organic phase was extracted with hydrochloric acid. The acidic phase was neutralized with sodium carbonate and the 7-(N-ethyl-N-β-hydroxyethylaminoethyl)-8-benzyltheophilline was extracted with dichloromethane. The solvent was evaporated and the free base of 7-(N-ethyl-N-β-hydroxyethylaminoethyl)-8-benzyltheophilline was dissolved in methanol. Hydrochloride of 7-(N-ethyl-N-β-hydroxyethylaminoethyl)-8-benzyltheophilline was obtained by addition to the solution the hydrochloric acid; yield 81%, melting point 185-186°C.

References

Ridder R.R.; DE Patent No. 3,120,909; 1982-04-08; Applicant CYRISNIAENS SAA (BE)

BAMIPINE

Therapeutic Function: Antihistaminic, Antiallergic

Chemical Name: 1-Methyl-N-phenyl-N-(phenylmethyl)-4-piperidinamine

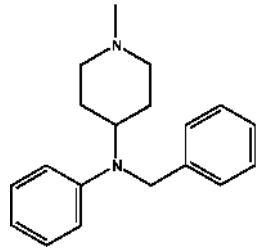
Common Name: Bamipine; Piperamine

Chemical Abstracts Registry No.: 4945-47-5

Raw Materials

Aniline
Acetic acid
1-Methyl-piperidone-4
Activated borings of aluminum

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Bamipine	Pharm Chemical Shanghai Lansheng Corporation	-	-
Soventol	Knoll	-	-
Soventol	Rentschler	-	-
Soventol Comp.	Adco Co.	-	-
Soventol Comp.	Knoll	-	-

Manufacturing Process

80 g of 1-methyl-piperidone-4 and 70 g of aniline are boiled, using a water separator in 350 ml of toluene to which several drops of glacial acetic acid have been added, until the theoretical quantity of water (12.7 ml) has separated out. The toluene is then distilled off and the remains are fractionated at reduced pressure. At a boiling point of 156°C/13 mm of Hg pressure, 118 g of a weakly yellow colored oil of the anil of 1-methyl-1-piperidone-4 are obtained.

100 g of the above described anil of 1-methyl-1-piperidone-4 are boiled for 8 hours, using a reflux condenser, with 30 g of activated borings of aluminum in 300 ml of methanol diluted with 60 ml of water. The liquid phase is then separated from the solid phase, the solvent is evaporated and the residuum is fractionated at reduced pressure, 95 g of a colorless oil being obtained boiling at 163-165°C at 15 mm of Hg pressure. The oil solidifies at once to a mass of crystals of 4-N-phenylaimno-1-methylpiperidine. After having been recrystallized from dibutyl ether the base melts at 87°C, its dihydrochloride has the melting point of 246°C.

95 g of 4-N-phenylamino-1-methylpiperidine are boiled together with 22 g of pulverized sodium amide in 300 ml of benzene, using a reflux condenser, while nitrogen is passed through the reaction mixture, until the evolution of ammonia has ceased. 64 g of benzyl chloride are then gradually added drop by drop to the boiling reaction product and boiling is continued for several hours. After having been cooled the solution is shaken with water and subsequently dried with potassium carbonate. The solvent having been evaporated the remaining base of 4-(N-phenyl-N-benzyl)-amino-1-methylpiperidine solidifies with the formation of crystals, the yield amounting to 123 g. The base is recrystallized from dibutyl ether and has a melting point of 115°C; its dihydrochloride melts at 189°C.

References

Merck Index, Monograph number: 983, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Kallischnigg R., US Patent No. 2,683,714; July 13, 1954; Knoll A.G., Ludwigschaffen (Rhine), Germany

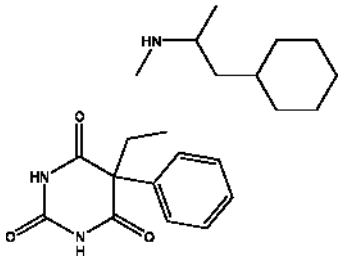
BARBEXACLONE

Therapeutic Function: Antiepileptic

Chemical Name: (-)-N-α-Dimethylcyclohexaneethylamine compound with 5-ethyl-5-phenyl-5-phenylbarbituric acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 4388-82-3

Trade Name	Manufacturer	Country	Year Introduced
Maliasin	Knoll	Italy	1983

Raw Materials

Phenyl ethyl barbituric acid
1-Cyclohexyl-2-methylamino propane hydrochloride

Manufacturing Process

25.4 g of sodium salt of phenyl ethyl barbituric acid and 19.1 g of 1-cyclohexyl-2-methylamino propane hydrochloride are boiled under reflux in a mixture of 125 cc of acetic acid ethyl ester and 125 cc of ethanol. After boiling for half an hour, the solution is filtered, while still hot, to separate the precipitated sodium chloride. The filtrate is concentrated by evaporation to about half its volume. After cooling 42.5 g of the salt of 1-cyclohexyl-2-methylamino propane and of phenyl ethyl barbituric acid are obtained in crystalline form. Its melting point is 130°-133°C.

References

Kleeman and Engel p. 73
I.N. p. 115
Suranyi, L.; US Patent 3,210,247; October 5, 1965; assigned to Knoll A.G.

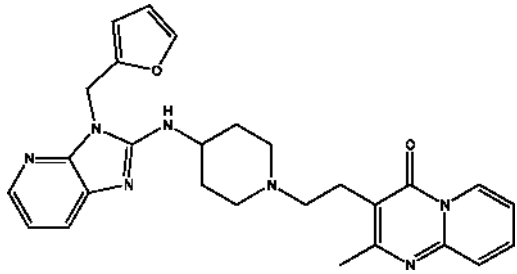
BARMASTINE

Therapeutic Function: Antihistaminic

Chemical Name: 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-(2-(4-((3-(2-furanylmethyl)-3H-imidazo[4,5-b]pyridin-2-yl)amino)-1-piperidinyl)ethyl)-2-methyl-

Common Name: Barmastine; Ramastine

Structural Formula:



Chemical Abstracts Registry No.: 99156-66-8

Trade Name	Manufacturer	Country	Year Introduced
Barmastine	ZYF Pharm Chemical	-	-

Raw Materials

Thiophene	N-(3-Nitro-2-pyridinyl)-2-furanylmethanamine
Ammonia	Platinum on charcoal
Hydrogen	Mercury (II) oxide
Sulfur	Ethyl 4-isothiocyanato-1-piperidinecarboxylate
Acetic acid	Potassium hydroxide
Hydrobromic acid	Sodium carbonate
	3-(2-Hydroxyethyl)-2-methyl-pyrido[2,1-b]pyrimidin-4-one

Manufacturing Process

A mixture of N-(3-nitro-2-pyridinyl)-2-furanylmethanamine, of a solution of thiophene in ethanone 4% and of methanol saturated with ammonia was hydrogenated at normal pressure and at room temperature with platinum-on-

charcoal catalyst 5%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was crystallized from acetonitrile, yielding the N^2-(2-furanylmethyl)-2,3-pyridinediamine.

A mixture of 54 parts of ethyl 4-isothiocyanato-1-piperidinecarboxylate, 48 parts of N^2-(2-furanylmethyl)-2,3-pyridinediamine and 450 parts of tetrahydrofuran was stirred and refluxed overnight. The reaction mixture was evaporated and the residue was crystallized from a mixture of 2-propanone and 2,2'-oxybispropane. The product was filtered off and dried, yielding 76 parts (75%) of ethyl 4-[[[2-[(2-furanylmethyl)amino]-3-pyridinyl]aminothioxomethyl]amino]-1-piperidinecarboxylate; melting point 132.7°C.

A mixture of 74 parts of ethyl 4-[[[2-[(2-furanylmethyl)amino]-3-pyridinyl]aminothioxomethyl]amino]-1-piperidinecarboxylate, 96 parts of mercury (II) oxide, 0.1 parts of sulfur and 800 parts of ethanol was stirred and refluxed for 3 h. The reaction mixture was filtered over Hyflo and the filtrate was evaporated to give 52.5 parts (79%) of ethyl 4-[[3-(2-furanylmethyl)-3H-imidazo[4,5-b]pyridin-2-yl]amino]-1-piperidinecarboxylate; melting point 149.2°C (crystallized from acetonitrile).

A mixture of ethyl 4-[[3-(2-furanylmethyl)-3H-imidazo[4,5-b]pyridin-2-yl]amino]-1-piperidinecarboxylate and of a hydrobromic acid solution 48% in water was stirred and heated for 3 h at about 80°C. The reaction mixture was evaporated and the residue was dried, yielding the 3-(2-furanylmethyl)-N-(4-piperidinyl)-3H-imidazo[4,5-b]pyridin-2-amine dihydrobromide (crystallized from methanol).

A mixture of 3-(2-hydroxyethyl)-2-methyl-pyrido[2,1-b]pyrimidin-4-one, of acetic acid and of a hydrobromic acid solution 67% in acetic acid was stirred and heated to reflux. Stirring was continued overnight at reflux temperature. The reaction mixture was evaporated and the solid residue was triturated in 2-propanone. The product was filtered off and dried, yielding 3-(2-bromoethyl)-2-methyl-pyrido[1,2-a]pyrimidin-4-one monohydrobromide.

A mixture of 3-(2-bromoethyl)-2-methyl-pyrido[1,2-a]pyrimidin-4-one monohydrobromide, 3-furan-2-yl-methyl-(3H-imidazo[4,5-b]pyridine-2yl)-4-piperidinyl)-amine dihydrobromide, of sodium carbonate and of N,N-dimethylformamide was stirred and heated overnight at about 70°C. The reaction mixture was poured onto water. The product was extracted with trichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (94:6 by volume), saturated with ammonia, as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from acetonitrile, yielding 3-(2-(4-((3-(2-furanylmethyl)-3H-imidazo[4,5-b]pyridin-2-yl)amino)-1-piperidinyl)ethyl)-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one; melting point 202°C.

References

Janssens F.E. et al.; US Patent No. 5,025,014; June18, 1991; Assigned: Janssen Pharmaceutica N.V., Beerse, Belgium

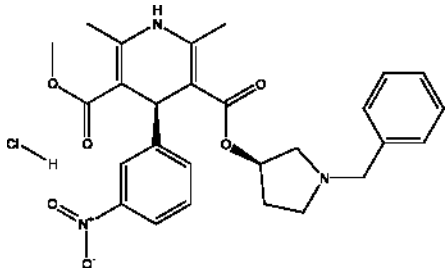
BARNIDIPINE HYDROCHLORIDE

Therapeutic Function: Coronary vasodilator

Chemical Name: (+)-(3'S,4S)-1-Benzyl-3-pyrrolidinyl methyl 1,4-dihydro-2,6-dimethyl-4-(m-nitrophenyl)-3,5-pyridinedicarboxylate monohydrochloride

Common Name: Barnidipine hydrochloride; Mepirodipine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 104713-75-9 (Base); 104757-53-1

Trade Name	Manufacturer	Country	Year Introduced
Barnidipine hydrochloride	Yamanouchi	-	-
Cyress	Yamanouchi	-	-
Libradin	Sigma-Tau Industrie Farmaceutiche Riunite spa	-	-
Libradin	Andromaco	-	-
Vasexten	Yamanouchi	-	-
Vasexten	Fournier	-	-

Raw Materials

3-Nitrobenzaldehyde
1-Benzyl-3-acetoacetyloxypyrrolidine
β-Aminocrotonic acid

Manufacturing Process

In 5 ml of isopropyl alcohol were dissolved 1.5 g (0.01 mole) of 3-nitrobenzaldehyde, 2.6 g (0.01 mole) of 1-benzyl-3-acetoacetyloxypyrrolidine, and 1.3 g (0.01 mole) of β-aminocrotonic acid methyl ester and then the solution was refluxed for 8 hours. The solvent was distilled off under reduced pressure, the residue obtained was dissolved in a small amount of chloroform, and the solution was applied to silica gel column chromatography (column diameter 1.5 cm, height 20 cm, and about 200 ml of chloroform was used as the eluent). The eluates were collected and concentrated to give 3.4 g of oily

2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-(1-benzylpyrrolidin-3-yl)ester-5-methyl ester: $[\alpha]_D^{20} = +64.8°$ (c = 1 in methanol).

In practice it is usually used as monohydrochloride.

References

Kojima Tadao, Takenaka Toichi; US Patent No. 4,220,649; September 2, 1980; Assigned to Yamanouchi Pharmaceutical Co., Ltd. (Tokyo, JP)

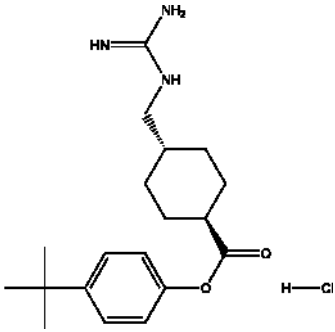
BATEBULAST HYDROCHLORIDE

Therapeutic Function: Antiallergic, Anti-asthmatic

Chemical Name: p-tert-Butylphenyl trans-4-(guanidinomethyl) cyclohexanecarboxylate monohydrochloride

Common Name: Batebulast hydrochloride; Telbulast hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 81907-78-0 (Base); 83373-31-3

Trade Name	Manufacturer	Country	Year Introduced
Batebulast hydrochloride	Onbio Inc.	-	-
Batebulast hydrochloride	Nippon Chemiphar	-	-

Raw Materials

trans-4-Guanidinomethylcyclohexanecarboxylic acid
p-t-Butylphenol
Dicyclohexylcarbodiimide

Manufacturing Process

A mixture of 9.4 g of trans-4-guanidinomethylcyclohexanecarboxylic acid, 7.2 g of p-t-butylphenol and 10.0 g of dicyclohexylcarbodiimide was suspended in a solution of 61 ml of dry pyridine and ml of dry dimethylformamide, and the suspension was stirred at room temperature for 24 h.The solvent was removed under reduced pressure.The residue was washed and dried.There was obtained the 4'-t-butylphenyl trans-4-guanidinomethylcyclohexane-carboxylate.

In practice it is usually used as hydrochloride.

References

Muramatsu M. et al.; US Patent No. 4,465,851; August 14, 1984; Assigned: Nippon Chemiphar Co., Ltd., Tokyo, Japan

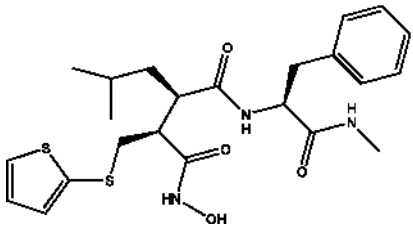
BATIMASTAT

Therapeutic Function: Antineoplastic

Chemical Name: Butanediamide, N4-hydroxy-N1-(2-(methylamino)-2-oxo-1-(phenylmethyl)ethyl)-2-(2-methylpropyl)-3-((2-thienylthio)methyl)-, (2R-(1(S*),2R*,3S*))-

Common Name: Barinatrix; Batimastat

Structural Formula:



Chemical Abstracts Registry No.: 130370-60-4

Trade Name	Manufacturer	Country	Year Introduced
Batimastat	British Biotech	-	-

Raw Materials

Leucine, D-
Sulfuric acid
Sodium bicarbonate
Potassium t-butoxide
Potassium bromide
Sodium nitrite
Dibenzyl malonate
Hydroxy benztriazole

N-Methylmorpholine	Ammonium formate
Palladium on charcoal	Phenylalanine-N-methylamide
Piperidine	Formaldehyde
Thiophenethyol	Dicyclohexylcarbodiimide
N-(Dimethylaminoethyl)-N'-ethylcarbodiimide	

Manufacturing Process

D-Leucine (100.0 g, 0.76 mol) and potassium bromide (317.5 g, 2.67 mol) were dissolved in aqueous acid (150 ml concentrated sulfuric acid in 500 ml of water). The solution was cooled to -2°C and sodium nitrite (69.6 g, 0.95 mol in water) was added over 1 h taking care to maintain the temperature between -1°C and -2°C. After addition was complete the mixture was kept at 0°for a further hour, then DCM was added and the mixture stirred for a few minutes. The layers were separated and the aqeous phase was washed with further portions of DCM (5 x 250 ml). The combined organic layers were dried over magnesium sulfate then the solvent removed to give the 2R-bromo-5-methylpentanoic acid as a pale yellow oil (123.1 g, 0.63 mol, 83%).

2R-Bromo-5-methylpentanoic acid (123.0 g, 0.63 mol) was dissolved in DCM (400 ml) and the solution cooled to -40°C while isobutene was condensed in to roughly double the volume. Maintaining the temperature at -40°C concentrated sulfuric acid (4 ml) was added dropwise. When the addition was complete the reaction was allowed to warm to room temperature overnight. The resultant solution was concentrated to half the volume by removing the solvent at reduced pressure, then the DCM was washed twice with an equal volume of 10% sodium bicarbonate solution. The organic layer was dried over magnesium sulfate and the solvent removed under reduced pressure to leave the t-butyl 2R-bromo-5-methylpentanoate as a yellow oil (148.1 g, 0.59 mol, 94%).

Dibenzyl malonate (124.5 g, 0.44 mol) was taken up in dry DMF and potassium t-butoxide (49.2 g, 0.44 mol) was added portionwise with stirring and cooling. When a homogeneous solution had formed it was cooled to 0°C, then t-butyl-2R-bromo-5-methylpentanoate (110.1 g, 0.44 mol) in DMF (200 ml) was added dropwise over 1 h. When addition was complete the reaction was transfered to a cold room at 5°C and left for 4 days. The reaction mixture was partitioned between ethyl acetate and saturated ammonium chloride then the aqueous layer extracted with further ethyl acetate (4 x 500 ml), drying and solvent removal left an oil (228.0 g) heavily contaminated with DMF. This oil was taken into ether (1 L) and washed with brine (2 x 11) then the organic layer dried (magnesium sulfate), solvent removed under reduced pressure to leave the benzyl (2-benzyloxycarbonyl-3R-(t-butoxycarbonyl)-5-methylhexanoate (179.0 g) contaminated with a small amount of dibenzyl malonate.

Benzyl (2-benzyloxycarbonyl-5-methyl-3R-t-butoxycarbonyl)hexanoate (281.4 g, 0.56 mol) was taken up in 5% water in TFA (410 ml) and allowed to stand at 5°C overnight. After this time the TFA was evaporated under reduced pressure then the residue partitioned between DCM (1 L) and brine (200 ml). Solvent removal left an oil which crystallised on standing (230.0 g). The crude acid from this reaction was dissolved in DMF (1 L), then hydroxy benztriazole (95.3 g, 0.64 mol), N-methylmorpholine (64.0 g, 0.64 mol) and

phenylalanine-N-methylamide (113.1 g, 0.64 mol) were added at room temperature. The mixture was cooled to 0°C before dropwise addition of dicyclohexylcarbodiimide (131.0 g, 0.64 mol) in THF (1 L). This solution was stirred to room temperature over the weekend. The precipitated dicyclohexylurea was removed by filtration then the solvents were removed from the filtrate under reduced pressure to leave an oil. This oily residue was dissolved methyl acetate then washed with 10% citric acid, 10% sodium bicarbonate and saturated brine. The organic layer was dried (magnesium sulfate), filtered then the solvent removed under reduced pressure to give the title compound as an oil (400.0 g). This material was columned on silica using gradient elution (0-50% ethyl acetate in hexane) to remove impurities and separate a small amount of the minor diastereoisomer. The material from the column (195.0 g) was recrystallised from diisopropyl ether to give the [4-benzyloxy-3-benzyloxycarbonyl-2R-isobutylsuccinyl]-L-phenylalanine-N-methylamide as a white crystalline solid (140.2 g, 0.25 mol, 47%), melting point 98°-99°C.

The 4-benzyloxy-3-benzyloxycarbonyl-2R-isobutylsuccinyl]-L-phenylalanine-N-methylamide (29.6 g, 53 mmol) was taken up in ethanol, ammonium formate (16.7 g, 265 mmol) added followed by 10% palladium on charcoal (6.0 g) as a slurry in isopropyl alcohol. After 30 min at room temperature the catalyst was removed by filtration, then washed with ethanol to give a solution of the crude diacid. To this was added piperidine (5.0 g) and the mixture stirred at room temperature for 15 min before addition of aqueous formaldehyde (40% solution, 25 ml). After 18 h at room temperature the mixture was refluxed for 1 h. Solvents were removed under reduced pressure and the residue partitioned between ethyl acetate and citric acid. The acid layer was extracted with further portions of ethyl acetate (2 x 250 ml), the combined organic layers were extracted with potassium carbonate (3 x 200 ml). These base extracts were acidified to pH 4 and reextracted with DCM then the organic layer dried over magnesium sulfate. Solvent removal under reduced pressure gave the [4-hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-phenylalanine-N-methylamide as a white solid (9.35 g, 27.0 mmol, 51%), melting point 149°-151°C.

The [4-hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-phenylalanine-N-methylamide (400.0 mg, 1.16 mmol) was dissolved in thiophenethyol and the mixture stirred in the dark under nitrogen at 60°C for 2 days. Ether was added to the cooled reaction mixture and the precipitated product collected by filtration. The solid was washed with large volumes of ether and dried under vacuum to give the [4-N-hydroxy-2R-isobutyl-3S-(thienylthiomethyl)succinyl]-L-phenylalanine-N-methylamide (320.0 mg, 0.73 mmol, 63%), melting point 184°-186°C.

The [4-N-hydroxy-2R-isobutyl-3S-(thienylthiomethyl)succinyl]-L-phenylalanine-N-methylamide and hydroxy benztriazole were dissolved in DCM/DMF (4:1) and the mixture cooled to 0°C before adding N-(dimethylaminoethyl)-N'-ethylcarbodiimide and N-methylmorpholine. The mixture was stirred at 0°C or 1 h to ensure complete formation of the activated ester. Hydroxylamine hydrochloride and NMM were dissolved in DMF then this mixture added dropwise to the cooled solution of the activated ester. After 1 h the reaction was poured into ether/water (1:1) whereupon the desired product precipitated as white crystals. These were collected by filtration, further washed with ether and water then dried under vacuum at

50°C. So the [4-(N-hydroxyamino)-2R-isobutyl-3S-(thienylthiomethyl) succinyl]-L-phenylalanine-N-methylamide was obtained, melting point 236°-238°C (recrystallised from methanol/ water 1:1).

References

Campion C. et al.; US Patent No. 5,240,958; August 31,1993; Assigned: British Bio-Technology Limited, Oxford, England

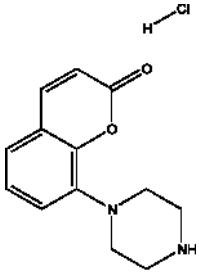
BATOPRAZINE HYDROCHLORIDE

Therapeutic Function: Psychotropic

Chemical Name: 8-(1-Piperazinyl)-2H-1-benzopyran-2-one monohydrochloride

Common Name: Batoprazine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 105684-52-4

Trade Name	Manufacturer	Country	Year Introduced
Batoprazine hydrochloride	Duphar	-	-

Raw Materials

5-Amino-1-benzopyran-2-one
Sodium hydroxide
Bis-(2-chloroethyl)amine hydrochloride

Manufacturing Process

5-Amino-1-benzopyran-2-one and bis-(2-chloroethyl)amine hydrochloride were suspended in chlorobenzene. The mixture was heated at 130°C for about 66 h while stirring.

The reaction mixture was cooled to 90°C and diluted with ethyl acetate. The solid was filtered off, washed with ethyl acetate and dried. So the 1-[5-(1-benzopyran-2-one)]piperazine hydrochloride was obtained, melting point 250°C (dec.; recrystallized from ethanol).

To obtained the base, 1-[5-(1-benzopyran-2-one)]piperazine, the 1-[5-(1-benzopyran-2-one)]piperazine hydrochloride was treated by solution of sodium hydroxide.

References

Hartog J. et al.; EU Patent No. 0,189,612; August 6, 1986

BATROXOBIN

Therapeutic Function: Hemostatic

Chemical Name: See under structural formula; no defined name

Common Name: -

Structural Formula: It is a complex enzyme of molecularweight no greater than 40,000 in monomeric form.

Chemical Abstracts Registry No.: 9039-61-6

Trade Name	Manufacturer	Country	Year Introduced
Defibrase	Serono	W. Germany	1982
Botrophase	Ravizza	Italy	-
Ophidiase	Labaz	Switz.	-
Reptilase	Disperga	Austria	-
Reptilase	Knoll	W. Germany	-

Raw Materials

Venom of Bothrops Atrox (A Pit Viper)
Phenol

Manufacturing Process

The process for preparing the enzyme composition comprises treating an aqueous solution of the snake venom at a pH of about 4 to 6 with phenol or a phenol derivative in order to precipitate an insoluble complex containing the active venom fraction and decomposing the complex in order to release the thrombinlike enzyme composition.

References

Merck Index 1010

DOT 18 (4) 169 (1982)
I.N.p. 117
Percs, E.E., Stocker, K.F., Blomback, B., Blomback, M.and Hessel, B.;US Patent 3,849,252; November 19, 1974; assigned to Pentapharm A.G.

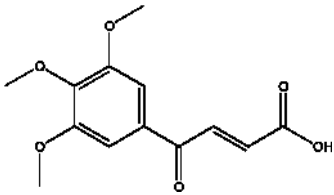
BAXITOZINE

Therapeutic Function: Gastric cytoprotective; Antiulcer

Chemical Name: 2-Butenoic acid, 4-oxo-4-(3,4,5-trimethoxyphenyl)-, (E)-

Common Name: Baxitozine; RU 38086

Structural Formula:



Chemical Abstracts Registry No.: 84386-11-8

Trade Name	Manufacturer	Country	Year Introduced
Baxitozine	ZYF Pharm Chemical	-	-

Raw Materials

Glyoxylic acid
Acetic acid
Sodium carbonate
Hydrochloric acid
3,4,5-Trimethoxy acetophenone

Manufacturing Process

29.6 g of glyoxylic acid of 50% by weight are heated in water under reduced pressure until elimination of 80% of the water present, whereupon, after cooling, 84.1 g of 3,4,5-trimethoxy acetophenone are introduced into the reaction mixture. Heating is effected for 2 h at 95°-100°C under reduced pressure (about 50 mm/Hg), at the same time distilling off the residual water present.

After cooling of the medium, 120 ml of water containing 11.6 g of sodium carbonate and ether are introduced, the aqueous phase is decanted and washed with : ether, whereupon the aqueous phase is acidified to a pH of 1 with 50% hydrochloric acid. The desired product is extracted with ethyl acetate. After elimination of the extraction solvent 31.5 g of the 4-(3,4,5-trimethoxyphenyl)-4-oxo-2-hydroxy butanoic acid, melting point 119°-120°

are obtained (recrystallization from 1,2-dichloroethane).

15.8 g of 4-(3,4,5-trimethoxyphenyl)-4-oxo-2-hydroxy butanoic acid, 20 ml of acetic acid and 20 ml of concentrated hydrochloric acid (d-1.18) are heated for 2.5 h under reflux. The reaction medium is cooled and precipitated by water. The precipitate formed is filtered off. 10.5 g of the (E)-4-(3,4,5-trimethoxyphenyl)-4-oxo-2-butenoic acid, melting point 140°C are obtained (recrystallization from ethanol-water 1:1).

References

Christidis Y, Fournex R.; US Patent No. 4,450,292; May 22, 1984; Assigned: Roussel Uclaf, Paris, France

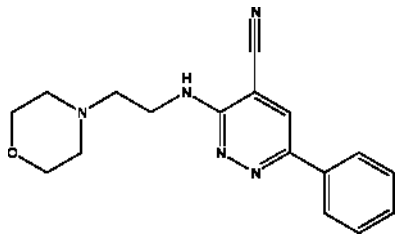
BAZINAPRINE

Therapeutic Function: Antidepressant

Chemical Name: 4-Pyridazinecarbonitrile, 3-((2-(4-morpholinyl)ethyl)amino)-6-phenyl-

Common Name: Bazinaprine; SR 95191

Structural Formula:



Chemical Abstracts Registry No.: 94011-82-2

Trade Name	Manufacturer	Country	Year Introduced
SR 95.191	Clin Midy/Sanofi Winthrop	-	-

Raw Materials

Ethyl malonate	Potassium carbonate
Potassium iodide	Phenacyl chloride
Hydrazine hydrate	Acetic acid
Ammonia	Phosphorus oxychloride
Sulfuric acid	N-(2-Aminoethyl)morpholine
Sodium hydroxide	Bromine

Manufacturing Process

240.25 g of ethyl malonate, 138.0 g of potassium carbonate, 5.0 g of potassium iodide and 154.0 g of phenacylchloride in 2 L of anhydrous acetone are heated under reflux overnight. After the inorganic salts have been filtered off, the filtrate is evaporated to dryness and the excess ethyl malonate is then distilled off under reduced pressure (pressure: 0.5 mbar; temperature: about 60°C). The distillation residue is chromatographed on a silica column using a cyclohexane/ethyl acetate mixture (9:1) as the eluent. The ethyl phenacylmalonate is obtained in the form of a red oil. Yield: 80.3%.

40.5 g of the ethyl phenacylmalonate are dissolved in 70 ml of absolute ethanol, and 7.25 g of hydrazine hydrate are added dropwise to the reaction medium at 0°C, with stirring. When the reaction medium has returned to room temperature, it is stirred for 24 h and the beige precipitate obtained, which corresponds to the expected pyridazinone, is then filtered off. The filtrate is treated with 3.62 g of hydrazine hydrate. After stirring for 24 h, an additional quantity of pyridazinone can be filtered off. The same operation is repeated once more on the filtrate. After purification by passage through a silica column using a cyclohexane/ethyl acetate mixture (1:1) as the eluent, the 4-ethoxycarbonyl-6-phenyl-4,5-dihydro-2H-pyridazin-3-one is obtained. Yield: 37%.

9.0 g of the 4-ethoxycarbonyl-6-phenyl-4,5-dihydro-2H-pyridazin-3-one are dissolved in 200 ml of acetic acid, and 11.18 g of bromine are then added to the solution, with stirring. Decolouration of the medium occurs after 5 min. After 2 h at room temperature, and with stirring, the medium is poured into 200 ml of water, the mixture is then extracted with methylene chloride and the organic phase is evaporated to dryness. The residue is taken up 3 times with cyclohexane. The beige powder obtained is chromatographed on a silica column using a cyclohexane/ethyl acetate mixture (1:1) as the eluent. The 4-ethoxycarbonyl-6-phenyl-2H-pyridazin-3-one, melting point 150°C is obtained. Yield: 51%.

2.0 g of the 4-ethoxycarbonyl-6-phenyl-2H-pyridazin-3-one are added to 40 ml of concentrated ammonia solution and the mixture is stirred overnight at room temperature. The solid is filtered off and dried to give the 6-phenyl-3-oxo-2H-pyridazine-4-carboxamide, melting point >300°C. Yield: 86%.

1.5 g of the 6-phenyl-3-oxo-2H-pyridazine-4-carboxamide are dissolved in 20 ml of phosphorus oxychloride and the solution is then heated at 80°C for 5 h. The mixture is poured into 50 ml of water. A precipitate appears, which is filtered off and dried. There are obtained 58.3% of 3-chloro-4-cyano-6-phenylpyridazine, melting point 206°C.

7.3 g of the 3-chloro-4-cyano-6-phenylpyridazine are dissolved in 60 ml of n-butanol, and 8.0 g of N-(2-aminoethyl)-morpholine are added. The mixture is heated under reflux for 3 h and then poured into 1000 ml of water. The organic phase is extracted with ether and the ether solution is then extracted with a 1 N solution of sulfuric acid. The aqueous phase is separated off, rendered alkaline with sodium hydroxide and extracted with ether. The ether phase is dried over magnesium sulfate and the solvent is then evaporated off to dryness in vacuo to give the 3-(2-morpholinoethylamino)-4- cyano-6-phenylpyridazine, as yellow solid, melting point 138°C. Yield: 81.3%.

References

Kan J.-P. et al.; US Patent No. 4,631,280; December 23, 1986; Assigned: Sanofi, Paris, France

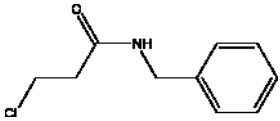
BECLAMIDE

Therapeutic Function: Anticonvulsant

Chemical Name: 3-Chloro-N-(phenylmethyl)propanamide

Common Name: Benzchloropropamide; Benzylchloropropionamide; Chloroethylphenamide

Structural Formula:



Chemical Abstracts Registry No.: 501-68-8

Trade Name	Manufacturer	Country	Year Introduced
Posedrine	Biosa	Switz.	-
Posedrine	Aron	France	1970
Beclamid	Aron	W. Germany	1975
Neuracen	Promonta	W. Germany	-
Nydrane	Lipha	UK	-
Nydrane	Aron	France	-
Posedrine	Lasa	Spain	-
Posedrine	Byk Gulden	-	-
Posedrine	Spemsa	Italy	-
Seclar	Andromaco	Argentina	-

Raw Materials

Benzylamine
p-Chloropropionyl chloride
Sodium hydroxide

Manufacturing Process

A 100 gallon lined jacketed kettle provided with cooling is charged with 100 lb of benzylamine and 150 liters of water. The mixture is cooled to 5°C and with stirring 119 lb of β-chloropropionyl chloride and a solution of 45 lb of sodium hydroxide pellets in 40 liters of water are added simultaneously at such a rate that the temperature does not exceed 10°C. During this period the pH of the

mixture should be on the alkaline side but below pH 9.5. When the addition is complete the pH should be about 8. The mixture is stirred overnight in the cold, and the solid product is filtered. The filter cake is reslurred with about 80 gallons of water, filtered, and air-dried. Yield, 128 pounds.

The crude material is recrystallized by dissolving it in the minimal quantity of hot methanol (about 50 gallons), adding Norite, and filtering hot. Upon cooling slowly (finally to about 5°C) large crystals separate: they are filtered and air-dried. Yield, 109 pounds. Melting point 92° to 93°C.

References

Merck Index 1017
Kleeman and Engel p. 74
I.N. p. 118
Cassell, R.T. and Kushner, S.; US Patent 2,569,288; September 25, 1951: assigned to American Cyanamid Company

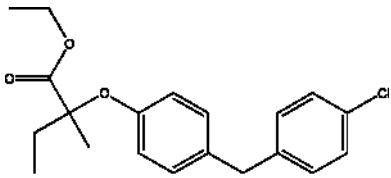
BECLOBRATE

Therapeutic Function: Antihyperlipidemic

Chemical Name: Butanoic acid, 2-(4-((4-chlorophenyl)methyl)phenoxy)-2-methyl-, ethyl ester, (+/-)-

Common Name: Beclobrate; Turec

Structural Formula:



Chemical Abstracts Registry No.: 55937-99-0

Trade Name	Manufacturer	Country	Year Introduced
Beclobrate	ZYF Pharm Chemical	-	-
Beclipur	SIEGFRIED HOLDING AG	-	-

Raw Materials

4-Chloro-4'-hydroxydiphenylmethane
Potassium carbonate
2-Bromo-2-ethyl-2-methylacetic acid ethyl ester

Manufacturing Process

87.0 g (0.4 mol) of 4-chloro-4'-hydroxydiphenylmethane are heated together with 27.0 g (0.2 mol) of anhydrous potassium carbonate in 350 ml of anhydrous xylene for 30 min to reflux temperature, whereafter a solution of 83.5 g (0.4 mol) of 2-bromo-2-ethyl-2-methyl acetic acid ethyl ester in 50 ml of anhydrous xylene is added. The mixture is kept for 24 hours and with vigorous stirring at reflux temperature. After filtering off the precipitated potassium bromide and evaporating the solvent in a Buchi rotary evaporator, the residue is taken up in ether and extracted with normal sodium hydroxide solution. The ether extracts are washed with water, dried over $MgSO_4$ and concentrated by evaporation. The brown oil (82.0 g) thereby obtained is dissolved in n-hexane and filtered through a column of 200 g of basic Al_2O_3. After evaporating the solvent and distillation at reduced pressure, 34.7 g of pure ethyl (+/-)-2-((α-(p-chlorophenyl)-p-tolyl)oxy)-2-methylbutyrate are obtained with the boiling point 200-204°C/0.01-0.1 mm Hg.

References

Thiele K., Quazi A., Adrian R., Jahn U.; US Patent No. 4,483,999; November 20, 1984; Assigned to Siegfried Aktiengesellschaft (Zofingen, CH)

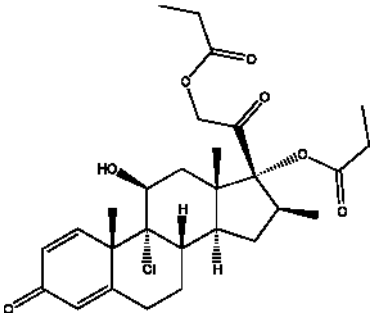
BECLOMETHASONE DIPROPIONATE

Therapeutic Function: Topical antiinflammatory, Glucocorticoid

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

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 5534-09-8; 4419-39-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Propaderm	Kyowa Hakko	Japan	1972
Eecotide	Allen and Hanburys	UK	1972
Cleniderm	Chiesi	Italy	1974
Sanasthmyl	Glaxo	W. Germany	1975
Becotide	Glaxo	France	1976
Beconase	Glaxo	W. Germany	1976
Vanceril	Schering	US	1976
Beclotide Nasal	Glaxo	Italy	1977
Becotide	Glaxo	Japan	1978
Aldesin	Shionogi	Japan	1978
Beclovent	Glaxo	US	1979
Becotide	Glaxo	Switz.	1981
Becloforte	Allen and Hanburys	UK	1982
Aldecin	Schering	-	-
Anceron	Essex	Argentina	-
Beclacin	Kaigai	Japan	-
Beclacin	Morishita	Japan	-
Beclamet	Orion	Finland	-
Beclo-Asma	Aldo Union	Spain	-
Beclomet	Orion	Finland	-
Beclosona	Spyfarma	Spain	-
Beclovent	Meyer	US	-
Becotide	Pliva	Yugoslavia	-
Betozon	Ohta	Japan	-
Betozon	Ono	Japan	-
Bronco-Turbinal	Valeas	Italy	-
Clenil	Chiesi	Italy	-
Dermisone Beclo	Frumtost	Spain	-
Entyderma	Taiyo	Japan	-
Gnadion	Pliva	Yugoslavia	-
Hibisterin	Nippon Zoki	Japan	-
Inalone	Lampugnani	Italy	-
Korbutone	Nippon Glaxo	Japan	-
Proctisone	Chiesi	Italy	-
Propaderm	Duncan	Italy	-
Propavent	Glaxo	UK	-
Rino-Clenil	Chiesi	Italy	-
Turbinal	Valeas	Italy	-
Vaderm	Schering	-	-
Viarex	Essex	Italy	-
Viarex	Schering	US	-
Viarox	Byk-Essex	W. Germany	-
Zonase	Script Intal	S. Africa	-
Zonide	Script Intal	S. Africa	-

Raw Materials

16β-Methyl-1,4-pregnadiene-11β,17α,21-triol-3,2-dione-21-acetate
Methanesulfonyl chloride
Sodium methoxide
N-Chlorosuccinimide
Perchloric acid

Manufacturing Process

6 grams of 6β-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione-21-acetate is dissolved in a mixture of 35 ml of dimethylformamide and 6 ml of pyridine. To the resulting solution is added 2.5 ml of methanesulfonyl chloride and the reaction mixture maintained at 80°-85°C for about 1 hour. The resulting red solution is cooled in an ice bath and treated successively with 55 ml of methanol, 240 ml of 5% aqueous sodium bicarbonate and finally with 360 ml of water. The resulting reaction mixture is then allowed to stand at room temperature overnight after which the precipitated product is removed by filtration, washed repeatedly with water and dried to a constant weight in air at about 50°C to produce 6β-methyl-1,4,9(11)-pregnadiene-11α,21-diol-3,20-dione-21-acetate.

Hydrolysis of the acetate ester with alkali, e.g., sodium methoxide in methanol, affords the free alcohol, 16β-methyl-1,4,9(11)-pregnadiene-17α,21-diol-3,20-dione. To a suspension of 3 grams of 6β-methyl-1,4,9(11)-pregnadiene-17α,21-diol-3,20-dione-21-acetate 40 ml of acetone is added at 0°C with stirring 2 grams of N-chlorosuccinimide and then 7 ml of a perchloric acid solution prepared by dissolving 0.548 ml of 70% perchloric acid in 33 ml of water. The resulting reaction mixture is stirred at 0° for about 4 hours 45 minutes.

The excess of N-chlorosuccinimide is destroyed by the addition of about 15 drops of allyl alcohol and 180 ml of water is then added with stirring. This mixture is held at 0°C for about one hour. The precipitated 16β-methyl-1,4-pregnadiene-9α-chloro-11β,17α,21-triol-3,20-dione-21-acetate is recovered filtration. A solution of 250 mg of the chlorohydrin in 5 ml of 0.25N perchloric acid in methanol is stirred for about 18 hours at room temperature to produce 16β-methyl-9α-chloro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione which is recovered by adding water to the reaction mixture and allowing the product to crystallize. Propionic anhydride is then used to convert this material to the dipropionate.

References

Merck Index 1018
Kleeman and Engel p.74
PDR pp.906, 1659
DOT 9 (8) 335 (1973)
I.N. p.118
REM p. 962
Merck and Co., Inc. British Patent 912,378; December 5, 1962
Taub, D., Wendler, N.L. and Slates, H.L.; US Patent 3,345,387; October 3, 1967; assigned to Merck and Co., Inc.

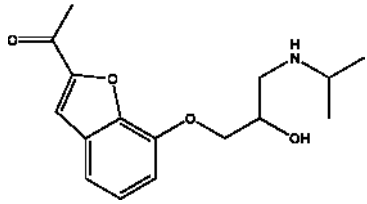
BEFUNOLOL

Therapeutic Function: Beta-adrenergic blocker

Chemical Name: 2-Acetyl-7-(2-hydroxy-3-isopropylaminopropoxy)benzofuran

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 39552-01-7

Trade Name	Manufacturer	Country	Year Introduced
Bentos	Kakenyaku Kako	Japan	1983

Raw Materials

2-Acetyl-7-hydroxybenzofuran
Epichlorohydrin
Isopropylamine

Manufacturing Process

To 8.8 g of 2-acetyl-7-hydroxybenzofuran were added 80 ml of epichlorohydrin and 0.2 g of piperidine hydrochloride and the mixture was heated at 105°C for 3 hours. After the reaction, the excess of epichlorohydrin was evaporated and the resultant was distilled under reduced pressure to give 9.3 g of 2-acetyl-7-(2,3-epoxypropoxy)benzofuranhaving a boiling point of 175° to 176°C/0.7 mm Hg. 6 g of the product was dissolved in 30 ml of ethanol and to the solution was added 10 ml of isopropylamine. After refluxing the mixture for 40 minutes, the solvent was evaporated from the reaction mixture. The resulting residue was recrystallized from cyclohexane-acetone to give 6 g of 2-acetyl-7-(2-hydroxy-3-isopropylaminopropoxy)benzofuran having a melting point of 115°C.

References

Merck Index 1022
DFU 6 (10) 601 (1981)
Ito, K., Mashiko, I., Kimura, K. and Nakanishi, T.; US Patent 3,853,923; December 10, 1974; assigned to Kakenyaku Kakko Co., Ltd.

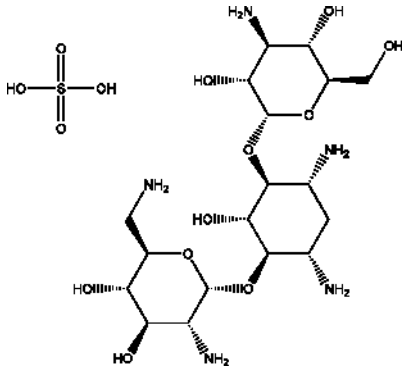
BEKANAMYCIN SULFATE

Therapeutic Function: Antibacterial

Chemical Name: D-Streptamine, O-3-amino-3-deoxy-α-D-glucopyranosyl-(1-6)-O-[2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl-(1-4)]-2-deoxy sulfate (1:1)

Common Name: Aminodeoxykanamycin

Structural Formula:



Chemical Abstracts Registry No.: 29701-07-3; 4696-76-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Kanendomycin	Meiji Seika	Japan	1969
Stereocidin	Crinos	Italy	1980
Coltericin	Argentia	Argentina	-
Kanendomicina	Lefa	Spain	-
Kanendos	Crinos	Italy	-
Visumetazone Antibiotica	ISF	Italy	-
Visumicina	ISF	Italy	-

Raw Materials

Bacterium S. Kanamyceticus
Nutrient broth

Manufacturing Process

200 liters of the medium containing 2.0% starch, 1.0% soybean meal, 0.05% KCl, 0.05% $MgSO_4 \cdot 7H_2O$, 0.3% NaCl, 0.2% $NaNO_3$ was placed in the 400 liter fermenter, the pH was adjusted to 7.5, and the medium was then sterilized (pH after the sterilization was 7.0) for 30 minutes at 120°C, inoculated with 1,000 ml of 40 hour shake-cultured broth of S. kanamyceticus (a selected subculture of K2-J strain) and tank-cultured at 27°-29°C. As antifoam,

soybean oil (0.04%)and silicone (0.04%) were added. The broth after 48 hours was found to contain 250 mcg/ml of kanamycin.

A portion (950 ml) of the rich eluate was adjusted to pH 6.0 by the addition of sulfuric acid. Ultrawet K (7.0 g) in 70 ml water was added slowly to the neutralized eluate to precipitate kanamycin B dodecylbenzenesulfonate which was collected by filtration after adding filter aid (Dicalite). The cake was washed with water and extracted with 100 ml methanol. After filtering and washing with methanol, sulfuric acid was added to the filtrate until no more kanamycin B sulfate precipitated. After addition of an equal volume of acetone to provide more complete precipitation, the kanamycin B sulfate was collected by filtration, washed with methanol and dried in vacuo at 50°C.

References

Merck Index 5118
Kleeman and Engel p. 75
I.N. p. 120
REM p. 1181
Umezawa, H., Maeda, K. and Ueda, M.; US Patent 2,931,798; April 5, 1960.
Johnson, D.A. and Hardcastle, G.A.; US Patent 2,967,177; January 3,1961; assigned to Bristol-Myers Co.
Rothrock, J.W. and Potter, I.; US Patent 3,032,547; May 1, 1962; assigned to Merck and Co., Inc.

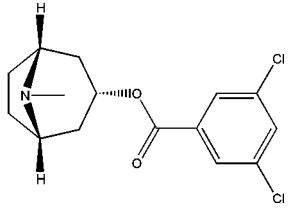
BEMESETRON

Therapeutic Function: Serotonin antagonist

Chemical Name: Benzoic acid, 3,5-dichloro-, (endo)-8-methyl-8-azabicyclo [3.2.1]oct-3-yl ester

Common Name: Bemesetron

Structural Formula:



Chemical Abstracts Registry No.: 40796-97-2

Trade Name	Manufacturer	Country	Year Introduced
Bemesetron	Merrel Dow	-	-

Raw Materials

Tropine
3,5-Dichlorobenzoylchloride

Manufacturing Process

Tropine (34.24 g) is treated with anhydrous diethyl ether and ethereal hydrogen chloride and the precipitated hydrochloride is isolated by evaporation of the solvent. 3,5-Dichlorobenzoylchloride (51.7 g) is added and the mixture stirred at 140°C for 15 minutes during which time the mixture liquifies, evolves hydrogen chloride gas and resolidifies. After heating for a further 15 minutes the cooled solid is dissolved in water, an excess of an aqueous solution of potassium carbonate is added, and the base is extracted with ethyl acetate. Evaporation of the dried ethyl acetate solution yields a solid, which is recrystallized from aqueous methanol to yield 3,5-dichlorobenzoic acid 8-methyl-8-aza-bicyclo[3.2.1]oct-1-yl ester (endo). MP: 95°C (51.8 g).

References

Fozard J. R. et al.; US Patent No. 4,563,465; January 7, 1986; Assigned to Merrell Dow Pharmazeuticals Inc., Cincinnati, Ohio

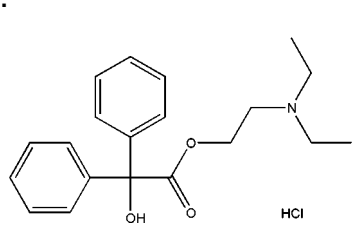
BENACTYZINE HYDROCHLORIDE

Therapeutic Function: Tranquilizer; Anticholinergic

Chemical Name: α-Hydroxy-α-phenylbenzene acetic acid-2-(diethylamino) ethyl ester hydrochloride

Common Name: β-Diethylaminoethylbenzilate hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 57-37-4; 302-40-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Suavitil	Merck Sharp and Dohme	US	1957
Phebex	Hoechst	US	1958

Trade Name	Manufacturer	Country	Year Introduced
Cedad	Recordati	Italy	-
Cevanol	I.C.I.	UK	-
Deprol	Wallace	US	-
Lucidil	Smith and Nephew	UK	-
Morcain	Tatsumi	Japan	-
Nutinal	Boots	UK	-
Parasan	Medix	Spain	-
Parpon	Santen	Japan	-
Phobex	Lloyd	-	-
Phobex	Dabnev and Westerfield	-	-

Raw Materials

Ethyl benzilate
β-Diethylaminoethanol
Sodium
Hydrogen chloride

Manufacturing Process

114 parts of ethyl benzilate, 175 parts of β-diethylaminoethanol and 0.2 part of metallic sodium were placed in a flask attached to a total-reflux variable take-off fractionating column. The pressure was reduced to 100 mm and heat was applied by an oil bath the temperature of which was slowly raised to 90°C. During three hours of heating 17 parts of ethanol distilled (35.5°C). When the distillation of the ethanol became slow, the bath temperature was raised to 120°C. When the vapor temperature indicated distillation of the amino alcohol the take off valve was closed and the mixture was refluxed for one hour. At the end of this period the vapor temperature had dropped and two more parts of ethanol were distilled, The remaining aminoalcohol was slowly distilled for three hours. The pressure was then reduced to 20 mm and the remainder of the aminoalcohol distilled at 66°C. During the reaction the color of the solution changed from yellow to deep red. The residue was dissolved in 500 parts of ether, washed once with dilute brine, and three times with water, dried over sodium sulfate and finally dried over calcium sulfate. 500 parts of a saturated solution of HCl in absolute ether was added and the resulting precipitate filtered. Dry HCl gas was passed into the filtrate to a slight excess and the precipitate again filtered. The combined precipitates were washed with cold acetone. The 106 parts of product was purified by recrystallization from acetone as fine white crystals which melt at 177°-178°C.

References

Merck Index 1028
Kleeman and Engel p.76
PDR p.1874
OCDS Vol.1 p.93 (1977)
DOT 9 (6) 241 (1973)
I.N. p.120
Hill, A.J. and Holmes, R.B.; US Patent 2,394,770; February 12, 1946; assigned to American Cyanamid

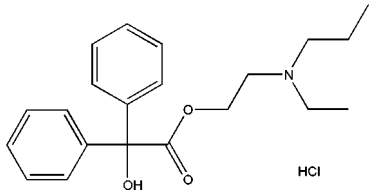
BENAPRYZINE HYDROCHLORIDE

Therapeutic Function: Anticholinergic, Antiparkinsonian

Chemical Name: α-Hydroxy-α-phenylbenzeneacetic acid 2-(ethylpropylamino)ethyl ester hydrochloride

Common Name: 2-Ethylpropylaminoethyl diphenylglycollate hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 3202-55-9; 22487-42-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Brizin	Beecham	UK	1973

Raw Materials

Sodium methoxide
Hydrogen chloride
2-Ethylpropylaminomethanol
Methyl α,α-diphenyl glycollate

Manufacturing Process

A methanolic solution of sodium methoxide [from sodium (0.2 gram) and dry methanol (3 ml)] was added dropwise during 20 minutes to a boiling solution of methyl α,α-diphenylglycollate (11 grams) and 2-ethylpropylaminoethanol (6 grams) in light petroleum (150 ml, BP 80°-100°C) and the methanol that separated was removed by using a Dean and Starke apparatus. At the end of 5 hours no further separation of methanol occurred and the reaction mixture after being washed with water (3 x 20 ml) was extracted with 1N hydrochloric acid (3 x 30 ml).

The acid extracts (after washing with 50 ml ether) were made alkaline with aqueous 5 N sodium hydroxide solution, the liberated base was extracted into ether (4 x 50 ml) and the ether extracts were dried ($MgSO_4$). Treatment of the extracts with hydrogen chloride gave the hydrochloride (11 grams, 70%), which was obtained as rectangular plates, MP 164° to 166°C, after several crystallizations from butanone.

References

Merck Index 1030
Kleeman and Engel p. 77

OCDS Vol.2 p.74 (1980)
DOT 9 (6) 241 (1973)
I.N. p.121
Mehta, M.D. and Graham, J.; US Patent 3,746,743; July 17, 1973; assigned to Beecham Group Limited

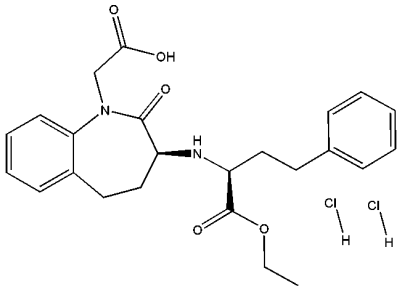
BENAZEPRIL HYDROCHLORIDE

Therapeutic Function: Antihypertensive

Chemical Name: 1H-1-Benzazepine-1-acetic acid, 2,3,4,5-tetrahydro-3-((1-(ethoxycarbonyl)-3-phenylpropyl)amino)-2-oxo-, monohydrochloride,(S-(R*,R*))-, monohydrochloride

Common Name: Benazepril hydrochloride; Labopal

Structural Formula:



Chemical Abstracts Registry No.: 86541-74-4; 86541-75-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Lotensin	Novartis	-	-
Benazepril hydrochloride	DSM Catalytica Pharmaceuticals, Inc.	-	-
Cibace	Ciba-Geigy	-	-
Cibacen	Novartis	-	-
Labopal	Morrith	-	-
Labopal	Beecham	-	-
Normacen	Normal	-	-
Tensanil	CRINOS Industria Farmacobiologica S.p.A	-	-
Zinadril	ERREKAPPA EUROTERAPICI	-	-

Raw Materials

Sodium azide
1,2,4,5-Tetrahydrobenzo[b]azepin-2-one
Sodium cyanoborohydride
2-Oxo-4-phenylbutyric acid ethyl ester

Manufacturing Process

The synthesis of benzazepril based on a benzazepinone. It started by chlorination of lactam - 1,2,4,5-tetrahydrobenzo[b]azepin-2-one to the dichloro derivative 3,3-dichloro-1,2,4,5-tetrahydrobenzo[b]azepin-2-one. Catalytic reduction removed one of the gem chloro substituents to give 3-chloro-1,2,4,5-tetrahydrobenzo[b]azepin-2-one; the halogen was then displaced with sodium azide to give 3-azido-1,3,4,5-tetrahydrobenzo[b]azepin-2-one. Alkylation of the amide with ethyl bromoacetate in the presence of base yielded the ester (3-azido-2-oxo-2,3,4,5-tetrahydrobenzo[b]azepin-1-yl)acetic acid ethyl ester. Hydrogenation then converted the azide to an amino group to give 3-amino-2-oxo-2,3,4,5-tetrahydrobenzo[b]azepin-1-yl)acetic acid ethyl ester. It was then resolved by classical salt formation and crystallization. Saponification of the S enantiomer - S-(3-amino-2-oxo-2,3,4,5-tetrahydrobenzo[b]azepin-1-yl)acetic acid ethyl ester with sodium hydroxide afforded (3-amino-2-oxo-2,3,4,5-tetrahydrobenzo[b]azepin-1-yl)acetic acid. Reductive alkylation of it with 2-oxo-4-phenylbutyric acid ethyl ester and sodium cyanoborohydride gave the desired product as 70:30 mixture of diastereoisomers. The isolation of the predominant isomer gave benazepril. The epimerization occurred thermally and therefore required a sufficiently high temperature. The high temperature condition can be achieved by either using a high boiling-point solvent such as xylene or by heating the reaction mixture under pressure to increase its boiling-point temperature. Good results can be achieved in both polar and non-polar solvent systems. For example, both p-xylene and ethylene glycol-water systems are found suitable to conduct this process. The crude product acid 3-[(1-ethoxycarbonyl)-3-phenyl-(1S)-propylamino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid was heated to reflux temperature for 30 hours in p-xylene. The mixture was cooled down to room temperature. Solvent removal resulted in a solid, which was then dried at reduced pressure to give a 98:2 diasteriomeric mixture as determined by HPLC, MP: 287°-290°C. IR and 1H-NMR spectrum analysis. was confirmed the structure of product.

References

Lednicer D., The Organic Chemistry of Drug Synthesis; v. 5; pp. 135-136; 1995; Wiley and Sons Inc.
W-Hong Tseng et al.; US Patent No. 6,548,665B2; April 15, 2003; Assigned to Scinopharm, Taiwan, Ltd., Tainan (CN)

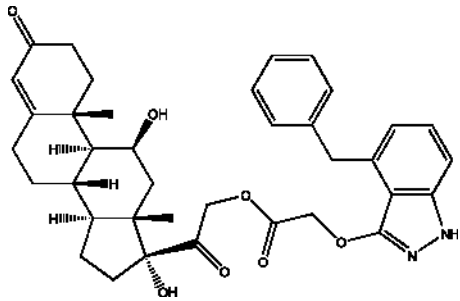
BENDACORT

Therapeutic Function: Glucocorticoid

Chemical Name: 21-Ester of [(1-benzyl-1H-indazol-3-yl-oxy]-acetic acid with 11β,17α-dihydroxy-pregn-4-ene 3,20-dione

Common Name: Ester of Bendazac with hydrocortisone

Structural Formula:



Chemical Abstracts Registry No.: 53716-43-1

Trade Name	Manufacturer	Country	Year Introduced
Versacort	Angelini	Italy	1978

Raw Materials

Hydrocortisone
Bendazac chloride ([(1-benzyl-1H-indazol-3-yl)oxy]acetic acid chloride)

Manufacturing Process

Hydrocortisone (25 g) and bendazac chloride (21 g) are suspended in anhydrous dioxane (250 ml). Pyridine (6 ml) is added and the solution is kept under stirring for 2 hours at room temperature. Pyridine hydrochloride which separates is filtered and the clear dioxane solution is added, under strong stirring, to a solution of sodium bicarbonate (20 g) in distilled water (2,500 ml). The colorless precipitate which is formed is filtered, washed with water and dried on a porous plate. The substance crystallizes from ethanol. Needles. MP 174°-176°C. Yield: 75%.

References

Merck Index 4689
Baiocchi, L.; US Patent 4,001,219; January 4, 1977

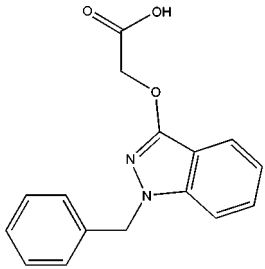
BENDAZAC

Therapeutic Function: Antiinflammatory

Chemical Name: [(1-Benzyl-1H-indazol-3-yl)oxy]acetic acid

Common Name: Bendazolic acid

Structural Formula:



Chemical Abstracts Registry No.: 20187-55-7

Trade Name	Manufacturer	Country	Year Introduced
Versus	Angelini	Italy	1970
Zildasac	Chugai	Japan	1979
Hubersil	Hubber	Spain	-
Versus	Werfft Chemie	Austria	-

Raw Materials

1-Benzyl-3-oxy-indazole
Chloroacetonitrile
Hydrogen chloride

Manufacturing Process

11 grams of the sodium salt of 1-benzyl-3-oxy-indazole are dissolved in 70 ml of absolute ethanol by heating the resulting solution to boiling and stirring. 3.5 grams of chloroacetonitrile dissolved in 5 ml of absolute ethanol are then added within 2-3 minutes and after 10 minutes a further portion of 1.7 grams of chloroacetonitrile are added. The reaction is finally brought to completion with an additional 45 minutes of boiling. The reaction mixture is allowed to cool at room temperature and is then filtered. The alcohol solution is evaporated to dryness under reduced pressure; the resulting residue is taken up again with ether and the ether solution is washed in sequence with dilute HCl, water, NaOH and water. The solution is dried on Na_2SO_4 and then the solvent is removed. The residue consists of (1-benzyl-indazole-3)oxyacetonitrile which is crystallized from methanol. It has a melting point of 93°C.

1 gram of the (1-benzyl-indazole-3)oxyacetonitrile is pulverized and is added with stirring to 5 ml concentrated HCl. By heating on a boiling water bath for 2-3 minutes, the nitrile product melts and soon thereafter solidifies. The precipitate is cooled, then filtered and washed well in a mortar with water. After dissolution in 10% Na_2CO_3 it is precipitated again with dilute HCl. After

crystallization from ethanol, 1-benzyl-indazole-3-oxyacetic acid is obtained. It has a melting point of 160°C.

References

Merck Index 1033
Kleeman and Engel p.79
OCDS Vol.2 p.351 (1980)
I.N. p.121
Palazzo, G.; US Patent 3,470,194; September 30, 1969; assigned to Aziende Chimiche Riunite Angelini, Francesco ACRAF SPA, Italy

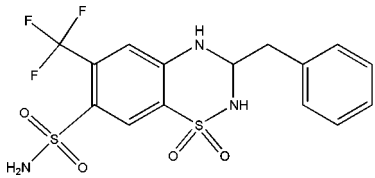
BENDROFLUMETHIAZIDE

Therapeutic Function: Diuretic, Antihypertensive

Chemical Name: 3,4-Dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

Common Name: Benzydroflumethiazide; Benzylhydroflumethiazide; Bendrofluazide

Structural Formula:



Chemical Abstracts Registry No.: 73-48-3

Trade Name	Manufacturer	Country	Year Introduced
Naturetin	Squibb	US	1959
Sinesalin	I.C.I.	W. Germany	-
Naturine Leo	Leo	France	1961
Benuron	Bristol	US	1965
Aprinox	Boots	UK	-
Benzide	Protea	Australia	-
Berkozide	Berk	UK	-
Bristuric	Bristol	US	-
Bristuron	Bristol	-	-
Centyl	Leo	Denmark	-
Centyl	Leo-Sankyo	Japan	-
Corzide	Squibb	US	-
Neo-Naclex	Glaxo	UK	-
Neo-Rontyl	Leo	Denmark	-

Trade Name	Manufacturer	Country	Year Introduced
Notens	Farge	Italy	-
Pluryl	Leo	Denmark	-
Polidiuril	Bios	Italy	-
Poliuron	Lepetit	Italy	-
Rauzide	Squibb	US	-
Salural	ICE	Italy	-
Salures	Ferrosan	Denmark	-
Seda-Repicin	Boehringer Ingelheim	W. Germany	-
Sinesalin	Arcana	Austria	-
Sodiuretic	Squibb	Italy	-
Tensionorm	Leo	France	-
Urizid	Rekah	Israel	-

Raw Materials

α,α,α-Trifluoro-m-toluidine
ω-Ethoxystyrene
Phenylacetaldehyde
Ammonia
Chlorosulfonic acid

Manufacturing Process

The process is described in US Patent 3,392,168 as follows:

(A) Preparation of 5-Trifluoromethylaniline-2,4-Disulfonylchloride - 113 ml of chlorosulfonic acid is cooled in an ice bath, and to the acid is added dropwise while stirring 26.6 grams of α,α,α-trifluoro-m-toluidine. 105 grams of sodium chloride is added during 1-2 hours, where after the temperature of the reaction mixture is raised slowly to 150° - 160°C which temperature is maintained for three hours. After cooling the mixture, ice-cooled water is added, whereby 5-trifluoromethylaniline-2,4-disulfonyl chloride separates out from the mixture.

(B) Preparation of 5-Trifluoromethyl-2,4-Disulfamylaniline - The 5-trifluoromethylaniline-2,4-disulfonyl chloride obtained in step (A) is taken up in ether and the ether solution dried with magnesium sulfate. The ether is removed from the solution by distillation, the residue is cooled to 0°, and 60 ml of ice-cooled, concentrated ammonia water is added while stirring. The solution is then heated for one hour on a steam bath and evaporated in vacuo to crystallization. The crystallized product is 5-trifluoromethyl-2,4-disulfamylaniline, which is filtered off, washed with water and dried in a vacuum-desiccator over phosphorus pentoxide. After recrystallization from a mixture of 30% ethanol and 70% water, the compound has a MP of 247°-248°C.

(C) Preparation of 3-Benzyl-6-Trifluoromethyl-7-Sulfarnyl-3,4-Dihydro-1,2,4-Benzothiadiazine-1,1-Dioxide - 6.4 grams of 5-trifluoromethyl-2,4-disulfamylaniline is dissolved in 12 ml of dioxane, 2.7 ml of phenylacetaldehyde and a catalytic amount of p-toluenesulfonic acid are added. After boiling for a short time under reflux, the reaction mixture crystallizes, and, after filtration and recrystallization from dioxane, the desired

product is obtained with a MP of 224.5°-225.5°C.

(D) Alternative to (C) - 9.6 grams of 5-trifluoromethyl-2,4-disulfarnylaniline and 4.9 grams of ω-ethoxystyrene are dissolved in 35 ml of n-butanol. 0.5 grams of p-toluenesulfonic acid is added, and the mixture is heated on a steam bath while stirring. When the solution is clear, 55 ml of hexane is added, whereafter the mixture is heated further for one and a half hours. After cooling, the substance identical to that of Example (C) is filtered off and has a MP of 222°-223°C.

Sterile compositions containing Bendroflumethiazide for parenteral administration may be prepared as described in US Patent 3,265,573.

References

Merck Index 1036
Kleeman and Engel p.79
PDR pp.1741, 1753, 1767
OCDS Vol.1 p.358 (1977)
DOT 16(3) 94 (1980)
I.N. p.122
REM p.938
Goldberg, M.; US Patent 3,265,573; August 9, 1966; assigned to E.R. Squibb and Sons, Inc.
Lund, F., Lyngby, K. and Godtfredsen, W.O.; US Patent 3,392,168; July 9, 1968; assigned to Lovens Kemiske Fabrik ved A. Kongsted, Denmark

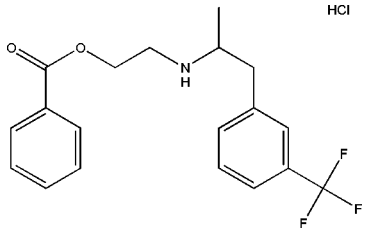
BENFLUOREX HYDROCHLORIDE

Therapeutic Function: Antihyperlipidemic, Cardiovascular

Chemical Name: 1-(m-Trifluoromethylphenyl)-2-(β-benzoyloxyethyl) aminopropane hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 23642-66-2; 23602-78-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Mediator	Servier	France	1976
Mediaxal	Stroder	Italy	1981
Mediaxal	Servier	Switz.	1982
Minolip	Chiesi	Italy	-

Raw Materials

1-(m-Trifluoromethylphenyl)-2-(β-hydroxyethyl)amino propane
Benzoyl chloride

Manufacturing Process

To a solution of 24.7 parts of 1-(m-trifluoromethylphenyl)-2-(β-hydroxyethyl)amino propane in 140 parts of anhydrous benzene, there were added successively 15 parts of 4.7N hydrochloric ether and a solution of 14 parts of benzoyl chloride in 24 parts of anhydrous benzene. The addition required 10 minutes, the reaction mixture was then refluxed for 8 hours.

The solid product was collected by filtration and after recrystallization from 230 parts of ethyl acetate, there were obtained 15 parts of 1-(m-trifluoromethylphenyl)-2-(β-benzoyloxyethyl)amino propane hydrochloride melting at 161°C.

10 parts hydrochloride are put in suspension in 100 parts of water, 80 parts ether are added, then 10 parts of a concentrated solution of ammonium hydroxide. The mixture is stirred a few minutes until the salt is dissolved, then the ethered solution is poured off and dried. After the ether is eliminated, 9 parts of 1-(m-trifluoromethylphenyl)-2-(β-benzoyloxyethyl)amino propane are obtained; the base is a colorless oil.

References

Merck Index 1037
DFU 2 (8) 557 (1976)
Kleeman and Engel p.80
DOT 13 (1) 12 (1977)
I.N. p.122
Beregi, L. Hugon, P. and Le Douarec, J.C.; US Patent 3,607,909; September 21, 1971; assigned to Science Union et Cie Societe Francaise de Recherche Medicale

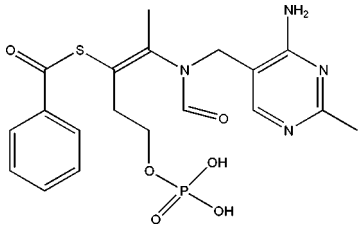
BENFOTIAMINE

Therapeutic Function: Analgesic

Chemical Name: Benzoic acid, thio-, S-ester with N-((4-amino-2-methyl-5-pyrimidinyl)methyl)-N-(4-hydroxy-2-mercapto-1-methyl-1-butenyl) formamide dihydrogen phosphate (ester)

Common Name: Benfotiamine; Benphothiamin; Benzoylthiamine monophosphate

Structural Formula:



Chemical Abstracts Registry No.: 22457-89-2

Trade Name	Manufacturer	Country	Year Introduced
Biotamin	Sankyo	-	-
Vitanevril	Sanofi Winthrop	-	-
Milgamma	Worwag Pharma GmbH and Co	-	-
Benfogamma	Worwag Pharma GmbH and Co	-	-
Bio-Towa	Towa Pharmaceutical Co., Ltd.	-	-
Benfothiamin	Shanghai BR Chemical Co., Ltd.	-	-
Benfotiamin	Shanghai Lansheng Corporation	-	-

Raw Materials

Phosphoric acid
Thiamine hydrochloride
Benzoyl chloride

Manufacturing Process

28.6 g 84% phosphoric acid was heated to temperature about 270°C. After cooling to 100°C 4 g thiamine hydrochloride (vitamin B_1 hydrochloride) was added and left at temperature 100°C before an isolation of HCl was ended. After adding of an ice water and acetone, phosphate ester of vitamin B_1 was fallen. The precipitate was dissolved in 17 ml 1 N HCl and stood at ambient temperature 7 days for a hydrolysis. Then a solution was with acetone diluted and the mixture was cooled, whereupon vitamin B_1 monophosphate hydrochloride was isolated.

The solution of 4.3 parts vitamin B1 monophosphate hydrochloride in 16 parts of water was diluted with 11 parts 15% NaOH, 2.1 parts benzoyl chloride was dropwise added with stirring and cooling. The obtained mixture was neutralized, evaporated in vacuum, acidified with concentrated HCl to pH 3.5-4, whereupon a crude S-derivative of vitamin B_1 monophosphate ester was precipitated. The product was suspended in water, was bringing with NaOH to pH 7 and was acidified to pH 4. 3.4 g refined S-benzoylthiamine O-monophosphate was prepared; MP: 165°C (with decomposition).

References

Sankyo Kabushiki Kaisha, Tokyo; D.B. Patent No. 1,130,811; April 14, 1960

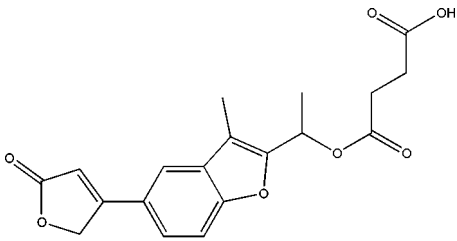
BENFURODIL HEMISUCCINATE

Therapeutic Function: Coronary vasodilator; Cardiotonic

Chemical Name: Succinic acid monoester with 4-[2-(1-hydroxyethyl)-3-methyl-5-benzofuranyl]-2(5H)-furanone

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 3447-95-8

Trade Name	Manufacturer	Country	Year Introduced
Eucilat	Clin Midy	France	1970
Clinodilat	Mack-Midy	W. Germany	1981
Eucilat	Midy	Italy	1981
Eucilat	Clin-Comar-Byla	France	-

Raw Materials

Aluminum chloride
Succinic anhydride
Acetyl chloride
4-(4-Methoxyphenyl)-2-oxo-2,5-dihydrofuran
Chloroacetone
Hydrogen chloride
Sodium borohydride

Manufacturing Process

(A) Preparation of 4-(3-Acetyl-4-Hydroxyphenyl)-2-Oxo-2,5-Dihydrofuran (1567 CB): A solution of 57 grams of 4-(4-methoxyphenyl)-2-oxo-2,5-dihydrofuran (0.3 mol) in 300 ml of methylene chloride is added slowly to 200 grams of anhydrous powdered aluminum chloride, while stirring and cooling in a bath of iced water. When this is completed, one removes the bath and leaves the reagents in contact for 10 minutes, and then introduces 72 grams of acetyl chloride at a speed sufficient to maintain refluxing of the solvent. One subsequently heats under reflux for 3 hours 30 minutes, decomposes by pouring on to crushed ice, filters off the crystalline product and washes it with water. 56 g, MP = 200°C. Yield: 80%. The product is recrystallized from acetic acid and then melts at 201°-202°C.

(B) Preparation of 4-[3-Acetyl-4-(2-Oxopropyloxy)Phenyl]-2-Oxo-2,5-Dihydrofuran: 5.45 grams (0.025 mol) of compound 1567 CB prepared according to (A) dissolved in 50 ml of dimethyl formamide is stirred at room temperature for 15 minutes with 5 grams of potassium carbonate and 1 gram of sodium iodide, and 5 grams of chloracetone are then added drop by drop. The temperature spontaneously rises a few degrees. The disappearance of the phenolic compound is checked by testing with an alcoholic solution of ferric chloride; this test should be negative at the end of the reaction (approximately 2 hours). One then dilutes with 10 volumes of water, filters the product which crystallizes out under these conditions and recrystallizes it from acetic acid. It has the form of yellow needles (4 grams yield: 63%). MP, = 155°-157°C.

(C) Preparation of 2-Acetyl-3-Methyl-5-(2-Oxo-2,5-Dihydro-4-Furyl)Benro[b]Furan (3556 CB): (1) A suspension of 2 grams of the compound prepared according to (B) in 20 ml of concentrated hydrochloric acid, is heated to about 50°C, just until it dissolves. There after it is heated for 2 minutes to 70°C, just until precipitation commences. The mixture is allowed to cool, diluted with water, filtered, the residue washed, dried, and sublimed at 200°C and 0.1 mm pressure. 1.4 grams of product (Yield: 70%) is obtained. MP_c=218°-221°C. A second sublimation produces a chemically pure product. MP_c= 221°-222°C. (2) Compound 1567 CB and chloracetone are caused to react as in (B), the mineral salts subsequently filtered, 12 ml of concentrated hydrochloric acid are added to the solution in dimethyl formamide without dilution with water, and the mixture heated for 40 minutes on a water bath. The product crystallizes in the warm mixture, the mixture is cooled to room temperature, filtered, the residue washed with water and crystallized from acetic acid. MP_c= 222°C. Yield: 60% based on compound 1567 CB.

(D) Preparation of 2-(1-Hydroxyethyl)-3-Methyl-5-(2-Oxo-2,5-Dihydro-4-Furyl)Benzo[b]-Furan (3574 CB): 13.2 grams of compound 3556 CB of which the preparation is described in (C) are treated successively with 66 ml of methylene chloride, 27 ml of methanol and, with stirring, 1.6 grams of sodium borohydride added in stages. The reaction takes 1 hour. The mixture is poured into water acidified with a sufficient amount of acetic acid, the solvents are stripped under vacuum, the crystalline product removed, washed with water, and recrystallized from ethyl acetate. Yield: 90%. MP_k= 158°C.

(E) Preparation of 2-(1-Succinyloxyethyl)-3-Methyl-5-(2-Oxo--2,5-Dihydro-4-

Furyl)Benzo[b]-Furan (409_1, CB): 8.65 grams of compound 3574 CB in 43 ml of pyridine are warmed for 30 minutes, on a water bath, with succinic anhydride. At the end of this, the pyridine is stripped off in vacuo. The mixture is treated with dilute sulfuric acid and with ether, the crystalline product filtered off, washed with water and with ether, and recrystallized from ethyl acetate (9.35 grams). MP_c=144°C (measured after drying at 90°C and 0.1 mm). Yield: 77%. The product yields an equimolecular compound with morpholine. MP_c=136°C (from ethyl acetate).

References

Kleeman and Engel p.81
OCDS Vol.2 p.355 (1980)
DOT 6 (6) 203 (1970)
I.N. p. 123
Schmitt, J.; US Patent 3,355,463; November 28, 1967; assigned to Etablissements Clin-Byla, France

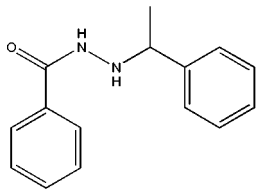
BENMOXIN

Therapeutic Function: Antidepressant

Chemical Name: 1-Benzoyl-2-(alpha-methylbenzyl)hydrazine

Common Name: Benmoxin; Mebamoxine

Structural Formula:



Chemical Abstracts Registry No.: 7654-03-7

Trade Name	Manufacturer	Country	Year Introduced
Neuralex	Millot	-	-

Raw Materials

Acetylhydrazine	Acetophenone
Hydrogen	Palladium on carbon

Manufacturing Process

A mixture of 29.6 parts of acetylhydrazine, 48 parts of acetophenone and 140 parts of ethanol is heated under reflux for 18 hours and is then cooled to 20-

25°C and filtered. The solid residue, M.P. 135-136°C, is washed with diethyl ether and dried at 40°C. 28.5 parts of this dried product in 180 parts of methanol is shaken in an atmosphere of hydrogen under a pressure of 100 atmospheres and at a temperature of 25°C in the presence of 3 parts of a 5% palladium on carbon catalyst until the theoretical amount of hydrogen is absorbed. The mixture is filtered and the filtrate is evaporated. The residue is fractionally distilled under reduced pressure and there is thus obtained 1-(α-methylbenzyl)-2-acetylhydrazine, B.P. 182-186°C/15 mm, M.P. 72-74°C.

References

Merck Index, Monograph number: 1072, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Crowther A.F. et al.; US Patent No. 3,297,530; Jan. 10, 1967; Assigned to Imperial Chemical Industrie Limited, London, England
Brevet DInvention FR Patent No. 1,314,362; Dec. 22, 1962; Assigned to Imperial Chemical Industries Limited residant en Gdande-Bretagne

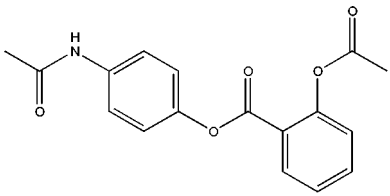
BENORYLATE

Therapeutic Function: Analgesic, Antiinflammatory, Antipyretic

Chemical Name: 2-(Acetyloxy)benzoic acid 4-(acetylamino)phenyl ester

Common Name: Fenasprate; p-N-Acetamidophenyl acetylsalicylate

Structural Formula:



Chemical Abstracts Registry No.: 5003-48-5

Trade Name	Manufacturer	Country	Year Introduced
Benortan	Winthrop	Switz.	-
Benoral	Winthrop	UK	1972
Benortan	Winthrop	W. Germany	1975
Benortan	Winthrop	France	1976
Benorile	Rubio	Spain	-
Benortan	Pharmacal	Finland	-
Bentum	Inpharzam	Belgium	-
Salipran	Bottu	France	-

Trade Name	Manufacturer	Country	Year Introduced
Sinalgin	Robin	Italy	-
Triadol	Sterling Heath	UK	-
Winorylate	Sterwin Espanola	Spain	-

Raw Materials

N-Acetyl-p-aminophenol
Acetyl salicoyl chloride

Manufacturing Process

Example 1: 65 grams of N-acetyl-p-aminophenol were slurried with 400 ml of water and cooled to 10°C. 125 ml of 20% sodium hydroxide were slowly added to the mixture with stirring, the temperature being maintained between 10°and 15°C. To the solution obtained, 75 grams of acetyl salicoyl chloride were added with vigorous stirring over a period of 1/2 hr, the solution being maintained at a temperature of about 10°C. Towards the end of the reaction the pH was checked and adjusted to greater than 10 by the addition of a small amount of 20% sodium hydroxide. After all the acid chloride had been added, vigorous stirring was continued for half an hour during which time the crude product separated out. This product was filtered off, washed thoroughly with water and recrystallized from ethanol.

Example 2: 65 grams of sodium N-acetyl-p-aminophenol were slurried with 500 grams of dry benzene and 80 grams of acetyl salicoyl chloride added. The mixture was heated under reflux for four hours and filtered hot. The excess benzene was removed under vacuum and the crude acetyl salicyclic acid ester of N-acetyl-p-aminophenol crystallized from ethanol.

References

Merck Index 1043
Kleeman and Engel p.82
DOT 8 (6) 208 (1972)
I.N. p.123
Robertson, A.; US Patent 3,431,293; March 4, 1969; assigned to Sterling Drug, Inc.

BENOXAPROFEN

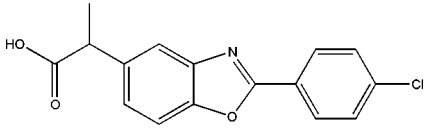
Therapeutic Function: Antiinflammatory, Analgesic

Chemical Name: 2-(2-p-Chlorophenyl-5-benzoxazolyl)propionic acid

Common Name: -

Chemical Abstracts Registry No.: 51234-28-7

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Opren	Dista Lilly	UK	1980
Coxigon	Lilly	W. Germany	1981
Inflamid	Lilly	France	1981
Coxigon	Lilly	Switz.	1982
Coxigon	Schweiz. Serum I	Switz.	1982
Oraflex	Lilly	US	1982
Bexopron	Lilly	-	-

Raw Materials

Ethyl-2-(3-hydroxy-4-amlnophenyl)propionate
p-Chlorobenzoyl chloride

Manufacturing Process

The 6-benzoxazolyl analog of the 5-benzoxazolyl product is prepared as follows:

(a) Ethyl 2-(2-p-chlorophenyl-6-benzoxazolyl)propionate: A solution of ethyl 2-(3-hydroxy-4-aminophenyl)propionate (2.5 g) in pyridine (15 ml) was treated with p-chlorobenzoyl chloride (1.65 ml) at 5°C. After stirring for 2 hours at room temperature the solution was evaporated to dryness.

The residue was heated at 220°C until no more water was evolved, then was allowed to cool. This yielded ethyl 2-(2-p-Chlorophenyl-6-benzoxazolyl)propionate.

(b) 2-(2-p-Chlorophenyl-6-benzoxazolyl)propionic acid: A solution of ethyl 2-(2-chlorophenyl-6-benzoxazolyl)propionate (4 g) in aqueous sodium hydroxide (30 ml) was heated on a steam bath for one-half hour. On cooling the black solution was washed with chloroform. On acidification of the black solution with hydrochloric acid the mixture was extracted with chloroform. This solution on evaporation yielded 2-(2-p-chlorophenyl-6-benzoxazolyl)propionic acid, MP 196°C.

References

Merck Index 1044
DFU 2 (9)565 (1977)
Kleeman and Engel p. 82
OCDS Vol. 2 p. 356 (1980)
DOT 16 (9) 283 (1980)

I.N.p. 123
Evans, D., Dunwell, D.W. and Hicks, A.; US Patent 3,912,748; October 14, 1975; assigned to Lillv Industries Ltd.
Evans, D., Dunwell, D.W. and Hicks, T.A.; US Patent 3,962,441; June 8, 1976; assigned to Lilly Industries, Ltd.
Evans, D., Dunwell, D.W. and Hicks, T.A.; US Patent 3,962,452; June 8, 1976; assigned to Lilly Industries, Ltd.

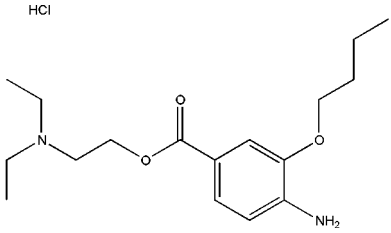
BENOXINATE HYDROCHLORIDE

Therapeutic Function: Local anesthetic

Chemical Name: 4-Amino-3-butoxybenzoic acid 2-(diethylamino)ethyl ester hydrochloride

Common Name: Oxybuprocaine

Structural Formula:



Chemical Abstracts Registry No.: 5987-82-6; 99-43-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Dorsacaine HCl	Dorsey	US	1953
Novesine	Marck-Chibret	France	1960
Anemixin	Zeria	Japan	-
Benoxil	Santen	Japan	-
Benoxinate	Barnes Hind	US	-
Cebesine	Chauvin-Blache	France	-
Colirio Anestesico	Collado	Spain	-
Collu-Blache	Chauvin-Blache	France	-
Conjuncain	Mann	W. Germany	-
Lacrimin	Santen	Japan	-
Minims Benoxinate	Smith and Nephew	UK	-
Novesin	Wander	Switz.	-
Novesin	Dispersa	Switz.	-
Prescaina	Llorens	Spain	-
Scarlene	Chauvin-Blache	France	-

Raw Materials

3-Oxy-4-nitrobenzoic acid
Potassium hydroxide
Thionyl chloride
Hydrogen
Ethanol
Butanol
Diethylaminoethanol
Hydrogen chloride

Manufacturing Process

25 grams of 3-oxy-4-nitrobenzoic acid are esterified (ethyl ester) and 26 grams of the ester are dissolved in 200 cc of absolute ether and treated with 7 grams of caustic potash in 20 cc of absolute methanol. The red potassium phenolate with 7 grams of pure butyl bromide and 7 grams of absolute alcohol are heated for 5 hours in the oven to 150°C. When cool, the alcohol is evaporated in vacuo and the butoxy-nitrobenzoic acid ethyl ester is precipitated with water. The substance is sucked off and saponified for 15 minutes with a solution of 2.5 grams of caustic potash in 30 cc of alcohol on a water bath. The alcohol is evaporated in vacuo and the 3-butoxy-4-nitrobenzoic acid is precipitated with hydrochloric acid. It forms needles which melt at 174°C. 7.9 grams of dry acid are boiled for 45 minutes under a reflux condenser with 25 cc of thionyl chloride. The excess of thionyl chloride is then removed in vacuo, and the oil is distilled. The acid chloride has a yellow color and solidifies.

7.3 grams of the acid chloride are treated with 6.6 grams of diethyl-amino-ethanol in 20 cc of absolute benzene. The mixture is then warmed for 1 hour on a water bath. When cold, it is treated with a solution of soda and washed with ether. After drying over potash, the ether and benzene are removed by distillation and 3-butoxy-4-nitrobenzoic acid diethylamino-ethyl ester is obtained, having a BP 215°C/2.5 mm.

5.0 grams of this product are hydrogenated in absolute alcohol solution with fresh Raney nickel. When the absorption of hydrogen ceases (5 hours), the solution is filtered and the alcohol evaporated in vacuo. The 3-butoxy-4-aminobenzoic acid diethyl-amino-ethyl ester boils at 215°-218°C at 2 mm pressure; it is an almost colorless oil.

By precipitation of a solution of the ester in absolute ether with hydrogen chloride gas, the dihydrochloride is obtained; upon recrystallization from alcohol/ether, it forms crystals which melt at 196°-197°C.

References

Merck Index 1045
Kleeman and Engel p. 671
I.N. p.716
REM p. 1057
Dr. A. Wander, AG, Switzerland; British Patent 654,484; June 20,1951

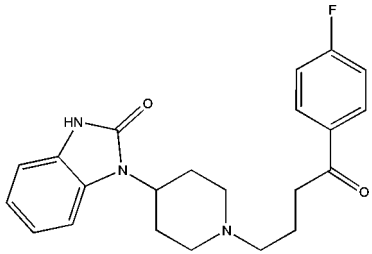
BENPERIDOL

Therapeutic Function: Tranquilizer

Chemical Name: 1-[1-[4-(4-Fluorophenyl)-4-oxobutyl]-4-piperidinyl]-1,3-dihydro-2H-benzimidazol-2-one

Common Name: Benzperidol

Structural Formula:



Chemical Abstracts Registry No.: 2062-84-2

Trade Name	Manufacturer	Country	Year Introduced
Frenactil	Clin-Comar-Byla	France	1965
Gliahimon	Tropon	W. Germany	1966
Anquil	Janssen	UK	1973

Raw Materials

γ-Chloro-4-fluorobutyrophenone
1-(4-Piperidyl)-2-benzimidazoline HCl

Manufacturing Process

A mixture of 3.4 parts of γ-chloro-4-fluorobutyrophenone, 4 parts of 1-(4-piperidyl)-2-benzimidazolinone hydrochloride, 6 parts of sodium carbonate and 0.1 part of potassium iodide in 176 parts of 4-methyl-2-pentanone is stirred and refluxed for 48 hours. The reaction mixture is cooled and 120 parts of water is added. The separated organic layer is dried over magnesium sulfate and the solvent is evaporated to leave an oily residue which is dissolved in dilute hydrochloric acid and boiled. The acidic solution is filtered and cooled at room temperature whereupon there crystallizes from solution 1-(1-[γ-(4-fluorobenzoyl)propyl] -4-piperidyl)-2-benzimidazolinone hydrochloride hydrate melting at about 134°-142°C.

References

Merck Index 1046
Kleeman and Engel p. 83

OCDS Vol. 2 p. 290 (1980)
I.N.p. 124
British Patent 989,755; April 22, 1965; assigned to N.V. Research Laboratorium Dr. C. Janssen
Janssen, P.A.J.: US Patent 3,161,645; December 15, 1964; assigned to Research Laboratorium Dr. C. Janssen N.V.

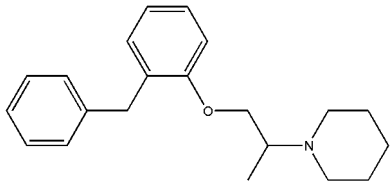
BENPROPERINE

Therapeutic Function: Antitussive

Chemical Name: 1-[1-Methyl-2-[2-(phenylmethyl)phenoxy]ethyl]piperidine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 2156-27-6

Trade Name	Manufacturer	Country	Year Introduced
Tussafug	Medipharm	Switz.	-
Blascorid	Guidotti	Italy	1968
Flaveric	Pfizer Taito	Japan	1970
Tussafugsaft	Robugen	W. Germany	1976
Pirexyl	Pharmacia	Sweden	-
Blascorid	Pharmacia	Sweden	-
Pectipront	Mack	W. Germany	-

Raw Materials

o-Benzylphenoxy-β-chloropropane
Piperidine

Manufacturing Process

A mixture of 26.1 g of o-benzylphenoxy-β-chloropropane and 17 g of piperidine is refluxed over a period of 32 hours until the temperature is about 124°C and a nearly solid mixture is formed due to the precipitation of a salt. The mixture is then refluxed over a period of 48 hours at about 160°C and the reaction product obtained is cooled and dissolved in methanol. The solution is concentrated under reduced pressure to yield an oil which is added

to 200 ml 3N hydrochloric acid whereupon the mixture is shaken with ether, 3 x 100 ml, until the aqueous phase is clear. The ether solution is washed with water, 3 x 50 ml, and the water present in the combined aqueous phase and water used for washing is evaporated under reduced pressure methanol being added three times when the residue appears to be dry. The impure hydrochloride of o-benzylphenoxy-β-N-piperidinopropane, 41 g, obtained is dissolved in 100 ml water and 100 ml 30% aqueous sodium hydroxide solution are added, whereupon precipitated oil is extracted with ether, 1 x 100 and 2 x 50 ml. The ether solution is washed with water, 4 x 50 ml, dried with magnesium sulfate and the ether is removed under reduced pressure. The residue, 25.2 g, is distilled under reduced pressure and the main fraction, 23.2 g, BP 159°-161°C/0.2 mm.

References

Merck Index 1047
Kleeman and Engel p. 83
OCDS Vol. 2 p. 100 (1980)
DOT 13 (6) 223 (1977)
I.N. p. 124
Rubinstein, K.; US Patent 3,117,059; January 7, 1964; assigned to A.B. Pharmacia

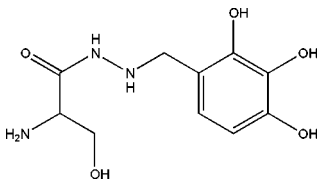
BENSERAZIDE

Therapeutic Function: Antiparkinsonian

Chemical Name: DL-Serine 2-[(2,3,4-trihydroxyphenyl)methyl]hydrazide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 322-35-0

Trade Name	Manufacturer	Country	Year Introduced
Madopar	Roche	Italy	1974
Madopar	Roche	UK	1975
Modopar	Roche	France	1975
Madopar	Roche	W. Germany	1975
Neodopasol	Daiichi	Japan	1980

Trade Name	Manufacturer	Country	Year Introduced
Madopar	Nippon Roche	Japan	1980
EC-Doparyl	Kyowa Hakko	Japan	1980
Madopark	Roche	-	-
Prolopa	Roche	-	-

Raw Materials

DL-Seryl hydrazide HCl
Pyrogallolaldehyde
Hydrogen

Manufacturing Process

35.5 grams of DL-seryl-hydrazide hydrochloride was dissolved in 350 ml of water and 35 grams of pyrogallolaldehyde (2,3,4-trihydroxy-benzaldehyde) added thereto at one time. In about 5-10 minutes a clear solution resulted, whereupon slow crystallization occurred and the temperature rose to about 6°-7°C. The crystallization was permitted to continue overnight at 5°C, and the very fine precipitate was then isolated by centrifugation and in the centrifuge washed with water, ethanol, and ether, yielding the dihydrate of DL-seryl-(2,3,4-trihydroxy-benzylidene) hydrazide hydrochloride, which melted at 134°-136°C and was poorly soluble in cold water, but very readily dissolved in hot water. The condensation was also effected in absolute ethanol yielding the anhydrous form of the hydrazone, which melted at 225°-228°C.

33.5 grams of the hydrazone-dihydrate was suspended in 330 ml of methanol and hydrogenated with 2.5 grams of palladium-carbon. After the absorption of 2.8 liters of hydrogen, the catalyst was filtered off and the solution evaporated in vacuo to a weight of about 52-55 grams. It was then immediately mixed with 160 ml of absolute ethanol and permitted to crystallize for 24 hours at room temperature and then for a further 24 hours at 0°C. The product was then filtered off with suction and washed with absolute ethanol and absolute ether. The so-obtained DL-seryl-(2,3,4-trihydroxy-benzyl)-hydrazide hydrochloride formed a white crystalline powder which was readily soluble in water and which melted at 146°-148°C.

References

Merck Index 1048
Kleernan and Engel p. 84
DOT 10 (9) 322 (1974)
I.N.p. 124
Hegedus, B.and Zeller, P.; US Patent 3,178,476; April 13, 1965; assigned to Hoffmann-La Roche Inc.

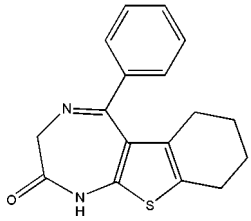
BENTAZEPAM

Therapeutic Function: Anticonvulsant, Tranquilizer

Chemical Name: 2H-[1]Benzothieno[2,3-e]-1,4-diazepin-2-one, 1,3,6,7,8,9-hexahydro-5-phenyl-

Common Name: Bentazepam; Liberan

Structural Formula:



Chemical Abstracts Registry No.: 29462-18-8

Trade Name	Manufacturer	Country	Year Introduced
Bentazepam	Laboratorios Made S. A.	-	-
Tiadipona	Knoll	-	-
Bentazepam	ZYF Pharm Chemical	-	-

Raw Materials

N-Phthalimidoacetic acid
2-Amino-3-benzoyl-4,5-tetramethylene thiophene

Manufacturing Process

To a solution of 3.4 kg N-phthalimidoacetic acid in 20 L of methylene chloride was added a solution of 2.8 kg of 1,1-carbonyl diimidazol in 20 L of methylene chloride. The mixture was refluxed for 1 hour. After cooling to the obtained solution was added a solution of 4.3 kg of 2-amino-3-benzoyl-4,5-tetramethylene thiophene in 30 L of methylene chloride and the reaction mixture was refluxed for 16 hours. After cooling the mixture was washed with 30 L of water, dried with sodium sulfate and filtered. After removing the solvent was obtained the 2-(N-phthalimidoacetylamino)-3-benzoyl-4,5-tetramethylene thiophene, yield 70%, melting point 230°C.

References

ES Patent No. 8,602,009; 1986-03-01; Assigned to MADE LABOR SA [ES]

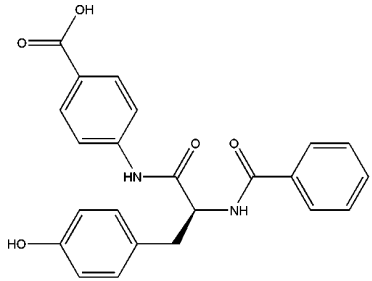
BENTIROMIDE

Therapeutic Function: Diagnostic aid (pancreatic function)

Chemical Name: 4-[[2-(Benzoylamino)-3-(4-hydroxyphenyl)-1-oxopropyl] amino]benzoic acid

Common Name: N-Benzoyl-L-tyrosyl-p-aminobenzoic acid

Structural Formula:



Chemical Abstracts Registry No.: 37106-97-1

Trade Name	Manufacturer	Country	Year Introduced
PFD Oral Sol	Eisai	Japan	1980
PFT Roche	Roche	Switz.	1982
Chymex	Adria	US	-

Raw Materials

L-Tyrosine
N-Methylmorpholine
Benzoyl chloride
p-Aminobenzoic acid

Manufacturing Process

A mixture was made of L-tyrosine (18.1 g, 0.1 mol) benzoyl chloride (7.0 g, 0.05 mol) and 200 ml anhydrous THF. After stirring at reflux for 2 hours, the mixture was cooled to room temperature, and the precipitate of tyrosine hydrochloride filtered off (11 g, 46 meq. Cl-). The THF was evaporated and the residue extracted with CCl_4 (3 X 100 ml at reflux, discarded) and then dissolved in ethyl acetate (200 ml) filtering off insolubles. The ethyl acetate solution was evaporated to yield 132 g solid product, MP 159°-162°C (93%). The tyrosine was recovered (8 g) by neutralization with aqueous alkali, from the hydrochloride.

A solution was made of N-benzyl-L-tyrosine (5.7 g, 20 mmols) and N-methylmorpholine (2.04 g, 20 mmols) in 60 ml of THF, at -15°C, and to it was added ethyl chloroformate (2.08 g, 20 mmols). After 12 minutes, p-aminobenzoic acid (2.74 g, 20 mmols) dissolved in 25 ml of THF and 0.38 g of p-toluenesulfonic acid (2 mmols) were added, and the temperature allowed to rise to 5°C. After 2 hours and forty minutes, the mixture was poured into l liter of 0.1 N cold HCl, stirred one-half hour, filtered and dried, to give 8,7 g, MP 192°-223°C. The product was recrystallized from 90 ml methanol and 40 ml water, to give 6 g (74%) of product, N-benzoyl-L-tyrosyl-p-aminobenzoic

acid, MP 240°-242°C.

References

Merck Index 1050
OCDS Vol. 3 p. 60 (1984)
DOT 16 (10) 354 (1980)
I.N. p. 125
De Benneville, P.L. and Greenberger, N.J.; US Patent 3,745,212; July 10,1973; assigned to Rohm and Haas Co.

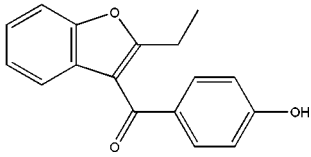
BENZARONE

Therapeutic Function: Antihemorrhagic

Chemical Name: Methanone, (2-ethyl-3-benzofuranyl)(4-hydroxyphenyl)-

Common Name: Benzarone; Venagil

Structural Formula:



Chemical Abstracts Registry No.: 1477-19-6

Trade Name	Manufacturer	Country	Year Introduced
Fragivix	Labaz	-	-
Fragivix	Sigma-Tau	-	-
Fragivix	Schwarz Pharma AG	-	-
Fragivix	C.P. Higiene	-	-
Vasoc	Lindopharm	-	-
Benzarone	Tohira Pharma Ltd.	-	-
Venagil	Erbamont Italia	-	-

Raw Materials

Salicylic aldehyde
Hydrazine hydrate
Tin tetrachloride
Coloroacetone
2-Metoxybenzoyl chloride
Pyridine hydrochloride

Manufacturing Process

The process of preparation of the 2-ethyl-3-(4'-hydroxybenzoyl)benzofurane

includes the next steps:

1. To 1 mol of potassium hydroxide in absolute ethanol is added 1 mole of salicylic aldehyde. The mixture is brought to boiling point in water bath until the potassium salt formed is dissolved. One mole of coloroacetone is gradually added and the solution boiled in a reflux condenser for 2 hours. On cooling the potassium chloride precipitate is separated off by filtration. The residue is distilled to give 2-acetyl-1-benzofurane, BP: 135°C/15 mm Hg.

2. It was reduced by hydrazine hydrate in an alkaline medium (by process of Hyuang-Minlon, J.A.C.S., 1946, 68, 2487) to give 2-ethyl-1-benzofurane BP: 211°-212°C.

3. 2-Ethyl-1-benzofurane is condensed with 2-metoxybenzoyl chloride in the presence of tin tetrachloride (according to the process described by Bisagni, J.C.S., 1955, 3694). Thus 2-ethyl-3-(4-methoxybenzoyl)-1-benzofyrane is obtained. BP: 226°C/15 mm Hg.

4. 1 part of 2-ethyl-3-(4-methoxybenzoyl)-1-benzofyrane is mixed with 2 parts of pyridine hydrochloride and heated at an oil bath at 210°C in N2 current for 1 hour. On cooling 10 parts of 0.5 N HCl are added. A water layer is mixed with 20 parts of 1% NaOH. The alkaline layer is separated, acidified with diluted HCl. The dropped precipitate (2-ethyl-3-(4'-hydroxybenzoyl) benzofurane) is recrystallized from acetic acid. MP: 124.3°C.

References

G.B. Patent No. 836,272; Dec. 12, 1957; Societe des Labaz, a Belgiam Body Corporate, of 168 Louise, Brusseles, Belgium

Shalk W. et al.; D.B. Patent No. 1,076,702; March 20, 1960; Societe des Laboratories Labaz, Bruessel

Hoi N.P.B., Beaudet C.; US Patent No. 3,012,042; Dec. 5, 1961; Assigned to Societe Belge l'Azote et Produits Chimiques du Marly, Liege, Belgium

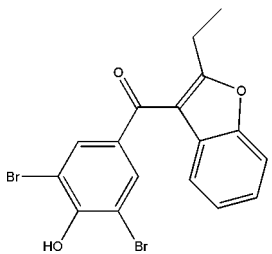
BENZBROMARONE

Therapeutic Function: Uricosuric, Antiarthritic

Chemical Name: (3,5-Dibromo-4-hydroxyphenyl)-(2-ethyl-3-benzofuranyl) methanone

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 3562-84-4

Trade Name	Manufacturer	Country	Year Introduced
Desuric	Labaz	Switz.	-
Uricovac	Labaz	W. Germany	1971
Desuric	Labaz	France	1976
Desuric	Sigma Tau	Italy	1977
Urinorm	Torii	Japan	1979
Azubromaron	Azupharma	W. Germany	-
Allomaron	Nattermann	W. Germany	-
Exurate	Mead Johnson	US	-
Hipuric	Labaz	-	-
Max-Uric	Labinca	Argentina	-
Minuric	Labaz	-	-
Narcaricin	Heumann	W. Germany	-
Normurat	Gruenenthal	W. Germany	-
Obaron	Mepha	Switz.	-

Raw Materials

Chloroacetone
Bromine
Anisoyl chloride
Hydrazine hydrate
Salicylic aldehyde

Manufacturing Process

The propyl analog of the benzbromarone intermediate containing an ethyl group is prepared as follows: to a solution of potassium hydroxide (56 g = 1 mol) in absolute ethyl alcohol (750 cc) is added one mol of salicylic aldehyde (122 grams). The mixture is brought to boiling point in a water-bath until the potassium salt formed is dissolved. One mol of ethyl chloromethyl ketone (106.5 grams) (methyl chloromethyl ketone or chloracetone in the case of benzbromarone) is gradually added and the solution boiled in a reflux condenser for two hours.

After cooling, the potassium chloride precipitate is separated off by filtration, and the greater part of the solvent removed by distillation. The residue is then puritied by distillation. In this way, 140 grams of 2-propionyl coumarone are obtained, boiling at 135°C under 15 mm Hg. A mixture is then prepared as follows: 215 grams of 2-propionyl coumarone, 550 cc of diethylene glycol and 200 grams of hydrazine hydrate at 85% and maintained at boiling point in a reflux condenser for 10 minutes. After cooling, 180 grams of potassium hydroxide are added and the mixture brought up to 120°-130°C. This temperature is maintained until no more nitrogen is liberated (about 1 hour). The mixture is then distilled by means of super-heated steam (150°-160°C).

The distillate is neutralized by means of concentrated HCl, decanted, and the aqueous layer extracted by means of ether. The oily layer and the ethereal extract are mixed, washed with diluted HCl, then with water, and finally dried over sodium sulfate. The solvent is removed and the residue rectified under

reduced pressure. In this way, 130 grams of 2-propyl coumarone are obtained, boiling at 112°C under 17 mm of mercury.

The following substances are then placed in a 250 cc flask fitted with a stirrer and a separatory funnel: 12.96 grams of 2-propyl coumarone, 55 cc of carbon sulfide and 14 grams of anisoyl chloride. The mixture is cooled by means of iced water and 21.5 grams of stannic chloride introduced dropwise, while the mixture is stirred. Stirring is continued for three hours at 0°C, after which the mixture is allowed to stand overnight. 50 cc of carbon sulfide is added and the mixture is treated, while being stirred, with the following: 20 cc of HCl and 100 cc of iced water. The organic layer is decanted and washed with water, dried over silica gel and rectified.

16.16 grams of 2-propyl-3-anisoyl coumarone are obtained (Yield: 72%), boiling at 189°C under 0.5 mm Hg. The methoxylated coumarone so obtained is mixed as follows: 1 part of 2-propyl-3-anisoylcoumarone and 2 parts of pyridine hydrochloride and the mixture maintained for one hour under a stream of dry nitrogen in an oil bath at 210°C (under a vertical condenser). After cooling, the mixture is triturated with 0.5 N hydrochloric acid (10 parts). The aqueous layer is separated and the residue extracted with ether. The ethereal extract is treated with 20 parts of 1% caustic soda. The alkaline layer is separated by decanting and acidified by means of diluted HCl. The precipitate is purified by recrystallization in aqueous acetic acid.

0.8 part of 2-propyl-3p-hydroxybenzoyl coumarone is obtained, melting at 123°C. Then the dibromo counterpart of benzbromarone may be prepared as follows: 8.05 g of 3-ethyl-2-p-hydroxybenzoyl coumarone, prepared as described above, are dissolved in very silght excess of 3% caustic soda. To this solution is gradually added a slight excess of bromine dissolved in a 25% aqueous solution of potassium bromide. The resultant solution is acidified with a 20% solution of sodium bisulfite, centrifuged, washed with water and then dried under vacuum. The product is then recrystallized in acetic acid and 13.6 g of 2-(4'-hydroxy-3',5'-dibromo-benzoyl)-3-ethyl coumarone obtained. MP 151°C.

References

Merck Index 1062
Kleeman and Engel p. 87
OCDS Vol. 2 p. 354 (1980)
I.N. p. 127
Hoi, N.P.B. and Beaudet, C.; US Patent 3,012,042; December 5, 1961; assigned to Societe Belge de l'Azote et des Produits Chirniques du Marly, Belgium

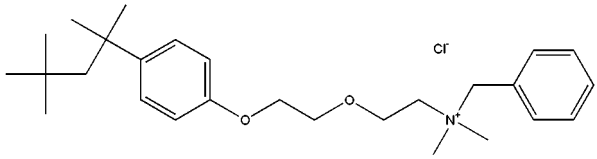
BENZETHONIUM CHLORIDE

Therapeutic Function: Topical antiinfective

Chemical Name: N,N-Dimethyl-N-[2-[2-[4-(1,1,3,3-tetrarmethylbutyl) phenoxy]ethyl]benzenemethanaminium chloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 121-54-0

Trade Name	Manufacturer	Country	Year Introduced
Phemerol	Parke Davis	US	1942
Premithyn	Flint	US	1959
Benzalcan	Siegfried	Switz.	-
Dalidyne	Dalin	US	-
Desamon	Streuli	Switz.	-
Hyarom	Teva	Israel	-
Sterilette	Farmitalia	Italy	-
Uni Wash	United	US	-

Raw Materials

p-Diisobutylphenol
Benzyl chloride
Dichlorodiethyl ether
Dimethylamine

Manufacturing Process

A mixture of 32 g of p-(α,α,γ,γ-tetramethylbutyl)phenoxyethoxyethyl-dimethylamine and 12.7 parts of benzyl chloride was warmed in 50 g of benzene for 2 hours. The benzene was then evaporated. The residual viscous mass gave a foamy, soapy solution in water.

The original starting materials are p-diisobutylphenol, dichlorodiethyl ether and dimethylamine.

References

Merck Index 1072
PDR pp. 829, 1826
I.N.p. 127
REM p. 1166
Bruson, H.A.; US Patents 2,115,250; April 26, 1938; 2,170,111; August 22, 1939; and 2,229,024; January 21, 1941; all assigned to Rohm and Haas Co.

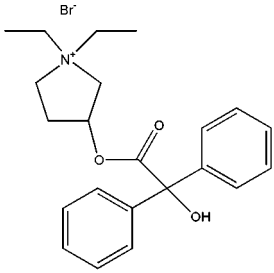
BENZILONIUM BROMIDE

Therapeutic Function: Anticholinergic

Chemical Name: Pyrrolidinium, 1,1-diethyl-3-((hydroxydiphenylacetyl)oxy)-, bromide

Common Name: Benzilonium bromide; Ulcoban

Structural Formula:



Chemical Abstracts Registry No.: 1050-48-2; 16175-92-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Benzilonium bromide	Pharm Chemical Shanghai Lansheng Corporation	-	-
Ulcoban	Parke-Davis	-	-

Raw Materials

1-Ethyl-3-hydroxypyrrolidine
Diphenylchloroacetyl chloride
Ethylbenzilate
Ethyl bromide

Manufacturing Process

A mixture containing of 23 g of 1-ethyl-3-hydroxypyrrolidine, 51.2 g of ethylbenzilate and 1.50 ml of benzene is subjected to azeotropic distillation to remove traces of water and then 250 mg of metallic sodium added to the residual solution. The mixture heated under reflux for about 8 hours while slowly drawing off the benzene-alcohol azeotrope formed. The reaction mixture is cooled, treated with 1 ml of acetic acid and washed with water. The benzene is removed by distillation and the residue distilled in vacuo to obtain the desired 1-ethyl-3-pyrrolidinyl benzilate as a viscous oil; yield 44 g, 68.1%; b.p. 164-170°C at 0.2 mm.

If desired, this same product can be prepared by adding 8 g of 1-ethyl-3-hydroxypyrrolidine in about 40 ml of dry methylene dichloride to 18.4 g of diphenylchloroacetyl chloride in about 40 ml of boiling methylene dichloride and refluxing the mixture for 1 hour. The solvent is evaporated and the residue heated on a steam bath with 200 ml of water for 5 min and then

allowed to stand at room temperature for 2 days. The mixture is treated with potassium carbonate, extracted with benzene and the benzene distilled from the extract to obtain crude l-ethyl-3-pyrrolidinyl benzilate. Distillation in vacuo yields the pure l-ethyl-3-pyrrolidinyl benzilate; yield 8 g (31%); b.p. 197°C at 2 mm.

22 g of 1-ethyl-3-pyrrolidinyl benzilate prepared by either of the above methods is mixed with 32 g of ethyl bromide in 100 ml of isopropanol and refluxed for 1 hour to give 23 g of 1,1-diethyl-3-pyrrolidinium bromide benzilate, m.p.196-197°C.

References

Merck Index, Monograph number: 1110, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.

Nguen Phac Bao Hoi, GB Patent No. 821,436; Dec. 5, 1961; Assigned to Societe Belge de l'Azote et des Produits Chimiques du Marly, Liege, Belqium

DE Patent No. 1,136,338; Fev. 12, 1957; Assigned to Parke, Davis and Co., Detroit, Michigan

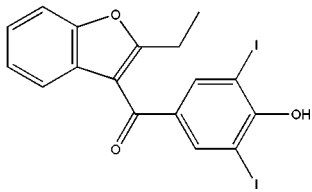
BENZIODARONE

Therapeutic Function: Coronary vasodilator, Uricosuric

Chemical Name: Methanone, (2-ethyl-3-benzofuranyl)(4-hydroxy-3,5-diiodophenyl)-

Common Name: Benziodarone; Ethofuridione

Structural Formula:



Chemical Abstracts Registry No.: 68-90-6

Trade Name	Manufacturer	Country	Year Introduced
Amplivix	Sigma-Tau	-	-
Amplivix	Sanofi Pharma AG	-	-
Amplivix	Sumitomo	-	-
Amplivix	C.P. Higiene	-	-
Dilafurane	Sanofi-Winthrop	-	-
Plexocardio	Benvegna	-	-

Raw Materials

Salicylic aldehyde	Chloroacetone
Tin tetrachloride	4-Methoxy-benzoylchloride
Potassium iodide	Iodine

Manufacturing Process

The starting product 2-ethyl-3-benzofuranyl p-hydroxyphenyl ketone (benzaron) was prepared in 4 steps:

1. First step was a reaction of salicylic aldehyde with chloroacetone to produce 2-acetyl-1-benzofuran.

2. It was reduced by hydrazine hydrate in an alkaline medium by process of Hyuang-Minlon, J.A.C.S., 1946, 68, 2487 to give 2-ethyl-1-benzofurane.

3. 2-Ethyl-3-(4-methoxybenzoyl)-1-benzofuran was obtained from 2-ethyl-1-benzofuran and 4-methoxy-benzoylchloride in a presence of tin tetrachloride.

4. It was heated with pyridine hydrochloride at 200°-220°C to give 2-ethyl-3-benzofuranyl p-hydroxyphenyl ketone (benzaron) as described in N.P.B.Hoi, C.Beaudet; US Patent No. 3,012,042; Dec. 5, 1961.

Benzaron (1 part) was dissolved in a very slight excess of 3% caustic soda. To this solution is gradually added a slight excess of iodine dissolved in a 25% aqueous solution of potassium iodide. The resultant solution is acidified with a 20% solution of sodium bisulphite, centrifuged, washed with water and then recrystallized in acetic acid to give of 2-ethyl-3-benzofuranyl 4-hydroxy-3,5-diiodophenyl ketone. MP: 167°C.

References

GB Patent No. 836,272; Dec. 17, 1957; Societe des Labaz, a Belgiam Body Corporate, of 168 Louise, Brusseles, Belgium

BENZOCTAMINE HYDROCHLORIDE

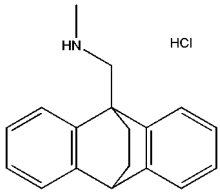
Therapeutic Function: Sedative, Muscle relaxant

Chemical Name: N-Methyl-9,10-ethanoanthracene-9(10H)-methanamine hydrochloride

Common Name: -

Chemical Abstracts Registry No.: 10085-81-1; 17243-39-9 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Tacitin	Ciba Geigy	Switz.	-
Tacitine	Ciba Geigy	France	1970
Tacitin	Ciba Geigy	UK	1971
Tacitin	Ciba Geigy	Italy	1971
Tacitin	Ciba Geigy	W. Germany	1972

Raw Materials

Anthracene
Methylamine
Acrolein
Hydrogen

Manufacturing Process

A solution of 10 g of 9:10-dihydro-9:10-ethano-(1:2)-anthracene-(9)aldehyde (made from anthracene and acrolein) and 10 g of monomethylamine in 100 cc of ethanol is heated at 80°C for 4 hours in an autoclave. The reaction mixture is then evaporated to dryness under reduced pressure to leave a crystalline residue which is dissolved in 150 cc of ethanol and, after the addition of 2 g of Raney nickel, hydrogenated at 40°C under atmospheric pressure. When the absorption of hydrogen has subsided, the catalyst is filtered off and the filtrate evaporated under reduced pressure. An oil remains which is covered with 100cc of 2N hydrochloric acid, The 9-methylamino-methyl-9:10-dihydro-9:10-ethano-(9:10)-anthracene hydrochloride crystallizes immediately; after crystallization from methanol it melts at 320°-322°C.

References

Merck Index 1087
Kleeman and Engel p. 88
DOT 6 (4) 123 (1970)
I.N. p. 129
Schmidt, P., Wilhelm, M. and Eichenberger, K.; US Patent 3,399,201; August 27, 1968; assigned to Ciba Corp.

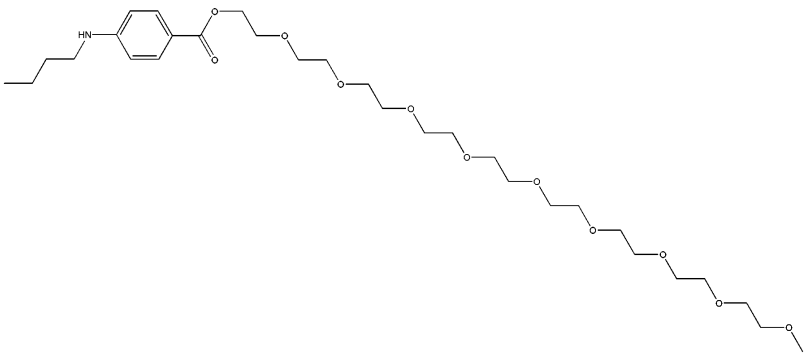
BENZONATATE

Therapeutic Function: Antitussive

Chemical Name: 4-(Butylamino)benzoic acid 3,6,9,12,15,18,21,24,27-nonaoxaoctacos-1-yl ester

Common Name: Benzononatine

Structural Formula:



Chemical Abstracts Registry No.: 104-31-4

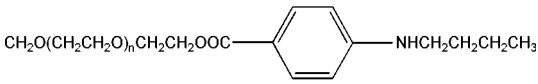
Trade Name	Manufacturer	Country	Year Introduced
Tessalon	Endo (Du Pont)	US	1958
Ventusasin	Warren Teed	US	1964
Tessalon	Ciba Geigy	Switz.	-

Raw Materials

p-Butylaminobenzoic acid ethyl ester
Nonaethylene glycol monomethyl ether

Manufacturing Process

4.42 parts of para-butylamino-benzoic acid ethyl ester are put with 16.0 parts of a mixture of polyethylene glycol monomethyl ethers, boiling at 180°-220°C at a pressure of 0.01 mm of mercury, in a closed reaction vessel which is fitted with an adjustable inlet tube for solvents and a connection for distilling off in vacuo. In order to dry the mixture completely, it is heated for an hour at 100°-105°C and absolute xylene is introduced under the surface of the mixture in vacuo at a pressure of 12 mm of mercury. There is thus a constant stream of xylene steam passing through the whole apparatus, which removes the last traces of moisture and any other volatile impurities. The xylene is condensed in a cooler. The whole is cooled to 20°-30°C and 0.06 part of sodium methylate dissolved in 0.6 part of methanol is added.



Thereupon xylene is introduced again in vacuo at a temperature of 100°-105°C whereby all the methanol and the ethanol formed during re-esterification evaporates. The re-esterification is continued under these conditions until a specimen of the reaction mass is clearly soluble in cold water, which occurs after about 2-3 hours. There is now obtained in almost quantitative yield the ester of the formula wherein n stands for approximately 7 to 9, which still contains an excess of polyethylene glycol monomethyl ether. The ester is purified by dissolving in benzene and being washed several times with a sodium carbonate solution of 5% strength. It is advantageous to agitate all the washing solutions with fresh benzene. In this distribution between benzene and sodium carbonate solution the new ester remains in the benzene, the excess polyethylene glycol monomethyl ether and a small amount of brown impurities are taken up by the dilute soda solution. By evaporating the dried and filtered benzene solution there is obtained the new ester in the form of a colorless to very faintly yellow oil which is easily soluble in most organic solvents with the exception of aliphatic hydrocarbons. The new ester is precipitated from aqueous solutions when heated to about 42°C. but it dissolves again readily on cooling.

References

Merck Index 1099
Kleeman and Engel p.89
PDR p. 862
I.N.p. 130
REM p. 870
Matter, M.; US Patent 2,714,608; August 2, 1955; assigned to Ciba Pharmaceutical Products, Inc.

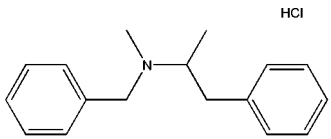
BENZPHETAMINE HYDROCHLORIDE

Therapeutic Function: Antiobesity

Chemical Name: N-α-Dimethyl-N-(phenylmethyl)benzeneethanamine hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 5411-22-3; 156-08-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Didrex	Upjohn	US	1960
Inapetyl	Upjohn	France	1969
Didrex	Upjohn	UK	-

Raw Materials

Benzyl chloride	d-Desoxyephedrine hydrochloride
Sodium hydroxide	Hydrogen chloride

Manufacturing Process

Fifty grams of d-desoxyephedrine hydrochloride was dissolved in a small amount of water and a molar excess of sodium hydroxide was .added thereto. The resulting forty grams of precipitated oily d-desoxyephedrine was collected in ether and the whole was thereafter dried with anhydrous potassium carbonate. The ether was then removed, the resulting oily residue having an n_D^{22} of 1.5045 was stirred in a flask with 40 grams of anhydrous sodium carbonate at 120°C, and 34.6 grams of benzyl chloride was added dropwise thereto over a period of thirty minutes. Stirring was continued for 2 hours, whereafter the reaction mixture was extracted with benzene.

The benzene was distilled from the extract and the residue of d-N-methyl-N-benzyl-β-phenylisopropylamine was distilled at reduced pressure. The thus obtained free base, distilling at 127°C at a pressure of 0.2 mm of mercury and having an n_D^{19} of 1.5515, was dissolved in ethyl acetate and a molar equivalent of ethanolic hydrogen chloride was added thereto. Anhydrous ether was added to the mixture and d-N-methyl-N-benzyl-β-phenylisopropylamine hydrochloride precipitated from the reaction mixture as an oil which was crystallized from ethyl acetate to give crystals melting at 129° to 130°C.

References

Merck Index 1122
Kleeman and Engel p.89
PDR p.1841
OCDS Vol. 1 p.70 (1977)
I.N. p.131
REM p.891
Heinzelman, R.V. and Aspergren, B.D.; US Patent 2,789,138; April 16, 1957; assigned to The Upjohn Company

BENZPYRINIUM BROMIDE

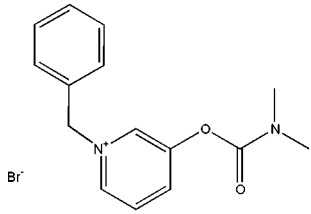
Therapeutic Function: Cholinergic

Chemical Name: 3-[[(Dimethylamino)carbonyl]oxy]-1-(phenylmethyl) pyridinium bromide

Common Name: -

Chemical Abstracts Registry No.: 587-46-2

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Stigmonene	Warner Lambert	US	1949

Raw Materials

Dimethylcarbamyl chloride
3-Pyridol
Benzyl bromide

Manufacturing Process

56 grams of dimethylcarbamyl chloride were gradually added over a period of 50 minutes to a solution of 45 grams of 3-pyridol in a mixture of 300 cc of benzene and 69 grams of triethylamine. The reaction mass was then agitated at 80°C for 3 hours and permitted to cool. The triethylamine hydrochloride was removed by filtration and solvents distilled from the filtrate under vacuum in a nitrogen atmosphere. The residual oil was then fractionated under vacuum whereby, after removal of unchanged dimethylcarbamyl chloride, a product distilling at 90°C at 0.3 mm was obtained; this product was the dimethylcarbamyl ester of 3-pyridol.

60 grams of the ester prepared as above described were dissolved in 225 cc of benzene and 92.5 grams of benzyl bromide were added thereto. The solution was stirred at room temperature for 24 hours and refluxed for 3 additional hours. At the end of this time the crude product which formed was separated, washed with benzene and dissolved in water. The aqueous solution was extracted with ether, filtered through charcoal and then evaporated to dryness in a nitrogen atmosphere; traces of water were removed by redissolving the oily residue in absolute alcohol, adding benzene and then evaporating the mixture to dryness under vacuum. The yellow oil thus obtained was then dissolved in a mixture of 300 cc of benzene and 55 cc of absolute alcohol under reflux, the solution cooled, and 340 cc of absolute ether added. The solution was then seeded and maintained at 5°C for two days. The crystalline product obtained was filtered and dried, a product melting between 115°C and 116°C being obtained. This product was the desired 1 benzyl-3-(dimethylcarbamyloxy)-pyridinium bromide.

References

Merck Index 1124
I.N. p. 131
Wuest, H.M.; US Patent 2,489,247; November 22, 1949; assigned to William R. Warner and Co., Inc.

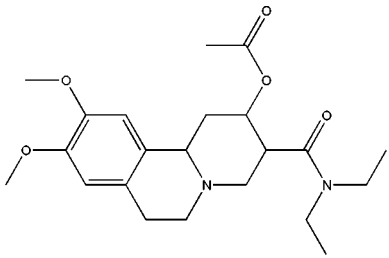
BENZQUINAMIDE

Therapeutic Function: Tranquilizer, Antinauseant

Chemical Name: 2-(Acetyloxy)-N,N-diethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2H-benzo[a]quinolizine-3-carboxamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 63-12-7; 30046-34-5 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Emete-Con	Roerig	US	1974
Promecon	Endopharm	W. Germany	1983
Quantril	Pfizer	US	-

Raw Materials

2-Oxo-3-carboxy-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b-H-benzopyridocoline
Diethylamine
Hydrogen
Hydrogen chloride

Manufacturing Process

According to US Patent 3,055,894, a solution consisting of 3.4 grams (0.01mol) of 2-oxo-3-carboethoxy-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b-H-benzopyridocoline and 0.8 grams (0.011 mol) of freshly distilled diethylamine dissolved in 50 ml of xylene was refluxed under a nitrogen atmosphere for 24 hours. After cooling to room temperature, the reaction mixture was successively extracted with four 100 ml portions of water. The aqueous phase was then discarded and the xylene layer was passed through a paper filter containing a bed of sodium sulfate and activated charcoal. The resulting filtrate was then heated under reduced pressure (65 mm Hg) via a water bath at 50°C in order to remove the xylene solvent, and the residual oil so obtained was cooled to approximately 5°C and held at that point until a semisolid formed (required approximately 16 hours). Recrystallization of the

semisolid from aqueous ethanol in the presence of activated charcoal afforded light yellow crystals of 2-oxo-3-(N,N-diethylcarboxamido)-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b-H-benzopyridocoline, MP 150°-152°C.

Then, as described in US Patent 3,053,845, one hundred grams (0.278 mol) of 2-oxo-3-(N,N-diethylcarboxamido)-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b-H-benzopyridocoline was dissolved in 1,500 ml of hot methanol and the resulting solution was allowed to cool to room temperature. After removal of all the dissolved oxygen therein by saturation of the solution with dry nitrogen, 5.0 grams of Adams' platinum oxide catalyst was introduced into the system in one portion while still maintaining same under a nitrogen atmosphere.

The reaction flask and its contents were then shaken at room temperature under slightly greater than one atmosphere of hydrogen pressure until the total hydrogen uptake was completed. Dissolved hydrogen gas was then removed from the reaction solution by saturation of same with respect to dry nitrogen, while the platinum black was removed by means of gravity filtration. Concentration of the resulting filtrate under reduced pressure on a steam bath then afforded a nearly quantitative yield of 2-hydroxy-3-(N,N-diethyicarboxamido)-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b-H-benzopyridocoline as a yellow crystalline solid (mixture of the axial and equatorial forms).

A mixture consisting of 2 grams of 2-hydroxy-3-(N,N-diethylcarboxamido)-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11 b-H-benzopyridocoline (OH-axial) hydrochloride (prepared by treating the base with hydrogen chloride gas in absolute ether) dissolved in 7 ml of acetic anhydride containing 3 ml of pyridine was heated at 100°C for 2 hours under a nitrogen atmosphere. At the end of this period, a crystalline precipitate had formed and the resultant mixture was subsequently diluted with an equal volume of diethyl ether and filtered.

The crystalline hydrochloride salt so obtained, i.e., the solid material collected on the filter funnel, was then converted to the corresponding free base by distribution in 10 ml of a benzene-aqueous 5% sodium carbonate system. The product recovered from the benzene extracts was then recrystallized from diisopropyl ether to afford 1.46 grams of 2-acetoxy-3-(N,N-diethylcarboxamido)-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b-H-benzopyridocoline (CH_3COO-axial), MP 130°-131.5°C.

References

Merck Index 1125
Kleeman and Engel p.90
PDR p.1523
OCDS Vol.1 p.350 (1977)
DOT 11 (1) 11 (1975); 9 (6) 233 (1973)
I.N. p. 131
REM p.807
Tretter, J.R.; US Patent 3,053,845; September 11, 1962; assigned to Chas. Pfizer and Co., Inc.
Lombardino, J.G. and McLamore, W.M.; US Patent 3,055,894; September 25, 1962; assigned to Chas. Pfizer and Co., Inc.

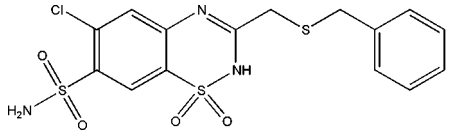
BENZTHIAZIDE

Therapeutic Function: Diuretic, Antihypertensive

Chemical Name: 6-Chloro-3-([(phenylmethyl)thio]methyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 91-33-8

Trade Name	Manufacturer	Country	Year Introduced
Exna	Robins	US	1960
Dytide	SK and F	UK	1960
Diteriam	Roussel	France	1962
Aquatag	Tutag	US	1965
Edemex	Savage	US	1970
Lemazide	Lemmon	US	1970
Aquapres	Coastal	US	-
Aquastat	Lemmon	US	-
Aquatag	Reid-Provident	US	-
Decaserpyl	Roussel	France	-
Dihydrex	Astra	Sweden	-
Exosalt	Bayer	W. Germany	-
Fovane	Taito Pfizer	Japan	-
Hydrex	Trimen	US	-
Hy-Drine	Zemmer	US	-
Proaqua	Reid-Provident	US	-
Regulon	Yamanouchi	Japan	-
Tensimic	Roussel	France	-
Urese	Pfizer	US	-

Raw Materials

2,4-Disulfamyl-5-chloroaniline
Chloroacetaldehyde
Benzyl mercaptan

Manufacturing Process

The preparation of the dihydro analog is as follows:

(A) Preparation of 3-Chloromethyl-6-Chloro-7-Sulfamyl-3,4-Dihydro-Benzothiadizine-1,1-Dioxide - To 8 ml of 40-50% chloroacetaldehyde aqueous solution and 7 ml of dimethylformamide are added 10 grams of 2,4-disulfamyl-5-chloroaniline. The mixture is heated on a steam bath for 2 hours after which it is concentrated at reduced pressure. The residue is triturated with water. The solid material is recrystallized from methanol-ether after treatment with activated carbon to give 7.2 grams of product, MP 229°-230°C.

(B) Preparation of Benzylthiomethyl-6-Chloro-7-Sulfamyl-3,4-Dihydrobenzothiadiazine-1,1-Dioxide - A mixture of 3-(chloromethyl)-6-chloro-7-sulfamyl-3,4-dihydrobenzothiadiazine-1,1-dioxide (0.02 mol) and benzylmercaptan (0.024 mol) in 20 ml of 10% sodium hydroxide and 20 ml of dimethylformamide is stirred at room temperature for 6 hours. After heating for 10 minutes on a steam bath, the mixture is cooled and acidified with 6 N HCl. The product, after recrystallization from acetone, melts at 210°-211°C.

References

Merck Index 1126
Kleeman and Engel p. 90
PDR pp. 1458, 1807
I.N.p. 132
REM p.938
McLamore, W.M. and Laubach, G.D.; US Patent 3,111,517; November 19, 1963; assigned to Chas. Pfizer and Co., Inc.

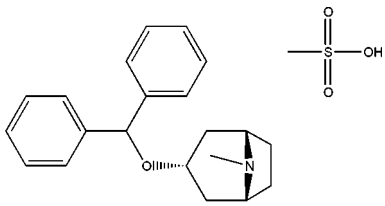
BENZTROPINE MESYLATE

Therapeutic Function: Antiparkinsonian

Chemical Name: 3-(Diphenylmethoxy)-8-methyl-8-azabicyclo[3.2.1]octane methanesulfonate

Common Name: Tropine benzohydryl ether methanesulfonate; Benzatropine Mesylate; Benztropine methanesulfonate

Structural Formula:



Chemical Abstracts Registry No.: 132-17-2

Trade Name	Manufacturer	Country	Year Introduced
Cogentin	Merck Sharp and Dohme	US	1954
Cogentinol	Astra	W. Germany	-
Cogentine	Merrell	France	1966
Cogentin	Merck-Banyu	Japan	-
Akitan	Farmos	Finland	-
Bensylate	ICN	Canada	-

Raw Materials

Diphenyldiazomethan
Hydrogen bromide
Methanesulfonic acid
Tropine
Sodium hydroxide

Manufacturing Process

Diphenyldiazomethane was prepared by shaking 7.9 grams of benzophenone hydrazone and 8.8 grams of yellow mercuric oxide in petroleum ether, filtering and evaporating off the petroleum ether from the filtrate under reduced pressure. To the residual diphenyldiazomethane 2.83 grams of tropine and 4.5 ml of benzene were added. The mixture was warmed in a pan of hot water at about 85°C under reflux for 24 hours after which time the original purple color had been largely discharged. The reaction mixture was dissolved by adding benzene and water containing hydrochloric acid in excess of the quantity theoretically required to form a salt. A rather large amount of water was required since the tropine benzohydryl ether hydrochloride was not very soluble and tended to separate as a third phase. The aqueous layer was separated, washed with benzene and with ether and made alkaline with an excess of sodium hydroxide. The resulting insoluble oil was extracted with benzene.

The benzene extracts were dried over potassium carbonate and evaporated under reduced pressure, leaving a residue of 4.1 grams. The residue (tropine benzohydryl ether) was dissolved in ether and treated with hydrogen bromide gas until an acidic reaction was obtained. The precipitate soon became crystalline and was collected on a filter and dried. The tropine benzohydryl ether hydrobromide weighed 4.1 grams. Recrystallization from absolute ethanol gave 3.3 grams of first crop melting at 247°-248°C (dec.).

Twelve grains of tropine benzohydryl ether hydrobromide was converted to the free base by warming with dilute aqueous sodium hydroxide. The oily base was extracted with toluene. The toluene extract was washed with water and then extracted with about 100 ml of water containing 28.1 ml of 1.10 N methanesulfonic acid, (an equimolecular quantity). The toluene solution was extracted twice more with fresh portions of water. The combined water extracts were evaporated under reduced pressure. Residual water was removed by dissolving the residue in absolute ethanol and evaporating under reduced pressure several times. Residual alcohol was then removed by dissolving the residue in acetone and evaporating under reduced pressure several times. The resulting residue was recrystallized by dissolving in acetone and adding ether. The crystalline precipitate was collected on a filter, washed

with ether and dried at 56°C in vacuo. The tropine benzohydryl ether methanesulfonate weighed 10.2 grams, MP 138°-140°C.

References

Merck Index 1127
Kleeman and Engel p.86
PDR pp.1149, 1606
DOT 18 (2) 91 (1982)
I.N.p.127
REM p.928
Phillips, R.F.; US Patent 2,595,405; May 6, 1952; assigned to Merck and Co., Inc.

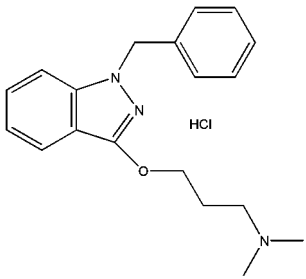
BENZYDAMINE HYDROCHLORIDE

Therapeutic Function: Analgesic, Antiinflammatory, Antipyretic

Chemical Name: 1-Propanamine, N,N-dimethyl-3-((1-(phenylmethyl)-1H-indazol-3-yl)oxy)-, monohydrochloride

Common Name: Benzidammina; Benzydamine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 132-69-4; 642-72-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Tantum	Angelini Pharmaceuticals	-	-
Afloben	Esseti	-	-
Afloben	Benedetti SpA	-	-
Andolex	3M Pharma	-	-
Benalgin	Polfa-Pabianice	-	-
Benzyrin	Yoshitomi	-	-
Benzydamine Hydrochloride	Shanghai Lansheng Corporation	-	-

Trade Name	Manufacturer	Country	Year Introduced
Difflam	Carnegie	-	-
Enzamin	Kowa	-	-
Salyzoron	Hishiyama	-	-
Saniflor	Esseti	-	-
Saniflor	Benedetti	-	-
Verax	Tosi	-	-
Lonol	Promero	-	-
Lonol	Boehringer Ingelheim Promeco	-	-
Multum	Lampugnani	-	-

Raw Materials

Hydrochloric acid
Sodium nitrite
Anthranilic acid methyl ester
Sodium hydroxide

Manufacturing Process

To a solution of 175 g of anthranilic acid methyl ester in 2 L of water and 120 ml of concentrated hydrochloric acid at 25°C was added concentrated solution of 80 g sodium nitrite. The product was dissolved in solution of 500 g NaOH in 1.5 L of water. To this solution under nitrogen was added 400 g of sodium bisulfite. The mixture was stirred for 6 hours at 75°C under nitrogen. The obtained solid product was dissolved in water and then to the solution was added 750 ml glacial acetic acid. The yield of 1-benzyl-3-(3-(dimethylamino) propoxy)-1H-indazole 70%, M.P. 154-156°C.

In practice it is usually used as monohydrochloride salt.

References

Merck Index, Monograph number: 1157, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Fr. Patent No. 1,382,855; 21.02.1964; Assigned to Aziende Chimiche Riunite Angeloni Francesco, residant en Italie

BEPHENIUM HYDROXYNAPHTHOATE

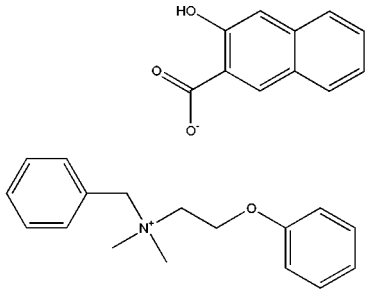
Therapeutic Function: Anthelmintic

Chemical Name: N,N-Dimethyl-N-(2-phenoxyethyl)benzenemethanaminium hydroxynaphthoate

Common Name: -

Chemical Abstracts Registry No.: 7181-73-9

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Alcopar	Wellcome	UK	1960
Alcopar	Wellcome	France	1965
Alcopara	Burroughs-Wellcome	US	1967
Alcopar	Wellcome-Tanabe	Japan	-

Raw Materials

Chloro-2-phenoxyethane
Dimethyl amine
Benzyl chloride
2-Hydroxy-3-naphthoic acid

Manufacturing Process

First, dimethylamino-2-phenoxyethanewas made by reacting chloro-2-phenoxyethane with dimethylamine. Benzyl chloride (10 grams) was then added to a solution of 1-dimethylamino-2-phenoxyethane (12.3 grams) in acetone (35 ml). The mixture warmed spontaneously and N-benzyl-N,N-dimethyl-N-2-phenoxyethylammonium chloride slowly crystallized. After 24 hours, this solid was filtered off, washed with fresh acetone and dried immediately in vacuo, MP 135°-136°C.

2-Hydroxy-3-naphthoic acid (1.88 grams) was dissolved in hot aqueous sodium hydroxide (0.5N; 20 ml) and the resulting solution was slowly added to a solution of N-benzyl-N,N-dimethyl-N-2-phenoxyethylammonium chloride (2.9 grams) in water (5 ml). A gum separated at first but it solidified on scratching. After the addition was complete, the mixture was allowed to stand at room temperature for 2 hours and then filtered. The residue was washed with water and dried in vacuo to give N-benzyl-N,N-dimethyl-N-2-phenoxyethylammonium 2-hydroxy-3-naphthoate, MP 170°-171°C.

References

Merck Index 1159
Kleeman and Engel p.93
DOT 4 (3) 114 (1968)
I.N. p. 134
Copp, F.C.; US Patent 2,918,401; December 22, 1959; assigned to BurroughsWellcome and Co.. Inc.

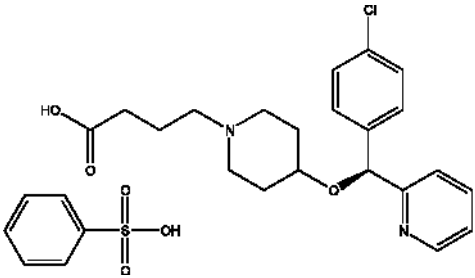
BEPOTASTINE BESILATE

Therapeutic Function: Antiallergic

Chemical Name: 1-Piperidinebutanoic acid, 4-((S)-(4-chlorophenyl)-2-pyridinylmethoxy)-, monobenzenesulfonate

Common Name: Bepotastine besilate; Betotastine besilate

Structural Formula:



Chemical Abstracts Registry No.: 190786-44-8; 190786-43-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Bepotastine besilate	Ube	-	-
Talion	TANABE SEIYAKU	-	-

Raw Materials

Trioxane
Palladium on carbon
4-Toluenesulfonic acid monohydrate
Lithium aluminum hydride
Magnesium
beta-Propiolactone
t-Butyldimethylsilyl chloride
Pyridine
Cerium (III) chloride heptahydrate
Dimethyl 3-methyl-2-oxo-hept-5-yne-phosphonate
Dicyclohexylcarbodiimide
Hydrogen
Sodium hydrogen carbonate
Thionyl chloride
Copper iodide
Diazomethane
Imidazole
Trifluoroacetic acid
Sodium methoxide
7-Bromo-3a,8b-cis-3a,8b-dihydro-3H-5-cyclopenta[b] benzofurancarboxylic acid

Manufacturing Process

Methyl 2-endo-hydroxy-1-exo-hydroxymethyl-3a,8b-cis-2,3,3a,8b-tetrahydro-1H-5-cyclopenta[b]benzofurancarboxylate:

To a suspension of 4 g of trioxane in 28 ml of acetic acid was added 1.2 ml of concentrated sulfuric acid, and the mixture was heated to 80°C with stirring.

To the solution was added in small portions 2 g of 7-bromo-3a,8b-cis-3a,8b-dihydro-3H-5-cyclopenta[b]benzofurancarboxylic acid. After being stirred at 80°C for 14 hours, the reaction mixture was cooled, and the acetic acid was removed under reduced pressure.

The residue was subjected to azeotropic operation with toluene two times, and ether was added to the residue. The precipitate derived from trioxane was removed by filtration and washed with ether, and the combined ethereal solutions were concentrated under reduced pressure. The residue was dissolved in ethyl acetate, and the solution was washed with water and aqueous saturated solution of sodium chloride, was dried, and was concentrated to give 4 g of an oily material. The oily material was dissolved in 20 ml of methanol and to the solution was added 20 ml of aqueous 1 N solution of sodium hydroxide, and the mixture was stirred for 14 hours at room temperature. After removal of methanol under reduced pressure, water was added to the mixture, and this solution was acidified to pH 3 with aqueous 2 N hydrochloric acid. The mixture was extracted five times with ethyl acetate, and the ethyl acetate extract was dried and concentrated to give 3.5 g of crude crystals. After addition of ethanol to the crude crystals, the crude crystals were filtered. The filtrate was concentrated, and to the residue was added ethanol and ethyl acetate, and precipitate was collected by filtration. The combined amount of the crude crystals was 1.6 g. After the combined crude crystals were methylated with diazomethane, the reaction product was dissolved in 20 ml of ethyl acetate. To this solution was added 1.5 g of sodium acetate and 300 mg of 10% palladium-carbon, and the mixture was stirred for 2 hours under hydrogen. Then, the reaction product was filtered, and after addition of aqueous saturated solution of sodium hydrogen carbonate to the filtrate, the mixture was extracted two times with ethyl acetate. The extract was washed with an aqueous saturated solution of sodium chloride, dried, and concentrated to give 1.3 g of crude crystals. The crude crystals were recrystallized from ethyl acetate to yield 765 mg of the title compound (melting point 134-135°C, yield 43%).

Methyl 3-methyl-trans-4a-cisoid-4a,5a-cis-5a-1,4a,5,5a,10b,10c-hexahydro-7-dioxin o[5,4-a]cyclopenta[b]benzofurancarboxylate:

To a stirred suspension of 3 g of methyl 2-endo-hydroxy-1-exo-hydroxymethyl-3a,8b-cis-2,3,3a,8b-tetrahydro-1H-5-cyclopenta[b]benzofuran-carboxylate in 30 ml of anhydrous tetrahydrofuran was added 1.5 ml of a solution which is obtained by dissolving 10 ml of 1,1-diethoxyethane and 200 mg of p-toluenesulfonic acid monohydrate into 10 ml of tetrahydrofuran followed by drying over molecular sieves, and the mixture was stirred for 14 hours at 60°C and then cooled. To the reaction mixture was added 100 mg of sodium hydrogen carbonate, and the mixture was stirred for 10 min at room temperature. Then, water was added to the reaction mixture and the mixture was extracted three times with ethyl acetate. The combined organic layers were washed with water and aqueous saturated solution of sodium chloride, was dried, and was concentrated to give 3.5 g of the crude crystals. The crude crystals were recrystallized from benzene-hexane to yield 2 g of the title compound (m.p. 162-163°C).

The filtrate was concentrated and the residue was dissolved again in 10 ml of anhydrous tetrahydrofuran. To this solution were added 2.5 ml of 1,1-diethoxyethane and 1 ml of the above-mentioned solution of p-toluenesulfonic

acid monohydrate in tetrahydrofuran and the mixture was stirred for 14 hours at 60°C and then cooled. To the reaction mixture was added 100 mg of sodium hydrogen carbonate, and the mixture was stirred for 10 min at a room temperature. After addition of water, the mixture was extracted three times with ethyl acetate. The combined organic layers were washed with water and aqueous saturated solution of sodium chloride, dried, and concentrated to give 1.5 g of crude crystals of methyl 3-methyl-trans-4a-cisoid-4a,5a-cis-5a-1,4a,5,5a,10b,10c-hexahydro-7-dioxino[5,4-a]cyclopenta[b]benzofurancarboxylate. The crude crystals were recrystallized from benzene-hexane to yield 740 mg of the title compound (m.p. 154-156°C, yield 83%).

3-Methyl-trans-4a-cosoid-4a,5a-cis-5a-1,4a,5,5a,10b,10c-hexahydro-7-dioxino[5,4-a]cyclopenta[b]benzofuranylmethanol:

To a suspension of 1 g of lithium aluminum hydride in 10 ml of anhydrous tetrahydrofuran cooled in an ice bath was added dropwise a solution of 1.94 g of methyl 3-methyl-trans-4a-cisoid-4a,5a-cis-5a-1,4a,5,5a,10b,10c-hexahydro-7-dioxino[5,4-a]cyclopenta[b]benzofurancarboxylate in 40 ml of anhydrous tetrahydrofuran. After being stirred for 30 min at room temperature, the reaction mixture was cooled in an ice bath. The excess of lithium aluminum hydride was decomposed by the addition of ethyl acetate, and aqueous saturated solution of potassium sodium tartarate was added to the reaction mixture. After filtration of the mixture, the filtrate was concentrated and the residue was dissolved in 10 ml of methanol. After addition of 2 g of potassium carbonate to the solution, the mixture was stirred for 3 hours at room temperature and was concentrated. After water was added to the residue, the aqueous mixture was extracted 3 times with ethyl acetate. The combined organic layers were washed with water and saturated aqueous solution of sodium chloride, dried, and concentrated to give 2 g of crude crystals. The crude crystals were recrystallized from ethyl acetate-hexane to yield 1.49 g of the pure crystals of the titled compound (m.p. 124-125°C, yield; 85%).

7-Chloromethyl-3-methyl-trans-4a-cisoid-4a,5a-cis-5a-1,4a,5,5a,10b,10c-hexahydrodioxino[5,4-a]cyclopenta[b]benzofuran:

To a solution of 1.14 g of 3-methyl-trans-4a-cisoid-4a,5a-cis-5a-1,4a,5,5a,10b,10c-hexahydro-7-dioxino[5,4-a]cyclopenta[b]benzofuranyl-methanol in 10 ml of dimethoxyethane cooled in an ice bath was added 0.43 ml of anhydrous pyridine and 0.38 ml of thionyl chloride, and the mixture was stirred for 3 hours at room temperature. After addition of ether to the reaction mixture, the precipitate was filtered, and water was added to the filtrate and the mixture was extracted three times with ether. The extract was washed with aqueous saturated solution of copper sulfate, water, aqueous saturated solution of sodium hydrogen carbonate and aqueous saturated solution of sodium chloride, dried, and concentrated to give 1.2 g of crude crystals. The crude crystals were recrystallized from ethyl acetate-hexane to yield 1 g of the pure titled chloride (m.p. 94-95°C, yield; 83%).

4-[3-Methyl-trans-4a-cisoid-4a,5a-cis-5a-1,4a,5,5a,10b,10c-hexahydro-7-dioxino[5,4-a]cyclopenta[b]benzofuranyl]butyric acid:

A solution of 482 mg of 7-chloromethyl-3-methyl-trans-4a-cisoid-4a,5a-cis-5a-1,4a,5,5a,10b,10c-hexahydrodioxino[5,4-a]cyclopenta[b]benzofuran in 5

ml of anhydrous tetrahydrofuran was added dropwise to 84 mg of turnings of metallic magnesium with stirring to prepare a Grignard reagent. To the thus prepared Grignard reagent cooled in an ice bath were added 30 mg of cuprous iodide and 0.1 ml of beta-propiolactone, and the mixture was stirred for one hour. Aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was acidified with 1 N hydrochloric acid to PH 3-4 to decompose the excess of magnesium. The resulting solution was extracted 5 times with ether, and the combined ethereal layers were washed with water and aqueous saturated solution of sodium chloride, dried and concentrated to give 500 mg of crude crystals. The crude crystals were recrystallized from ethyl acetate-hexane to yield 279 mg of the pure crystals of the carboxylic acid (melting point 148-149°C, yield; 54%).

Methyl 4-[2-endo-hydroxy-1-exo-hydroxymethyl-3a,8b-cis-2,3,3a,8b-tetrahydro-1H-5- cyclopenta[b]benzofuranyl]butyrate:

To a solution of 390 mg of 4-[3-methyl-trans-4a-cisoid-4a,5a-cis-5a-1,4a,5,5a,10b,10c-hexahydro-7-dioxino[5,4-a]cyclopenta[b]benzofuranyl] butyric acid in 5 ml of ethyl acetate cooled in an ice bath was added an excess of an ethereal solution of diazomethane, and after being stirred for 5 min the mixture was concentrated. The resulting oily material was dissolved in 3 ml of methanol, and to the solution was added 1 ml of 1 N hydrochloric acid and the mixture was stirred for 3 hours at room temperature. After concentration of the reaction mixture and addition of 1 ml of water, the mixture was extracted 3 times with each 5 ml of ethyl acetate. The combined layers of ethyl acetate were washed with 3 ml of water and 3 ml of aqueous saturated solution of sodium chloride, dried and concentrated to give 380 mg of crude crystals. The crude crystals were recrystallized from ethyl acetate-hexane to yield 200 mg of the pure captioned product (m.p. 56-57°C, yield; 53%).

Methyl 4-[2-endo-acetoxy-1-exo-hydroxymethyl-3a,8b-cis-2,3,3a,8b-tetrahydro-1H-5-cyclopenta[b]benzofuranyl]butyrate:

To a solution of 350 mg of methyl 4-[2-endo-hydroxy-1-exo-hydroxymethyl-3a,8b-cis-2,3,3a,8b-tetrahydro-1H-5-cyclopenta[b]benzofranyl]butyrate in 3.5 ml of anhydrous dimethylformamide cooled in an ice bath were added 140 mg of imidazole and 360 mg of t-butyldimethylsilyl chloride, and after the mixture was stirred for 3 hours at room temperature, dimethylformamide was removed under reduced pressure. The residue was dissolved in a mixture of 10 ml of acetic anhydride and 5 ml of pyridine. After the mixture was stirred for 2 hours at room temperature, the reaction mixture was concentrated. Then the residual oil was dissolved in 5 ml of acetic acid, and to the solution were added 5 ml of tetrahydrofuran and 2 ml of water. After the mixture was stirred for 14 hours at 50°C and concentrated, the residue was subjected to azeotropic operation two times with toluene. The residue was purified by column chromatography on silica gel using ethyl acetate-cyclohexane (1:2) to give 280 mg of the pure compound (yield; 70%).

Methyl ester of 11,15-dideoxy-11-acetoxy-16-methyl-15-oxo-18,19-tetradehydro-5,6,7-trinor-4,8-inter-m-phenylene PGI_2:

In 1.4 ml of a solution of 0.3 ml of pyridine in 10 ml of benzene was dissolved 178 mg of methyl 4-[2-endo-acetoxy-1-exo-hydroxymethyl-3a,8b-cis-

2,3,3a,8b-tetrahydro-1H-5- cyclopenta[b]benzofranyl]butyrate. To the solution were added 0.42 ml of the solution obtained by dissolving 0.14 ml of trifluoroacetic acid in 10 ml of dimethylsulfoxide and 320 mg of dicyclohexylcarbodiimide, and the mixture was stirred for 14 hours at room temperature. The precipitate was filtered and washed well with benzene. The filtrate was washed with water (3x3 ml), dried and concentrated to give 250 mg of crude aldehyde.

In the next step, 118 mg of sodium hydride (55% dispersion in mineral oil) was suspended in 20 ml of dimethoxyethane under argon. To the suspension was added a solution of 689 mg of dimethyl 3-methyl-2-oxohept-5-yne-phosphonate in 10 ml of dimethylformamide, and the mixture was stirred for 30 min at a room temperature.

To the thus prepared mixture was added a solution of 250 mg of the above-mentioned crude aldehyde in 5 ml of dimethoxyethane, and the mixture was stirred for 30 min at a room temperature. After neutralization (pH 7) with acetic acid the mixture was concentrated. The residue was dissolved in 10 ml of pentane and ether (1:1), and the precipitate was filtered, and the filtrate was concentrated to give 800 mg of an oily material. The oily material was purified by column-chromatography using ethyl acetate and cyclohexane (1:3) as an eluent to yield 162 mg of the pure captioned product (yield 70%).

11-Deoxy-11-acetoxy-16-methyl-18,19-tetradehydro-5,6,7-trinor-4,8-inter-m-phenylene PGI_2:

To a stirred solution of 122 mg of 11,15-dideoxy-11-acetoxy-16-methyl-15-oxo-18,19-tetradehydro-5,6,7-trinor- 4,8-inter-m-phenylene PGI2 in 10 ml of methanol was added 150 mg of cerium chloride heptahydrate, and then the solution was cooled in an ice bath, and 15 mg of sodium borohydride was added to the solution. After 10 min, to the mixture was added 2 ml of aqueous saturated solution of sodium hydrogen carbonate, and the mixture was further stirred for 10 min.

After concentration of the reaction mixture, 5 ml of ethyl acetate was added to the residue, and the precipitate was filtered and washed with ethyl acetate (2x2 ml). The combined organic layers were washed with water and aqueous saturated solution of sodium chloride, dried and concentrated to give 130 mg of an oily material. The oily material was purified by column-chromatography on silica gel using ethyl acetate and cyclohexane (1:2) as eluent to give 54 mg of the captioned compound.

Methyl ester of 16-methyl-18,19-tetradehydro-5,6,7-trinor-4,8-inter-m-phenylene PGI_2:

To a solution of 54 mg of methyl ester of 11-deoxy-11-acetoxy-16-methyl-18,19-tetradehydro-5,6,7-trinor-4,8-inter-m-phenylene PGI_2 in 4.5 ml of anhydrous methanol was added 0.001 ml of 4.8 N sodium methoxide under argon, and the reaction mixture was stirred for 1.5 hours at room temperature.

After addition of acetic acid to the reaction mixture and concentration of the mixture, the residue was dissolved in 20 ml of ethyl acetate, and the solution

was washed with aqueous saturated solution of sodium hydrogen carbonate, water and aqueous saturated solution of sodium chloride, dried and concentrated to afford 55 mg of an oily material.

This oily material was purified by column chromatography using ethyl acetate and cyclohexane (3:1) as eluent to give 48 mg of the methyl ester of 16-methyl-18,19-tetradehydro-5,6,7-trinor-4,8-inter-m-phenylene PGI_2.

References

EP Appl. 84,856
Ohno Kiyotaka, Nagase Hiroshi, Matsumoto Kazuhisa, Nishio Shintaro; US Patent No. 4,474,802; October 2, 1984 ; Assigned to Toray Industries, Inc. (Tokyo, JP)

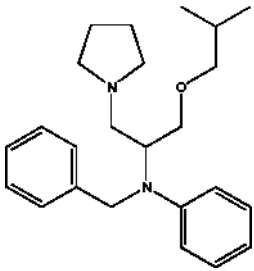
BEPRIDIL

Therapeutic Function: Antianginal

Chemical Name: 1-[2-(N-Benzylanilino)-3-isobutoxypropyl)pyrrolidine

Common Name:-

Structural Formula:



Chemical Abstracts Registry No.: 49571-04-2

Trade Name	Manufacturer	Country	Year Introduced
Cordium	Riom	France	1981
Angopril	Cerm	France	-
Angopril	Riom	France	-

Raw Materials

N-Benzylaniline	1-(3-Isobutoxy-2-hydroxy)propyl pyrrolidine
Sodium amide	Thionyl chloride

Manufacturing Process

The first step involves the preparation of 1-(3-isobutoxy-2-chloro)propyl

pyrrolidine as an intermediate. 345 ml of thionyl chloride dissolved in 345 ml of chloroform are added, drop by drop, to 275 g of 1-(3-isobutoxy-2-hydroxy)propyl pyrrolidine dissolved in 350 ml of chloroform, while maintaining the temperature at approximately 45°. The reaction mixture is heated to reflux until gas is no longer evolved. The chloroform and the excess of thionyl chloride are removed under reduced pressure. The residue is poured on to 400 g of crushed ice. The reaction mixture is rendered alkaline with soda and the resulting mixture is extracted twice with 250 ml of diethyl ether. The combined ethereal extracts are dried over anhydrous sodium sulfate. After evaporation of the solvent the residue is distilled under reduced pressure. 220 g of product are obtained having the following properties: boiling point = 96°C/3 mm, n_D^{24} = 1.4575.

The final product is prepared as follows. 23.4 g of sodium amide is added little by little to a solution of 92 g of N-benzylaniline in 500 ml of anhydrous xylene. The reaction mixture is then heated at 130°-135°C for 6 hours.

While maintaining the temperature at 110°C, 110 g of the product of the first step dissolved in 150 ml of xylene is added and the product heated for 6 hours at 120°C.

The product having been allowed to cool to ambient temperature, 200 ml of cold water are added. The organic phase is separated and extracted with an aqueous solution of hydrochloric acid.

After twice washing with 100 ml of diethyl ether, the aqueous phase is made alkaline with 50% caustic soda solution. The liberated base is twice extracted with 150 ml of diethyl ether. After the ether has been evaporated, the residue is distilled under reduced pressure and has a boiling point of 184°C/0.1 mm, n_D^{20} = 1.5538. 77 g of the pure base in the form of a viscous liquid is thus obtained. The hydrochloride, which is prepared in conventional manner, has a melting point of 128°C.

References

Merck Index 1160
DFU 2 (11) 713 (1977)
Kleeman and Engel p.93
OCDS Vol. 3 p. 46 (1984)
DOT 18 (9) 422 (1982)
I.N.p. 135
Mauvernay, R.Y., Busch, N., Moleyre, J., Monteil, A. and Simond, J.; US Patent 3,962,238; June 8,1976; assigned to Centre Europeen de Recherches Mauvernay "CERM"

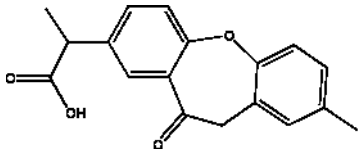
BERMOPROFEN

Therapeutic Function: Antiinflammatory, Antipyretic

Chemical Name: 10,11-Dihydro-α,8-dimethyl-11-oxodibenz[b,f]oxepin-2-acetic acid

Common Name: Bermoprofen

Structural Formula:



Chemical Abstracts Registry No.: 78499-27-1

Trade Name	Manufacturer	Country	Year Introduced
Bermoprofen	ZYF Pharm Chemical	-	-

Raw Materials

DL-2-[4-(2'-Carboxymethyl-4'-methylphenoxy)phenyl]propionic acid
Polyphosphoric acid

Manufacturing Process

A mixture of dl-2-[4-(2'-carboxymethyl-4'-methylphenoxy)phenyl]propionic acid (15.3 g) and polyphosphoric acid (92 g) was heated with stirring at 110-120°C for 2 hours. To the reaction mixture was added water and the resulting mixture was extracted with chloroform. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated. The residue was chromatographed on silica gel (75 g) using chloroform as an eluent to give a crude product, which was recrystallized from toluene to give the dl-2-(8-methyl-10,11-dihydro-11-oxodibenz[b,f]oxepin-2-yl)propionic acid (9.4 g, 65.3%), m.p. 128-129°C.

References

EP Appl. 3,893; Uno Hitoshi, Nagai Yasutaka, Nakamura Hideo; US Patent No. 4,238,620; Dec. 9, 1980; Assigned to Dainippon Pharmaceutical Co., Ltd. (Osaka, JP)

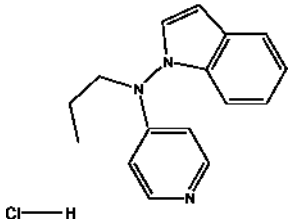
BESIPIRDINE HYDROCHLORIDE

Therapeutic Function: Cognition activator

Chemical Name: 1H-Indol-1-amine, N-propyl-N-4-pyridinyl-, monohydrochloride

Common Name: Besipirdine

Structural Formula:



Chemical Abstracts Registry No.: 130953-69-4

Trade Name	Manufacturer	Country	Year Introduced
Besipirdine hydrochloride	Hoechst-Roussel Pharmaceuticals, Inc.	-	-
Besipirdine hydrochloride	Aventis Pharmaceuticals, Inc.	-	-

Raw Materials

N-(4-Pyridinyl)-1H-indol-1-amine
1-Bromopropane
Hydrochloric acid
Sodium hydride
Maleic acid

Manufacturing Process

Part A: N-Propyl-N-(4-pyridinyl)-1H-indol-1-amine maleate:

A solution of N-(4-pyridinyl)-1H-indol-1-amine (6 g) in 25 ml of dimethylformamide was slowly added to an ice-cooled suspension of NaH (1.3 g of 60% NaH dispersion in mineral oil was washed with hexanes, the liquid was decanted and the residual solid was dispersed in 5 ml of dimethylformamide). After anion formation, a solution of 1-bromopropane (4 g) in 5 ml of dimethylformamide was added. After one hour of stirring at ambient temperature, the reaction mixture was stirred with ice-water and extracted with dichloromethane. The organic extract was washed with water and saturated sodium chloride solution, was dried over anhydrous magnesium sulfate, filtered and concentrated to 8 g of oil. This oil was purified by HPLC (silica, ethyl acetate) and thereafter by column chromatography (alumina, ether) to give 6.4 g oil. This oil was converted to the maleate salt and recrystallized from methanol/ether to give 6.8 g of crystals, m.p. 115-116°C.

Part B: N-Propyl-N-(4-pyridinyl)-1H-indol-1-amine hydrochloride:

N-Propyl-N-(4-pyridinyl)-1H-indol-1-amine maleate was converted to the free base by action of alcaline agent. Then the free base oil was converted to the hydrochloride salt which was recrystallized from methanol; m.p. 212-214°C.

References

Effland R.C., Klein J. T., Davis Larry Olsen, Gordon E.; US Patent No. 4,970,218; November 13, 1990; Hoechst-Roussel Pharmaceuticals Inc. (Somerville, NJ)

Kongsamut S., Smith C. P., Woods A. T.; US Patent No. 5,356,910; October 18, 1994; Assigned to Hoechst-Roussel Pharmaceuticals Inc. (Somerville, NJ)

Klein J.T., L. Davis, G.E. Olsen, G.S. Wong, M. Cornfeldt, F.P. Huger, C.P. Smith, W.W. Petko, J.C. Wilker, R.D. Blitzer, E. Landau, V. Hartoutunian, L.L. Martin and R.C. Effland. Synthesis and structure-activity relationships of N-propyl-N-(4-pyridinyl)-

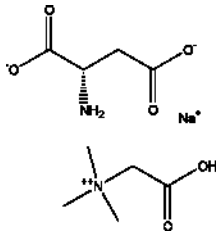
BETAINE ASPARTATE SODIUM

Therapeutic Function: Hepatoprotectant

Chemical Name: L-aspartic acid, ion (1-), 1-carboxy-N,N,N-trimethylaminium sodium salt

Common Name: Somatyl

Structural Formula:



Chemical Abstracts Registry No.: 52921-08-1

Trade Name	Manufacturer	Country	Year Introduced
Somatyl	TEOFARMA Srl	-	-
Somatyl	Anphar-Rolland	-	-

Raw Materials

Betaine
L-Aspartic acid

Manufacturing Process

Betaine aspartate was prepared from betaine and L-aspartic acid (molar ratio 1:1) in aqueous solution at pH 5.7-5.0.

In practice it is usually used as sodium salt.

References

Cote M.R.; FR Patent No. 1,356,945, Dec. 14, 1961
FR-M 2,462, Oct. 9, 1962

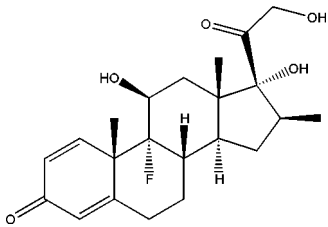
BETAMETHASONE

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	US	1961
Becort	Rachelle	US	-
Betacortil	Pfizer	US	-
Betalone	Firma	Italy	-
Betamamallet	Showa	Japan	-
Betapred	Glaxo	UK	-
Betasolon	Pharmax	Italy	-
Betnelan	Glaxo	UK	-
Betnesail	Glaxo	UK	-
Betnesol	Glaxo	UK	-
Celestan	Aesca	Austria	-
Celestene	Cetrane	France	-
Celestone	Essex	Spain	-
Cuantin	I.C.N.	Canada	-

Trade Name	Manufacturer	Country	Year Introduced
Dermovaleas	Valeas	Italy	-
Desacort-Beta	Caber	Italy	-
Diprosone	Byk-Essex	W. Germany	-
Diprosone	Unilabo	France	-
Diprostene	Centrane	France	-
Hormezone	Tobishi	Italy	-
Linosal	Wakamoto	Japan	-
Minisone	IDI	Japan	-
No-Rheumar	Janus	Italy	-
Pertene Vita	Vita	Italy	-
Rinderon	Shionogi	Japan	-
Sanbetason	Santen	Japan	-
Sclane	Promesa	Spain	-
Unicort	Unipharm	Israel	-
Valisone	Schering	US	-

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 US Patent 3,164,618.

References

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

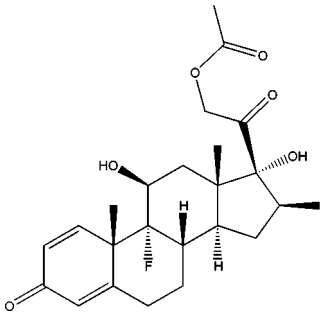
BETAMETHASONE ACETATE

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:



Chemical Abstracts Registry No.: 987-24-6

Trade Name	Manufacturer	Country	Year Introduced
Celestone Soluspan	Schering	US	1965
Betafluorene	Lepetit	France	-
Celestone Cronodose	Essex	Italy	-

Raw Materials

17β,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 0.215N 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-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-4-pregnadiene-3,20-dione 21-acetate. Alternately, Bacillus sphaericus may be utilized.

References

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

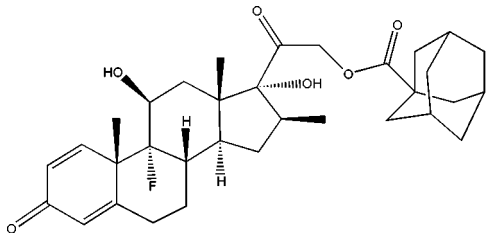
BETAMETHASONE ADAMANTOATE

Therapeutic Function: Glucocorticoid

Chemical Name: 9-Fluoro-11β,17-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 21-(tricyclo(3.3.1.13,7)dec-1-ylformate)

Common Name: Betamethasone adamantoate

Structural Formula:



Chemical Abstracts Registry No.: 40242-27-1

Trade Name	Manufacturer	Country	Year Introduced
Betamethasone Adamantoate	Zhejiang Xianju Pharmaceutical Co., Ltd.	-	-

Raw Materials

Betamethasone
Trifluorcacetic anhydride
Pyridine
Adamantane carboxylic acid
Sodium bicarbonate
Triethylamine adamantane carbonyl chloride

Manufacturing Process

3 Methods of producing of betamethasone 21-adamantane-1'-carboxylate:

1. A suspension of betamethasone (740.0 mg) in dioxan (20 ml) was treated with adamantane carboxylic acid (1.96 g) and trifluorcacetic anhydride (0.75 ml). The mixture was stirred at room temperature for 23 h during which time the steroid completely dissolved. Addition of sodium bicarbonate (2.0 g) and water gave a waxy semi-solid which was separated from the supernatant liquid by decantation. Water and a little methanol were added to the solid and the resulting granular material was removed by filtration and washed well with water. Fractional crystallization from methanol afforded adamantane carboxylic anhydride as the less soluble component and betamethasone 21-adamantane-1'-carboxylate as the more soluble component.

2. 9α-Fluoro-11β,17-dihydroxy-21-iodo-16β-methylpregna-1,4-diene-3,20-dione (76.65 g) was dissolved in warm acetone (400 ml) and then adamantanecarboxylic acid (54.0 g) and triethylamine (52.5 ml) was added and washed in with more acetone (100 ml). The solution was refluxed for 1 h and then poured with good stirring into cold water (2.5 L). Filtration of the precipitated material and recrystallisation from aqueous methanol with charcoaling afforded betamethasone 21-admantane-1'-carboxylate showing extensive melting 245°-250°C.

3. A solution of betamethasone (1.0 g) in dry tetrahydrofuran (40 ml) was treated with adamantane carbonyl chloride (about 2.2 equivalents) in dry tetrahydrofuran (5 ml) and then pyridine (0.8 ml) was added. The mixture was refluxed for 6 h and then most of the solvent was boiled off and the residue extracted with chloroform to afford a froth. The ether soluble portion of this froth was dissolved in chloroform and extracted repeatedly with dilute sodium bicarbonate solution. Evaporation of the chloroform layer gave a froth which was further purified by chromatography and crystallisation from chloroform-petroleum ether to yield betamethasone 21-adamantane-1'-carboxylate melting point 256°-259°C (dec.).

References

Phillipps G.H., English A.F.; GB Patent No. 1,391,443; July 5, 1971; Assigned: Glaxo Laboratories Limited, a British Company, of Greenford, Middlesex

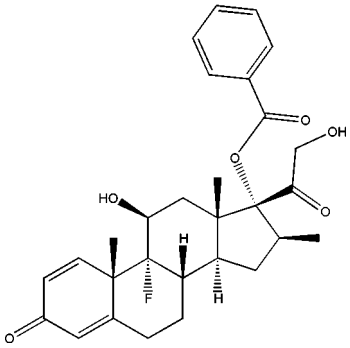
BETAMETHASONE BENZOATE

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	US	1973
Flurobate Gel	Texas Pharm	US	1973
Beben	Parke Davis	Italy	1974
Uticort Gel	Warner Lambert	US	1977

Trade Name	Manufacturer	Country	Year Introduced
Benisone	Cooper Vision	US	1979
Bebate	Warner	UK	-
Beben	Vister	Italy	-
Dermizol	Roux-Ocefa	Argentina	-
Euvaderm	Sasse	W. Germany	-
Parbetan	Parke Davis	W. Germany	-
Skincort	Parke Davis	W. Germany	-
Uticort	Parke Davis	US	-

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

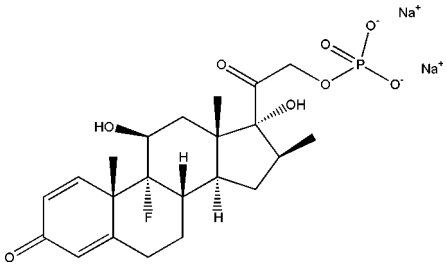
BETAMETHASONE DIHYDROGEN PHOSPHATE

Therapeutic Function: Glucocorticoid

Chemical Name: Pregna-1,4-diene-3,20-dione, 9-fluoro-11,17-dihydroxy-16-methyl-21-(phosphonooxy)-, (11βa,16β)-, disodium salt

Common Name: Bentelan; Betnesol; Celestan; Durabetason; Vista-Methasone

Structural Formula:



Chemical Abstracts Registry No.: 360-63-4

Trade Name	Manufacturer	Country	Year Introduced
Bentelan	Biofutura	-	-
Bentelan	Glaxo Wellcome	-	-
Celestan solubile	Essex	-	-

Raw Materials

Bistriethylamine phosphate
Phosphoric acid
Silver phosphate
Triethylamine
Hydrogen chloride
9α-Fluoro-11β,17α,21-trihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 21-methanesulfonate

Manufacturing Process

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

The salt of 9α-fluoro-11β,17α,21-trihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 21-phosphate may be converted to 9α-fluoro-11β,17α,21-trihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 21-phosphate by treatment with acid (for example HCl).

References

Metuchen J.M. Ch. et al.; US Patent No. 2,939,873; June 7, 1960; Assigned: Merck and Co., Inc., Rahway, N.J., a corporation of New Jersey

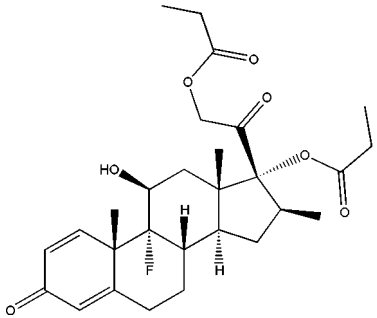
BETAMETHASONE DIPROPIONATE

Therapeutic Function: Glucocorticoid

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

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 5593-20-4

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

Trade Name	Manufacturer	Country	Year Introduced
Diprosalic	Schering	UK	-
Diprostene	Cetrane	France	-
Lortisone	Schering	US	-
Vanceril	Schering	US	-

Raw Materials

9α-Fluoro-11β-hydroxy-16β-methyl-17α,21-(1'-ethyl-1'-ethoxymethylene-dioxy)pregna-1,4-diene-32,0-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 and Engel p.99
PDR pp.888, 1429, 1601, 1614, 1631
I.N. p.138
Elks, J., May, P.J. and Weir, N.G.; US Patent 3,312,590; April 4, 1967; assigned to Glaxo Laboratories, Ltd.

BETAMETHASONE VALERATE

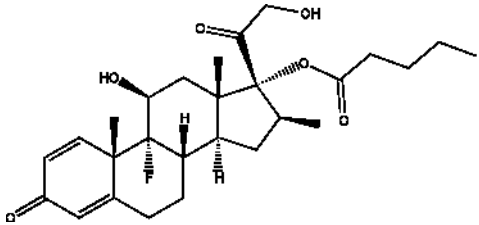
Therapeutic Function: Corticosteroid

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

Common Name: -

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

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Valisone	Schering	US	1967
Beta Dival	Fardeco	Italy	1978
Beta Val	Lemmon	US	1980
Cordel	Taisho	Japan	1981
Betatrex	Savage	US	1983
Betacort	ICN	Canada	-
Betacorten	Trima	Israel	-
Betaderm	K-Line	Canada	-
Betnesol	Glaxo	W. Germany	-
Betnelan	Glaxo	UK	-
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	UK	-
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 (20grams) 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 (20ml) 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 and 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.; US Patent 3,312,590; April 4, 1967; assigned to Glaxo Laboratories Limited, England

BETANIDINE SULFATE

Therapeutic Function: Antihypertensive

Chemical Name: Guanidine, 1-benzyl-2,3-dimethyl-, sulfate (2:1)

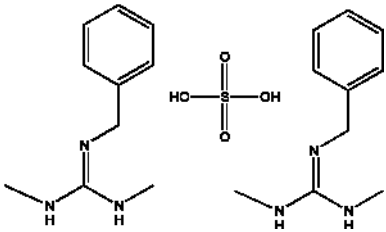
Common Name: Betanidine sulfate; Bethanidine sulfate; Regulin

Chemical Abstracts Registry No.: 55-73-2 (Base); 114-85-2

Raw Materials

2-Bromobenzylamine
S-Methylthiouronium sulfate

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Bendogen	Lagap Pharmaceuticals SA	-	-
Benzoxine	Plant Products	-	-
Bethanidine sulfate	Robins AH	-	-
Regulin	Gea	-	-
Regulin	Medica	-	-
Regulin	Nyco	-	-
Tenathan	Robins AH	-	-

Manufacturing Process

A mixture of 2-bromobenzylamine (12.5 g) and S-methylthiouronium sulfate (10 g) in water (20 ml) was heated for 1.5 hours on a steam bath in a hood, during which methylmercaptan escaped (as evidenced by a foul odour). The reaction mixture was then cooled and diluted with ethanol (100 ml). A colourless solid of 2-bromobenzylguanidine sulfate was separeted, and washed with ethanol. This solid melted at 230-232°C; it was recrystallized from water and then melted at 247-248°C. By action of a basic agent the salt obtained may be converted into free base.

References

Walton E., Ruffell G.K.; GB Patent No. 973,882; Dec. 15, 1960; Assigned to the Wellcome Foundation Ltd., London

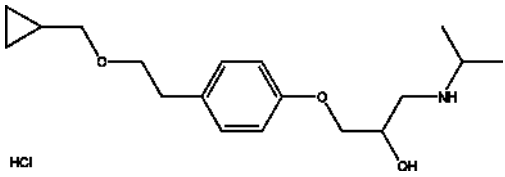
BETAXOLOL HYDROCHLORIDE

Therapeutic Function: Beta-adrenergic blocker

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

Sodium hydroxide
Hydrogen chloride
Isopropylamine
4-[2-(Cyclopropylmethoxy)ethyl]phenol
Epichlorohydrin

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-isopropylaminopropan-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.; US Patent 4,252,984; February 24, 1981; assigned to Synthelabo

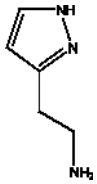
BETAZOLE

Therapeutic Function: Diagnostic aid (gastric secretion)

Chemical Name: 1H-Pyrazole-3-ethanamine

Common Name: β-Aminoethyipyrazole; Ametazole

Structural Formula:



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

Trade Name	Manufacturer	Country	Year Introduced
Histalog	Lilly	US	1953
Betazol	Lilly	W. Germany	-
Histimin	Shionogi	Japan	-

Raw Materials

γ-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 and Engel p.102
I.N. p.139
REM p.1124
Jones, R.G.; US Patent 2,785,177; March 12, 1957; assigned to Eli Lilly and Company

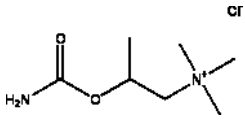
BETHANECHOL CHLORIDE

Therapeutic Function: Cholinergic

Chemical Name: 2-[(Aminocarbonyl)oxyl-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 CI	MSD	US	1949
Urecholine CI	MSD	Switz.	-
Duvoid	Norwich Eaton	US	1978
Besacolin	Elsai	Japan	-
Bethachorol	Nichiiko	Japan	-
Mechothane	Farillon	UK	-
Mictone	Kenyon	US	-
Mictrol	Misemer	US	-
Mycholine	Glenwood	US	-
Myo Hermes	Hermes	Spain	-
Myotonachol	Glenwood	US	-
Myotonine	Glenwood	UK	-
Paracholin	Kanto	Japan	-
Perista	Nissin	Japan	-
Urocarb	Hamilton	Australia	-
Urolax	Century	US	-

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

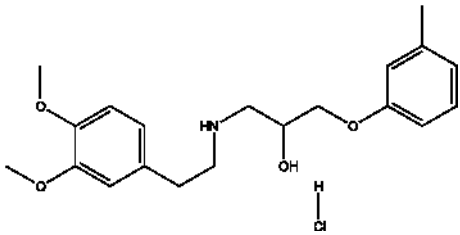
BEVANTOLOL HYDROCHLORIDE

Therapeutic Function: Antiarrhythmic, Beta-adrenergic blocker

Chemical Name: 2-Propanol, 1-((2-(3,4-dimethoxyphenyl)ethyl)amino)-3-(3-methylphenoxy)-, hydrochloride

Common Name: Bevantolol hydrochloride; Vantol

Structural Formula:



Chemical Abstracts Registry No.: 59170-23-9 (Base); 42864-78-8

Trade Name	Manufacturer	Country	Year Introduced
Bevantolol hydrochloride	Parke, Davis (Pfizer)	-	-

Raw Materials

Epichlorohydrin
3-Cresol
Sodium hydoxide
β-(3,4-Dimethoxyphenyl)ethylamine
Hydrogen chloride

Manufacturing Process

To a solution of 50 g (1.25 mol) of NaOH in 1200 ml H_2O was added 108 g (1 mol) of m-cresol freshly distilled and at 15°C in one lot 117ml (1.5 mol) of epichlorohydrin. The emulsion was stirred at room temperature for 16 hours in a creased flask. The product was taken up in 1000 ml of toluene and washed with 500 ml water. Distillation yielded 135.7 g=82% of 3-(m-tolyloxy)-1,2-epoxypropane, b.p. 61°C at 0.05 mm.

Preparation of bevantolol hydrochloride:

To a suitable reactor under a nitrogen blanket is added 13.7 kg of β-(3,4-dimethoxyphenyl)ethylamine. The amine is cooled to 5°C and 12.5 kg of 3-(m-tolyloxy)-1,2-epoxypropane is added maintaining the temperature between 5-10°C. After 10 hours, the mixture is seeded with bevantolol free base; seeding is repeated approximately every 2 hours until it is evident that crystallization has started. After stirring for 48 hours at 10°C, 26 L of hexane is added. The temperature is raised to 25°C and stirring is continued for 48 hours. The slurry is filtered and the collected solid is dried under vacuum. The product is dissolved in 60 L of isopropyl alcohol and the solution is filtered. The reactor and filter are rinsed with 186 L of isopropyl alcohol and 2.7 kg of anhydrous hydrogen chloride is added to the combined filtrate. The batch is heated to reflux for 2 hours. The temperature is adjusted to 65°C and the solution is seeded with bevantolol hydrochloride crystals. The mixture is held at this temperature with stirring until a heavy sand-like slurry is present. The mixture is allowed to cool to ambient temperature without stirring or artificial cooling. It is then cooled to 20°C. The slurry is centrifuged and the product rinsed with isopropyl alcohol until the filtrate is colorless. After being vacuum dried at 50-55°C the product is milled if necessary; yield of bevantolol hydrochloride 22.7 kg (78.6%); melting point 137-138°C.

References

Hoekstra M.S.; US Patent No. 4,994,618; February 19, 1991; Assigned to Warner-Lambert Company (Morris Plains, NJ)
Holmes A., Meyer R.F.; US Patent No. 3,857,891; Dec. 31, 1974; Assigned to Parke, Davis and Vcompany, Detroit, Mich.

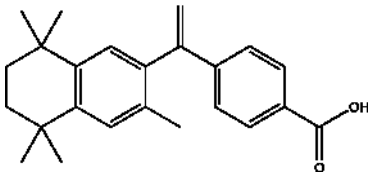
BEXAROTENE

Therapeutic Function: Antineoplastic

Chemical Name: Benzoic acid, 4-(1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)ethenyl)-

Common Name: Bexarotene

Structural Formula:



Chemical Abstracts Registry No.: 153559-49-0

Trade Name	Manufacturer	Country	Year Introduced
LGD1069	Ligand Pharmaceuticals Inc.	-	-
Targretin	R.P. Scherer St. Petersburg	USA	-
Targretin	Elan Pharmaceuticals, Inc.	-	-
Targretin	Ligand Pharmaceuticals Inc.	USA	-
Targrexin	Ligand Pharmaceuticals Inc.	USA	-

Raw Materials

Aluminum chloride
1,2-Dichloroethane
1,2,3,4-Tetrahydro-1,1,4,4,6-pentamethylnaphthalene
4-Carbomethoxybenzoyl chloride
Potassium hexamethyldisilazide
Methyltriphenylphosphonium bromide

Manufacturing Process

(a) Methyl [4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl) carbonyl]benzoate (1):

To a suspension of aluminum chloride (1.10 g, 8.25 mmol) in 30 mL of 1,2-dichloroethane under argon at room temperature was added a solution of 1,2,3,4-tetrahydro-1,1,4,4,6-pentamethylnaphthalene (1.52 g, 7.5 mmol) (Kagechika, H. et al., J. Med. Chem, 31:2182 (1988)) and 4-carbomethoxybenzoyl chloride (1.57 g, 7.87 mmol) in 15 mL of 1,2-

dichloroethane. The reaction mixture was stirred overnight and poured onto ice water and extracted with 40% ethyl acetate/hexane. The combined organic layers were washed with saturated aqueous NaHCO3and brine. The solution was dried over anhydrous $MgSO_4$, filtered and concentrated to afford a brown solid (2.56 g). Flash chromatography (60% dichloromethane/hexane) yielded the desired product (1) as a white, crystalline solid (1.733 g, 64 %): m.p. 146°-149°C; R_f 0.11 (50% CH_2Cl_2/hexane). The structure of the product was also confirmed using IR, ^1H NMR and mass spectroscopy.

(b) [4-(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl) carbonyl]benzoic acid (2):

To a suspension of the ester (1) (0.120 g, 0.329 mmol) in 75% aqueous methanol (2 mL) was added potassium hydroxide (0.055 g). The reaction mixture was stirred at 60°C for 1 h during which time the material dissolved. The solution was cooled to room temperature, acidified with 1 N aqueous hydrochloric acid, and then extracted with 80% ethyl acetate/hexane. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated to afford a white solid (0.109 g). Recrystallization from benzene/hexane afforded (2) as a white, crystalline solid (0.102 g, 89%): m.p. 209°-212°C. The structure of the product was also confirmed using IR, ^1H NMR and mass spectroscopy.

(c) Methyl 4-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)-1-ethenyl]benzoate (3):

To a suspension of methyltriphenylphosphonium bromide (0.196 g, 0.55 mmol) in 1 mL of benzene under argon at room temperature was added a 0.5 M solution of potassium hexamethyldisilazide in toluene (1.2 mL, 0.6 mmol), and the yellow solution was stirred for 5 min. A solution of keto-ester (1) (0.1 g, 0.274 mmol) in 1.5 mL of benzene was added and the orange solution was stirred for 3 h at room temperature. The reaction mixture was filtered through a plug of silica gel with 40% ethyl acetate/hexane. The filtrate was concentrated to afford a solid. Flash chromatography (30%; 40% dichloromethane/hexane) yielded the desired product (3) as a white solid (0.077 g, 78%): m.p. 167°-168°C; R_f 0.4 (50% dichloromethane/hexane). The structure of the product was also confirmed using IR, ^1H NMR and mass spectroscopy.

(d) [4-[1-(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)-1-ethenyl]benzoic acid (4):

To a suspension of the ester (3) (0.058 g, 0.16 mmol) in 75% aqueous methanol (2 mL) was added one pellet of potassium hydroxide (0.1 g). The mixture was stirred at 70°C for 1 h during which time the material dissolved. The solution was cooled to room temperature, acidified with 1 N aqueous hydrochloric acid and then extracted with 80% ethyl acetate/hexane. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated to afford a white solid. Recrystallization from dichloromethane/hexane afforded the desired acid (4) as a white, crystalline solid (42 mg, 91%): melting point 230°-231°C. The structure of the product was also confirmed using IR, ^1H NMR and mass spectroscopy.

References

Dawson M.L. et al.; US Patent No. 5,466,861; Nov., 14, 1995; Assigned: SRI International (Menlo Park, CA); La Jolla Cancer Research Foundation (La Jolla, CA)

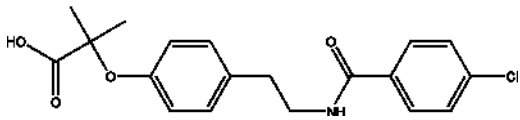
BEZAFIBRATE

Therapeutic Function: Antihyperlipidemic

Chemical Name: Propanoic acid, 2-(4-(2-((4-chlorobenzoyl)amino)ethyl) phenoxy)-2-methyl-

Common Name: Bezafibrate; Detrex

Structural Formula:



Chemical Abstracts Registry No.: 41859-67-0

Trade Name	Manufacturer	Country	Year Introduced
Bezafibrate	Eipico Co.	-	-
Bezalip	Glaxo Wellcom-Misr Co.	-	-
Cholestenorm	Natur Produkt	-	-
Azufibrat	Azupharma GmbH and Co.	-	-
Befibrat	Hennig Arzneimittel GmbH and Co. KG	-	-
Befizal	Roche	-	-
Befizal	Boehringer Mannheim France Pharma SA	-	-
Beza 1 A Pharma	AbZ-Pharma GmbH	-	-
Beza 200 von ct	AbZ-Pharma GmbH	-	-
Beza AbZ	AbZ-Pharma GmbH	-	-
Bezabeta	Betapharm Arzneimittel GmbH	-	-
Bezacur	Hexal	-	-
Detrex	Vargas	-	-
Bezafibrate	Topharman Shanghai Co., Ltd.	-	-

Raw Materials

Tyramine	p-Chlorobenzoyl chloride
Sodium	2-Bromo-2-methyl-propionic acid ethyl ester

Manufacturing Process

0.292 moles p-chlorobenzoyl chloride and 50 ml dry pyridine were added dropwise to 0.146 moles tyramine in 60 ml dry pyridine for 10 minutes. Then the mixture was poured in about 500 g of ice with water. The fallen-out crystals was filtered off, washed with diluted HCl, water and $NaHCO_3$ solution and dried. It was recrystallized from acetone to give di(4-chlorobenzoyl) tyramine; yield 98 %; MP: 203°-205°C.

0.11 moles above product in 400 ml methanol was mixed with 130 ml 2 N KOH and heated at 40°-45°C for 1 hour. On cooling 130 ml 2 N HCl was added. The fallen-out precipitate was filtered off, filtrate was distilled off to dryness. The residue was washed with water, $NaHCO_3$ solution and recrystallized from ethanol to give N-(4-chlorobenzoyl)tyramine; yield 91%; MP: 174°-176°C.

2.14 g sodium was dissolved in 50 ml of absolute methanol and mixed with 0.93 mole N-(4-chlorobenzoyl)tyramine. Methanol was removed in vacuum to dryness. The residue was slurried in 100 ml absolute toluene and 0.137 moles 2-bromo-2-methylpropionic acid ethyl ester was added. The suspension was heated for 25 hours at 80°C. Then it was distilled in vacuum to dryness and the residue was dissolved in CH_2Cl_2, washed with diluted HCl, NaOH and water, and dried over $CaCl_2$. On removing of the solvent, the crude 2-{4-[2-(4-chlorobenzoylamino)ethyl]phenoxy}-2-methylpropionic acid ethyl ester was obtained. After recrystallization from ether/ ligroin and acetone it had MP: 96°-97°C; yield 67 %.

0.1 mole above ester in 1.5 L of dioxane was slowly mixed with 200 ml 1 N KOH at ambient temperature and stood for 2 hours, then it was heated at 40°C for 1 hour. The substance was dissolved completely. On cooling the mixture was neutralized with 200 ml 1 N HCl. The solvents were removed in vacuum. The residue was washed with water and recrystallized from acetone to give 2-{4-[2-(4-chlorobenzoylamino)ethyl]phenoxy}-2-methylpropionic acid; yield 84%; MP: 186°C.

References

Witte E-Ch. et al; D.B. Patent No. 2,149,070; October 1, 1971; Assigned to Boehriger Mannheim GmbH, 6800 Mannheim

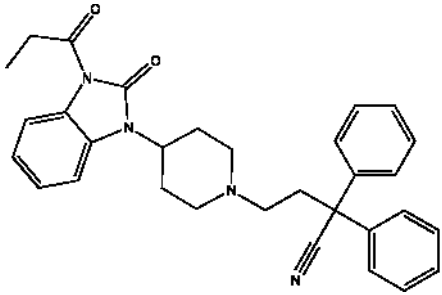
BEZITRAMIDE

Therapeutic Function: Narcotic analgesic, Antitussive

Chemical Name: 2-Benzimidazolinone, 1-(1-(3-cyano-3,3-diphenylpropyl)-4-piperidyl)-3-propionyl-

Common Name: Bezitramide

Structural Formula:



Chemical Abstracts Registry No.: 15301-48-1

Trade Name	Manufacturer	Country	Year Introduced
Bezitramide	ZYF Pharm Chemical	-	-

Raw Materials

4-Bromo-2,2-diphenylbutyronitrile
4-(2-Oxo-1-benzimidazolinyl)piperidine
Propionic anhydride
Sodium carbonate
Potassium iodide

Manufacturing Process

A mixture of 6.9 parts 4-bromo-2,2-diphenylbutyronitrile, 5 parts 4-(2-oxo-1-benzimidazolinyl)piperidine, 7.3 parts sodium carbonate, a few crystals of potassium iodide in 160 parts 4-methyl-2-pentanone is stirred and refluxed for 12 hours. After cooling the reaction mixture, 100 parts water is added. The aqueous layer is separated and extracted with 4-methyl-2-pentanone. The combined organic layer are dried over $MgSO_4$ and evaporated. The oily residue is dissolved in a mixture of 24 parts diisopropylether and 24 parts isopropanol. After cooling overnight to -20°C, 5.3 parts product are obtained. This crop is boiled in 72 parts 4-methyl-2-pentanone and cooled to 0°C, yielding 1-(3-cyano-3,3-diphenylpropyl)-4-(2-oxo-1-benzimidazolinyl) piperidine, melting point 225-226°C, as a grey-white amorphous powder.

A mixture of 5 parts 1-(3-cyano-3,3-diphenylpropyl)-4-(2-oxo-1-benzimidazolinyl)piperidine, 7.5 parts propionic acid anhydride and 80 parts benzene is stirred and refluxed for 16 hours. After cooling, the reaction mixture is washed twice with 100 parts water. The aqueous layer is dried over potassium carbonate, filtered and evaporated. The residue is recrystallized from 60 parts of ether, yielding 4 parts crude 1-(3-cyano-3,3-diphenylpropyl)-4-(2-oxo-3-propionyl-1-benzimidazolinyl)piperidine. This crop is recrystallized from 20 parts m-methyl-2-pentanone 4-ethyl-2-pentanone, yielding 1-(3-

cyano-3,3-diphenylpropyl)-4-(2-oxo-3-propionyl-1-benzimidazolinyl)piperidine with melting point: 124.5-126°C as a pale yellow amorphous powder.

References

Janssen P.A.J.; US Patent No. 3,196,157; July 20, 1965; Assigned to Research Laboratorium Dr.C.Janssen N.V., a corporation of Belgium

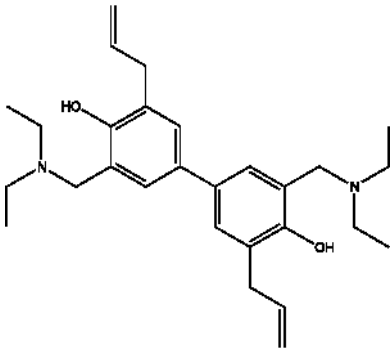
BIALAMICOL

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	US	1956

Raw Materials

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

Manufacturing Process

Paraformaldehyde (7.59) (0.25mol) 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.; US Patent 2,459,338; January 18,1949; assigned to Parke, Davis and Co.

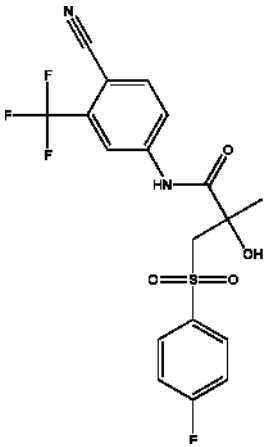
BICALUTAMIDE

Therapeutic Function: Antitumor

Chemical Name: Propanamide, N-(4-cyano-3-(trifluoromethyl)phenyl)-3-((4-fluorophenyl)sulfonyl)-2-hydroxy-2-methyl- (racemic mixture)

Common Name: Bicalutamide

Structural Formula:



Chemical Abstracts Registry No.: 90357-06-5

Trade Name	Manufacturer	Country	Year Introduced
Bicalutamide	AstraZeneca	-	-
Biprosta	Cytomed (A div. of Alembic)	India	-
Calutide-50	Cipla Limited	India	-
Casodex	AstraZeneca	-	-
Cosudex	AstraZeneca	-	-
Raffolutil	AstraZeneca	-	-

Raw Materials

Bromal
Dioxolanone
4-Fluorbenzenethiol
Thionyl chloride
Citramalic acid
2-Mercaptopyridine-N-oxide
4-Amino-2-trifluoromethylbenzonitrile

Manufacturing Process

[(4S)-4-Methyl-5-oxo-2-(tribromomethyl)-1,3-dioxolan-4-yl]acetic acid.

Bromal (25.0 g; 89.1 mmol) and (S)-citramalic acid (11.0 g; 74.2 mmol) were cooled to 0°C under inert atmosphere. Sulfuric acid/acetic acid (1/1; 25 ml) was added dropwise with stirring. After 2 h the contents were a yellow solution with a white precipitate. The ice bath was removed and the reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with ice and extracted 4 times with ethyl acetate. The organic layer was back extracted with water and then was dried with $MgSO_4$. After filtration, the filtrate was concentrated to an oil. The product was obtained as a white solid after crystallization from toluene/hexanes. Yield: 23.2 g (77%); mp 151°C (sublime).

(5R)-5-(Bromomethyl)-5-methyl-2-(tribromo-methyl)-l,3-dioxolan-4-one.

The above obtained [(4S)-4-Methyl-5-oxo-2-(tribromomethyl)-1,3-dioxolan-4-yl]acetic acid (102.5 mg; 0.250 mmol) and 2-mercaptopyridine- N-oxide (34.4 mg; 0.280 mmol) were suspended in $CBrCl_3$ (1.5ml). The reaction mixture was heated to reflux and a solution of dicyclohexyl carbodiimide (DCC) (103 mg; 0.500 mmol) in $CBrCl_3$ (1.0 ml) was added slowly over the course of 30 min. The reaction mixture was stirred for an additional hour. The product was purified by silica gel chromatography (CH_2Cl_2/hexanes (1:2)) and was obtained as white needles from the same solvents. Yield: 72 mg (65%); mp 110-113°C.

(2R)-3-[(4-Fluorophenyl)thio]-2-hydroxy-2-methyl-propanoic acid.

The above prepared protected hydroxyacid (184 mg; 0.413 mmol) was dissolved in 4 ml of a 1:1 mixture of isopropanol:1 M NaOH. After 3 h, the reaction mixture was a solution and no starting material was detectable by TLC. 4-Fluorobenzenethiol (70 ml; 0.65 mmol) was then added and the reaction mixture was stirred overnight. The reaction mixture was then

adjusted to pH 8 with HCl and was extracted twice with CH_2Cl_2. The aqueous layer was then adjusted to pH 1 and was extracted with CH_2Cl_2. This organic layer was concentrated to an oil, which crystallized on standing. The hydroxyacid was either used in the next reaction without further purification or was recrystallized from chloroform/petroleum ether. Yield 76 mg (80%).

(2R)-N-[4-Cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenul)thio]-2-hydroxy-2-methylpropanamide was prepared from above hydroxyacid (1.89 g; 8.22 mmol) and 4-amino-2-trifluoromethylbenzonitrile (2.05 g; 11.0 mol) were in dry DMA (15 ml) under inert atmosphere. After the solution had been cooled to -10°C, the thionyl chloride (0.75 ml; 10 mmol) was added slowly. The reaction mixture was stirred for 15 min at -10°C and then the ice bath was removed. After stirring overnight at room temperature, the reaction mixture was deluted with CH_2Cl_2 and was extracted one time with saturated $NaHCO_3$. The organic layer was dried with $MgSO_4$ and concentrated. The product was purified by silica gel chromatography (6% ethyl acetate in CH_2Cl_2). Yield 1.38 g (42%).

(2R)-N-[4-Cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methylpropanamide.

To a solution of the sulfide (1.27 g; 3.19 mmol) in CH_2Cl_2 (43 mL) was added mCPBA (1.65 g; 9.57 mmol). After stirring overnight at room temperature, the reaction mixture was diluted with ethyl acetate and extracted with Na_2SO_3 and $NaHCO_3$ (2x). The organic layer was dried with $MgSO_4$ and concentrated. After purification by silica gel chromatography using a step gradient of ethyl acetate in $CHCl_3$, the product was obtained as white crystals from benzene/petroleum ether. Yield 1.29 g (94%); ee>>99%; mp 178°C.

(2S)-N-[4-Cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methylpropanamide ee>>99%.

Product may be prepared from the starting materials.

References

James K.D., Ekwuribe N.N.; Tetrahedron, V. 58, Is. 29, pp.5905-5908, (2002)
Tucker H.; US Patent No. 4,636,505; Jan. 13, 1987; Assigned: Imperial Chemical Industries PLC (London, GB2)

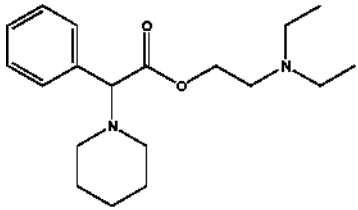
BIETAMIVERINE

Therapeutic Function: Spasmolytic

Chemical Name: 1-Piperidineacetic acid, alpha-phenyl-, 2-(diethylamino) ethyl ester

Common Name: Bietamiverine; Dietamiverine

Structural Formula:



Chemical Abstracts Registry No.: 479-81-2

Trade Name	Manufacturer	Country	Year Introduced
Bietamiverine	Shanghai Lansheng Corporation	-	-
Sparine	Tokyo Tanabe	-	-

Raw Materials

Phenylchloroacetic acid
Diethylaminoethanol
Piperidine

Manufacturing Process

To a solution of 117 g of diethylaminoethanol in 1000 ml of benzene was added a solution of 94.5 g phenylchloroacetic acid in 400 ml benzene (time of addition 1 hour). Then the reaction mixture was refluxed for 2 hours. To the obtained solution was added an aqueous solution of sodium carbonate. Then to the solution which was dried with sodium sulfate was added 85 g of piperidine and the solution was refluxed for 2 hours. The obtained solution was washed with water, dried with sodium sulfate and distilled. Yield of α-phenyl-1-piperidineacetic acid 2-diethylaminoethyl ester 115 g, K_{p1} 180°C.

References

Merck Index, Monograph number: 1252, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Reez Th.; DE Patent No. 859,892; July 8, 1949; Assigned to Nord-Werke G.m.b.H., Hamburg

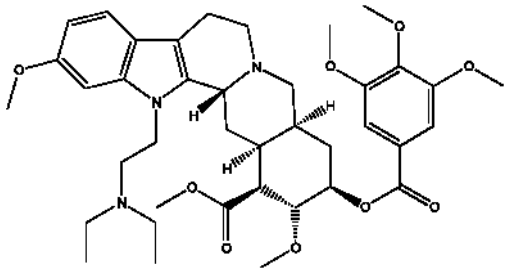
BIETASERPINE

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	Lefranco	France	1967
Pleiatensin	Guidotti	Italy	-
Pleiatensin	Byla	France	-

Raw Materials

Naphthalene
Sodium
Diethylaminochloroethane
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 nitrogen 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-reserpineis 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 and Engel p.105
I.N. p.142
Societe Nogentaise De Produits Chimiques and Buzas, A.; British Patent 894,866; April 26, 1962

BIFEMELANE HYDROCHLORIDE

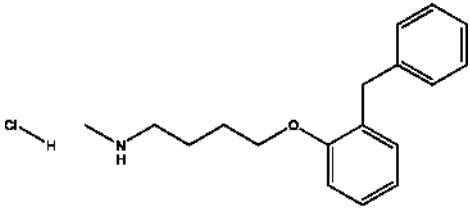
Therapeutic Function: Antidepressant, Antiulcer, Nootropic

Chemical Name: N-Methyl-4-[2-(phenylmethyl)phenoxy]-1-butanamine hydrochloride

Common Name: Bifemelane hydrochloride; Neurocine

Chemical Abstracts Registry No.: 90293-01-9 (Base); 62232-46-6

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Bifemelane hydrochloride	ABATRA Technology Co., Ltd.	-	-
Alnert	Fujisawa	-	-
Celeport	Eisai	-	-
Alemelano	ELVETIUM-ALET	-	-
Cordinal	Roemmers	-	-
Neurocine	Armstrong	-	-
Neurolea	Elea	-	-

Raw Materials

Methylamine
Sodium hydroxide
2-(5-Bromopentyloxy)diphenylmethane
Hydrogen chloride

Manufacturing Process

N-Methyl-4-[2-(phenylmethyl)phenoxy]-1-butanamine was prepared from 2-(5-bromopentyloxy)diphenylmethane and of methylamine in ethanol is at 50°C in a sealed tube (heating for 3 hours). Ethanol and excess methylamine are distilled in vacuo, 2 N NaOH aqueous solution is added, and the reaction product is extracted with ether. Dry hydrogen chloride gas is passed into the ether solution, and the precipitate collected by filtration. Recrystallization from ethanol-ether gives N-methyl-4-[2-(phenylmethyl)phenoxy]-1-butanamine hydrochloride, m.p. 87.5-89.5°C.

References

Kikumoto Ryoji, Tobe Akihiro, Tonomura Shinji, Ikoma Hidenobu; US Patent No. 4,091,114; May 23, 1978; Assigned to Mitsubishi Chemical Industries Limited (Tokyo, JA)
Tobe Akihiro, Tanaka Tadashi; EP No. 698,390; 1996-02-28; Assigned to MITSUBISHI CHEM CORP (JP)

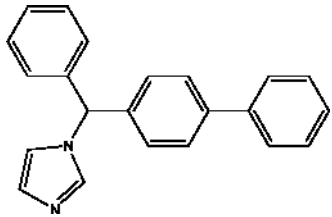
BIFONAZOLE

Therapeutic Function: Antifungal

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

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

Structural Formula:



Chemical Abstracts Registry No.: 60628-96-8

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

Raw Materials

4-Phenylbenzophenone
Sodium borohydride
Imidazole
Thionyl chloride

Manufacturing Process

38.8g (0.15 mol) of 4-phenylbenzophenone are dissolved in 200 ml of ethanol and 39 (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.; US Patent 4,118,487; October 3,1978; assigned to Bayer A.G.

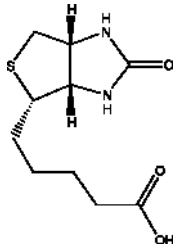
BIOTIN

Therapeutic Function: Vitamin

Chemical Name: 1H-Thieno(3,4-d)imidazole-4-pentanoic acid, hexahydro-2-oxo-, (3aS,4S,6aR)-

Common Name: Bios II; Biotin; Coenzym R; Skin factor; Vitamin B7; Vitamin Bw

Structural Formula:



Chemical Abstracts Registry No.: 58-85-5

Trade Name	Manufacturer	Country	Year Introduced
Biotin	Solgar	-	-
Biotin	Nature's Way	-	-
Biotin	Twinlab	-	-
Gabunat	Strathmann AG	Germany	-
Medebiotin	Medea	-	-
Priorin-Biotin	Roche Nicholas	France	-

Raw Materials

4,5-Dihydrothiophene
Ammonium formate
Sodium hydroxide

Manufacturing Process

4-Carbomethoxy-2-(4,5-dihydrothiophen-3(2H)-one)valeric acid methyl ester was prepared from 4,5-dihydrothiophene as it was described in Baker et al., J. Org. Chem., 12, 167 (1947).

A solution of 60.0 g (0.182 mole) this ester in 550 ml absolute ethanol was treated with 91.6 g (1.45 moles) of ammonium formate. The reaction mixture refluxed for 5.0 hours. Then it was cooled, concentrated, and partitionated in a separatory funnel between 200 ml dichloromethane and 150 ml water. The aqueous phase was extracted three times with 50 ml portions of dichloromethane. The organic extracts were collected, dried over anhydrous sodium sulfate, and evaporated. 50 g (0.182 mole, 100%) 3-amino-4-carbomethoxy-2,5-dihydro-2-thiophenevaleric acid methyl ester was obtained as a colorless oil.

To a solution of 27.3 g (1 mole) of 3-amino-4-carbomethoxy-2,5-dihydro-2-thiophenevaleric acid methyl ester in 250 ml dry methanol was added 4.0 g (0.1 mole) of sodium hydroxide pellets. The reaction mixture was refluxed 4.0 hrs, cooled and concentrated to a volume of 50 ml. The residue was taken up in 80 ml dichloromethane and transfered to a separatory funnel. After the addition of 150 ml of 10% by weight aqueous sodium bicarbonate solution, the aqueous layer was extracted twice with 50 ml portions of dichloromethane. The organic phases were combined, dried over anhydrous sodium sulfate, and evaporated to yield 6.4 g (0.0234 mole) of recovered starting material. The aqueous phase was adjusted to pH 1 with 6 N hydrochloric acid and extracted three times with 75 ml portions of dichloromethane. The organic phases were pooled, dried over anhydrous sodium sulfate, and evaporated to yield 18.3 g (0.071 mole, 71%) of 3-amino-4-carbomethoxy-2,5-dihydro-2-thiophenevaleric acid as a tan solid, upon trituration with pet. ether.

The recovered starting material, 6.4 g (0.0234 mole) was dissolved in 70 ml dry methanol and treated with 1.0 g (0.025 mole) sodium hydroxide. The mixture was refluxed 5.0 hrs, cooled concentrated, and taken up in 80 ml dichloromethane. The organic phase was treated in a separatory funnel with 100 ml of 10% by weight aqueous sodium bicarbonate solution. The aqueous phase was extracted twice with 40 ml portions of dichloromethane. The aqueous phase was acidified to pH 1 with 6 N hydrochloric acid and extracted two times with 50 ml portions of dichloromethane. The organic phases were cooled, dried over anhydrous sodium sulfate, and evaporated to dryness to afford an additional 5.3 g (0.021 mole, 21%) of 3-amino-4-carbomethoxy-2,5-dihydro-2-thiophenevaleric acid; m.p. 98°-102°C.

References

Confalone et al.; US Patent No. 3,979,396; Sept. 7, 1976; Assigned: Hoffmann-La Roche Inc. (Nutley, NJ)

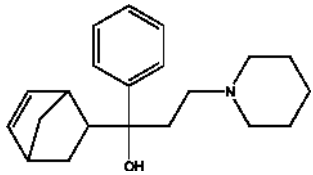
BIPERIDEN

Therapeutic Function: Antiparkinsonian

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 salt)

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

Raw Materials

Acetophenone
Hydrogen chloride
Magnesium
5-Chloro-2-norbomene
Piperidine hydrochloride
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-norbomene) 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 and 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.; US Patent 2,789,110; April 16, 1957; assigned to Knoll AG Chemische Fabriken, Germany

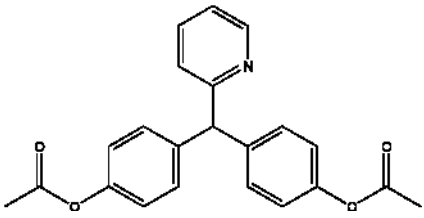
BISACODYL

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	Boehringer Ingelheim	US	1958
Dulcolax	Thomae	W. Germany	-
Dulcolax	Boehringer Ingelheim	Switz.	-
Contalax	Riker	France	1959
Bicol	Wampole	US	1974
Biscolax	Fleet	US	1975
Theralax	Beecham	US	1976
Alaxa	Angelini	Italy	-
Anan	Ono	Japan	-
Bisacolax	ICN	Canada	-
Biomit	Sampo	Japan	-
Brocalax	Brocades-Steethman	Netherlands	-

Trade Name	Manufacturer	Country	Year Introduced
Cathalin	Hokuriku	Japan	-
Coditax	Pharbil	Belgium	-
Contalax	Fischer	Israel	-
Darmoletten	Omegin	W. Germany	-
Deficol	Vangard	US	-
Delco-Lax	Delco	US	-
Durolax	Boehringer Ingelheim	W. Germany	-
Endokolat	Weiskopf	W. Germany	-
Ercolax	Erco	Denmark	-
Ethanis	Taisho	Japan	-
Eulaxen	Ferring	W. Germany	-
Evac-Q-Kwik	Adria	US	-
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	-
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	US	-
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	US	-
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 water bath. 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 and Engel p.107
PDR pp.561, 677, 879, 1569
I.N. p.145
REM p.800
Kottler, A. and Seeger, E.; US Patent 2,764,590; September 25, 1956; assigned to Dr. Karl Thomae GmbH, Germany

BISANTRENE HYDROCHLORIDE

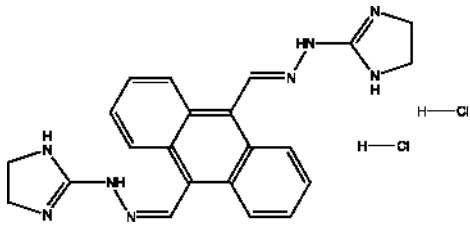
Therapeutic Function: Antineoplastic

Chemical Name: 9,10-Anthracenedicarboxaldehyde, bis((4,5-dihydro-1H-imidazol-2-yl)hydrazone), dihydrochloride

Common Name: Bisantrene hydrochloride

Chemical Abstracts Registry No.: 78186-34-2 (Base); 71439-68-4

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Bisantrene hydrochloride	ZYF Pharm Chemical	-	-

Raw Materials

Hydrazine hydrate
Hydrochloric acid
Silver oxide
2-Methylthio-2-imidazoline hydroiodide
9,10-Anthracenedicarboxaldehyde

Manufacturing Process

A 33.0 g (0.135 mole) of 2-methylthio-2-imidazoline hydroiodide is dissolved in 300 ml of water and treated with 8 ml (0.16 mole) of hydrazine hydrate. The mixture is stirred at room temperature for 20 hours and then taken to dryness under reduced pressure. The residue is dissolved in 250 ml of water and again taken to dryness under reduced pressure. The residue is redissolved in 250 ml of water and added to a mixture of 250 ml of water, 25 ml of concentrated hydrochloric acid and 25 g of silver oxide. The resulting mixture is stirred on a steam bath for 4 hours and then filtered. The filtrate is reduced to dryness under reduced pressure. The residue is dissolved in 300 ml of ethanol and 20 ml of water at the boil, clarified and cooled at -10°C. The precipitate is collected, washed with ethanol and ether and dried at 60°C and then 110°C under reduced pressure. Yield of the 2-hydrazino-2-imidazoline hydrochloride 11.6 g, melting point 177-180°C.

The 2-hydrazino-2-imidazoline monohydrochloride is converted to the dihydrochloride by treatment with ethanol and concentrated hydrochloric acid. A suspension of 3.46 g of the 2-hydrazino-2-imidazoline dihydrochloride and 2.34 g of 9,10-anthracenedicarboxaldehyde in 100 ml of ethanol is stirred and heated under reflux for two hours. The mixture is cooled and the solid is collected and washed with ethanol giving the desired product as a crystalline orange solid, m.p. 288-289°C (dec.).

References

Murdock Keith C., Durr; Frederick E.; US Patent No. 4,258,181; March 24, 1981; Assigned to American Cyanamid Company (Stamford, CT)
Tomcufcik Andrew Stephen, Wilkinson Raymond George, Child Ralph Grassing; US Patent No. 3,931,152; January 6, 1976; Assigned to American Cyanamid Company (Stamford, CT)

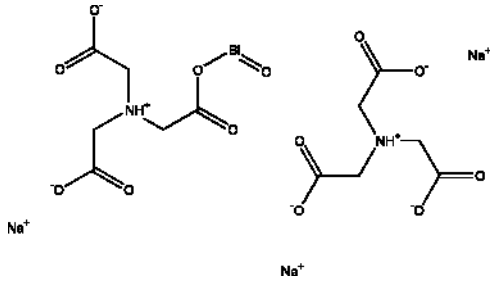
BISMUTH SODIUM TRIGLYCOLLAMATE

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 and Patch	US	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.; US Patent 2,348984; May 16, 1944

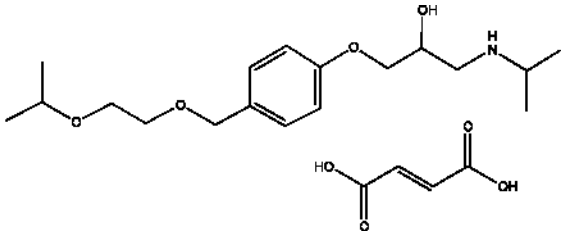
BISOPROLOL FUMARATE

Therapeutic Function: Beta-adrenergic blocker

Chemical Name: 2-Propanol, 1-(4-((2-(1-methylethoxy)ethoxy)methyl) phenoxy)-3-((1-methylethyl)amino)-, (E)-2-butenedioate (2:1) (salt)

Common Name: Bisoprolol fumarate

Structural Formula:



Chemical Abstracts Registry No.: 104344-23-2

Trade Name	Manufacturer	Country	Year Introduced
Bilol	Ecosol AG	Switz.	-
Biso-BASF	BC Biochemie Pharma GmbH	-	-
Bisobloc	Azupharma GmbH and Co.	-	-
Bisocar HT	Rusan Healthcare Pvt. Ltd.	India	-
Bisomerck	Merck AG	-	-
Biso 1A Pharma	1A Pharma	-	-
Biso-Puren	Alpharma-Isis GmbH	-	-
Concor	Merck AG	Switz.	-
Concor	E. Merck (India) Ltd.	India	-
Concor Cor	Merck AG	Switz.	-
Cordalin	AWD Pharma GmbH and Co. KG	-	-
Fondril	Procter and Gamble	Germany	-

Raw Materials

1-(p-2-Isopropoxyethoxymethylphenoxy)-2,3-epoxypropane
Ammonia
Nickel Raney

Manufacturing Process

A solution of 10 g of 1-(p-2-isopropoxyethoxymethylphenoxy)-3-

isopropylideneamino-propan-2-ol [obtainable by reacting 1-(p-2-isopropoxyethoxymethylphenoxy)-2,3-epoxy propane with ammonia to give 1-(p-2-isopropoxyethoxymethylphenoxy)-3-amino-propan-2-ol and subsequently reacting this with acetone] in 250 ml of ethanol was hydrogenated on 0.5 g of Raney nickel at 25°C under 1 atmosphere of pressure until 1 equivalent of H_2 had been absorbed. The mixture was filtered and the filtrate evaporated to give 1-(p-2-iso-propoxyethoxymethyl-phenoxy)-3-isopropylamino-propan-2-ol, fumarate, m.p. 100°C (after addition of equimolecular quantity of fumaric acid).

References

Jonas R. et al.; US Patent No. 4,171,370; Oct. 16, 1979; Assigned: Merck Patent Gesellschaft mit beschrankter Haftung (Darmstadt, DE)
Jonas R. et al.; US Patent No. 4,258,062; Mar. 24, 1981; Assigned: Merck Patent Gesellschaft mit beschrankter Haftung (Darmstadt, DE)

BIVALIRUDIN

Therapeutic Function: Anticoagulant

Chemical Name: L-Leucine, D-phenylalanyl-L-prolyl-L-arginyl-L-prolylglycylglycylglycylglycyl-L-asparaginylglycyl-L-α-aspartyl-L-phenylalanyl-L-α-glutamyl-L-α-glutamyl-L-isoleucyl-L-prolyl-L-α-glutamyl-L-α-glutamyl-L-tyrosyl

Common Name: Bivalirudin

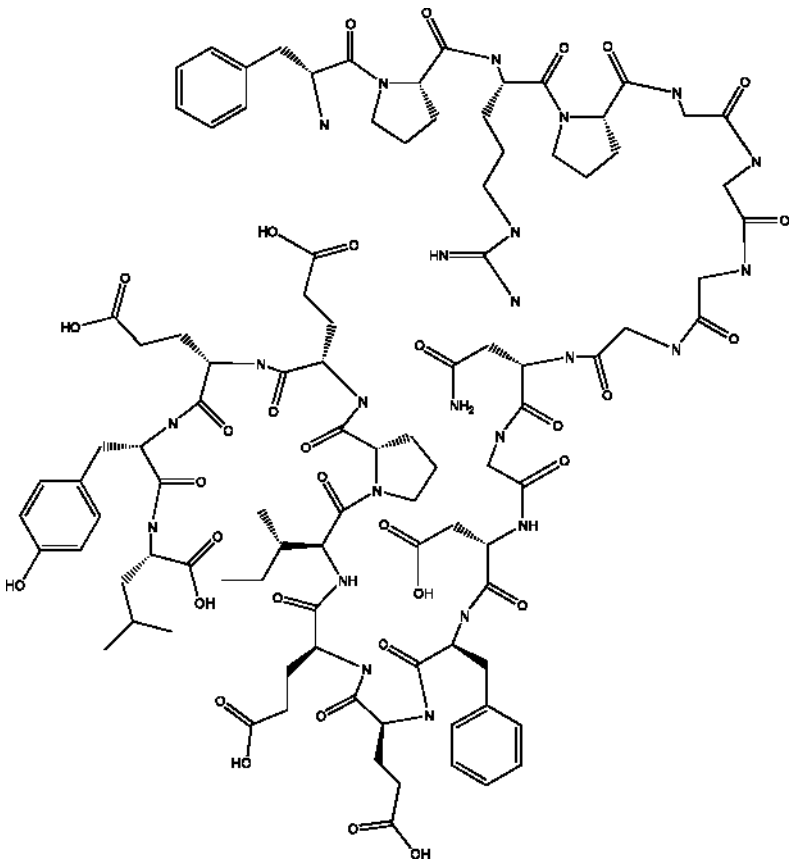
Chemical Abstracts Registry No.: 128270-60-0

Trade Name	Manufacturer	Country	Year Introduced
Angiomax	Oryx	-	-
Angiomax	Medicines Co.	-	-
Bivalirudin	Medicines Co.	-	-
Hirulog	Braine-L' Alleud	Belgium	-

Raw Materials

BOC-L-Leucine-O-divinylbenzene resin
BOC-L-Glutamic acid (γ-benzyl ester)
BOC-L-Proline
BOC-L-Phenylalanine
BOC-L-Asparagine
BOC-L-Arginine
4-Cresol
Trifluoroacetic acid
BOC-O-2,6-Dichlorobenzyl tyrosine
BOC-L-Aspartic acid (β-benzyl ester)
BOC-L-Isoleucine
BOC-Glycine
BOC-L-Phenylalanine
Hydrogen fluoride
Ethylmethyl sulfate

Structural Formula:



Manufacturing Process

A 20 amino acid polypeptide [1], bivalirudin (hirulog) is a synthetic version of hirudin. Its amino-terminal D-Phe-Pro-Arg-Pro domain, which interacts with the active site of thrombin, is linked via four Gly residues to a dodecapeptide analogue of the carboxy-terminal of hirudin. Like hirudin, bivalirudin also forms a 1:1 stoichiometric complex with thrombin. Once bound, however, the Arg-Pro bond at the amino-terminal of bivalirudin is cleaved by thrombin, thereby restoring active site functions of the enzyme complexes of α-thrombin [2].

Hirulog-8 has the formula: H-(D-Phe)-Pro-Arg-Pro-$(Gly)_4$-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu-OH. Hirulog-8 was synthesized by conventional solid-phase peptide synthesis employing an Applied Biosystems 430 A Peptide Synthesizer. This peptide was synthesized using BOC-L-Leucine-O-divinylbenzene resin. Additional t-BOC-amino acids (Peninsula Laboratories,

Belmont, Calif.) used included BOC-O-2,6-dichlorobenzyl tyrosine, BOC-L-glutamic acid (γ-benzyl ester), BOC-L-proline, BOC-L-isoleucine, BOC-L-phenylalanine, BOC-L-aspartic acid (β-benzyl ester), BOC-glycine, BOC-L-asparagine, BOC-L-phenylalanine, and BOC-L-arginine. In order to achieve higher yields in synthesis, the $(Gly)_4$ linker segment was attached in two cycles of manual addition of BOC-glycylglycine (Beckman Biosciences, Inc., Philadelphia, Pa.). After completion of synthesis, the peptide was fully deprotected and uncoupled from the divinylbenzene resin by treatment with anhydrous HF:p-cresol:ethylmethyl sulfate (10:1:1, v/v/v). Following removal from the resin, the peptide was lyophilized to dryness.

Crude Hirulog-8 was purified by reverse-phase HPLC employing an Applied Biosystems 151A liquid chromatographic system and a Vydac C_{18} column (2.2x25 cm). The column was equilibrated in 0.1% TFA/water and developed with a linear gradient of increasing acetonitrile concentration from 0 to 80% over 45 minutes in the 0.1% TFA at a flow-rate of 4.0 ml/min. The effluent stream was monitored for absorbance at 229 nm and fractions were collected manually. We purified 25-30 mg of crude Hirulog-8 by HPLC and recovered 15-20 mg of pure peptide.

The structure of purified Hirulog-8 was confirmed by amino acid and sequence analyses.

References

Maraganore J.M., Bourdon P., Jablonski J., Ramachandran K.L., Fenton J.W.; Design and characterization of hirulogs: a novel class of bivalent peptide inhibitors of thrombin. J. Clin. Invest. 1990;29:7095-101

Skrzypczak-Jankun E., Carperos V.E., Ravichandran K.G., Tulinsky A., Westbrook M., Maraganore J.M.; Structure of the hirugen and hirulog 1 complexes of alpha-thrombin. J. Mol. Biol. 1991;221:1379-93

Maraganore J. et al.; US Patent No. 5,196,404; Mar. 23, 1993; Assigned Biogen, Inc., Cambridge, Mass.; Health Research, Inc., Albany, N.Y.

BLEOMYCIN HYDROCHLORIDE

Therapeutic Function: Antibiotic

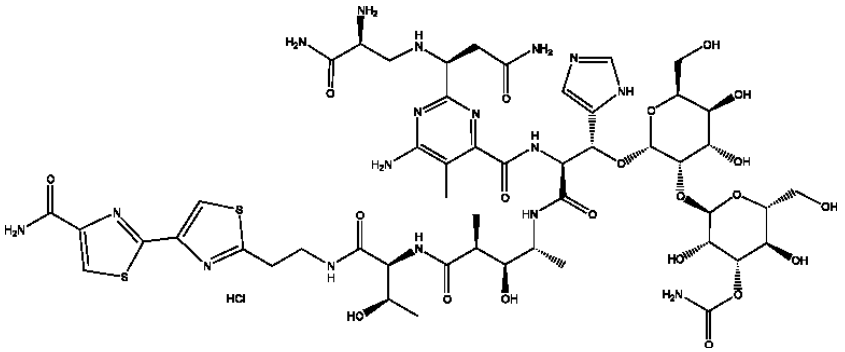
Chemical Name: Bleomycin B_1, mixture of several derivatives which differ from each other in the terminal amino function

Common Name: Bleomicina hydrochloride; Bleomycin hydrochloride

Chemical Abstracts Registry No.: 67763-87-5; 11056-06-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Bleomycin Hydrochloride	Nippon Kayaku, Co.	Japan	-

Structural Formula:



Raw Materials

3-Amino-propyldimethylsulfonium bromide hydrobromate
Streptomyces verticillus (ATCC No 15003)
Millet jelly
Soybean powder
Glucose

Manufacturing Process

To a medium having a composition of 6.4 % of millet jelly, 0.5 % of glucose, 3.5 % of soybean powder, 0.75 % of corn steep liquor, 0.3 % of sodium chloride, 0.1 % of potassium secondary phosphate, 0.05 % of zinc sulfate, 0.01 % of copper sulfate, 0.2 % of sodium nitrate and 0.01 % of Toho No. 1 (trade name for a surface active agent composed of polyoxyethylene manufactured by Toho Chemical Industry Co. Ltd., Japan) was added 3-amino-propyl-dimethylsulfonium bromide hydrobromate in a proportion of 0.4 mg/ml to adjust the pH of the medium to 6.5.

Each 100 ml of the thus treated medium was separately charged into a Sakaguchi flask and was then sterilized. Subsequently, Streptomyces verticillus (ATCC No. 15003) was inoculated in the medium and was cultured at 27°C for 8 days with stirring at 130 r.p.m. Thereafter, the culture liquors (4.5 L) were collected and filtered to obtain 3.0 L of a filtrate (potency 38.8 mg/ml, total potency 416.4 mg). This culture filtrate was passed through and adsorbed on a column packed with 200 ml of Amberlite IRC-50 and was washed with water and was eluted with 0.5 N hydrochloric acid. 1.0 L of the eluate was neutralized, was passed through and adsorbed on a column packed with 100 ml of active carbon, was washed and was then eluted by use of a 1:1 (by volume) mixture of acetone - 0.02 N aqueous hydrochloric acid solution, and fractions active to Mycobacterium 607 were collected and concentrated to dryness. The resulting residue was dissolved in 5 ml of an 80 % aqueous methanol solution and was charged into a column packed with 30 ml of neutral alumina, followed by elution with an 80 % aqueous methanol solution. Subsequently, bleomycin-containing fractions were collected and concentrated to dryness to obtain 195 mg of bleomycin hydrochloride (potency 650.7 mcg/mg, total potency 172 mg). The yield from the culture filtrate was 30.5 %.

References

Products of Toho Chemical Industry Co Ltd., Japan
Patent Specification (London), 1,038,242, Aug 10, 1966
Umezawa H. et al.; US Patent No. RE30,451; Dec. 16, 1980; Assigned: Zaidan Jojin Biseibutsu Kagaku Kenkyu Kai (Tokyo, JP)

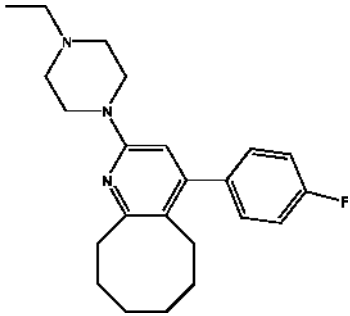
BLONANSERIN

Therapeutic Function: Antipsychotic

Chemical Name: Cycloocta[b]pyridine, 2-(4-ethyl-1-piperazinyl)-4-(1-fluorophenyl)-5,6,7,8,9,10-hexahydro-

Common Name: Blonanserin; AD 5423

Structural Formula:



Chemical Abstracts Registry No.: 132810-10-7

Trade Name	Manufacturer	Country	Year Introduced
Lonasen	Dainippon Pharmaceutical	-	-
Blonanserin	Almirall	-	-

Raw Materials

2-Chloro-4-(4-fluorophenyl)-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine
N-Ethylpiperazine
Potassium iodide

Manufacturing Process

Preparation of 2-(4-ethyl-1-piperazinyl)-4-(4-fluorophenyl)-5,6,7,8,9,10-hexahydrocyclooc ta[b]pyridine:

A mixture of 2-chloro-4-(4-fluorophenyl)-5,6,7,8,9,10-hexahydrocycloocta [b]pyridine (2.0 g), N-ethylpiperazine (2.4 g), and potassium iodide (1.1 g) is stirred at 170°C for 5 hours. After cooling, the reaction mixture is dissolved in ethyl acetate and water. The organic layer is washed with water and extracted with 5% hydrochloric acid. The extract is made alkaline with potassium carbonate, and extracted with ethyl acetate. The extract is washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure.

(a) The residue is recrystallized from acetonitrile to give the desired product (1.2 g), MP: 123°-124°C.

This product obtained in the above (a) is converted to the following salt thereof by treating the product with various acids.

References

Hino K.; US Patent No. 5,021,421; June 4. 1991; Assigned to Dainippon Pharmaceutical Co., Ltd., Osaka, Japan

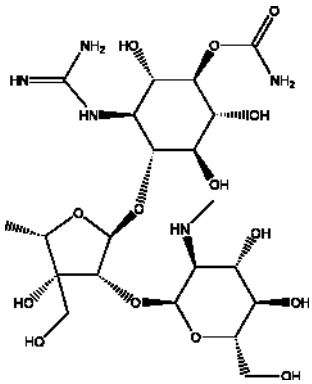
BLUENSOMYCIN

Therapeutic Function: Antibiotic

Chemical Name: Antibiotic obtained from cultures of Streptomyces verticillus, or the same substance produced by any other means

Common Name: Bluensomycin; Glebomycin

Structural Formula:



Chemical Abstracts Registry No.: 11011-72-6

Trade Name	Manufacturer	Country	Year Introduced
Bluencomycin	Shanghai Lansheng Corporation	-	-
Glebomycin	Banyu Pharm. Co., Ltd.	-	-
Glebomycin	DSMZ-Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH	-	-

Raw Materials

Streptomyces bluensis NRRL 2876
Polyacrylic acid cation exchange resin
Sea sand, adsorbent cotton and fossil flour
Carbon

Manufacturing Process

Bluensomycin was obtained from cultures of Streptomyces verticillus, or the same substance produced by any other means. For example antibiotic was prepared by growing of Streptomyces bluensis NRRL 2876 biological way and isolation from cultural solution by adsorption with a cation-exchange resin or a capillary adsorption method by elution with water-acid solution at pH from 1 to 6 or acidic water solution of acetone.

5350 L of cultivating liquid with pH 8.2 was mixed with 16 kg oxalic acid acidified with 1 N sulfuric acid to pH 2.9 and was filtered through about 160 kg fossil flour and washed with 500 L water. The filtrate (about 5400 L) was alkalified to pH 7.8-8 with 10% sodium hydroxide and was filtered through fossil flour filter. Then it was passed through two column with polyacrylic acid cation exchange resin in sodium form (US Patent No. 2,915,432).

Each column was 35 cm in diameter and contained 0.126 kg of above resin. The filtrate (5300 L) was passed with rate 19 L/minute. Then the columns were washed with deionized water, 1 N sulfuric acid to pH 1.2-1.5, and at last eluted with 4x100 L water. About 200 L of column effluent was alkalifed to pH 6.4 with 10% sodium hydroxide. The 1-st column effluent was mixed with 1200 g of activated carbon, the second effluent was mixed with 850 g of coal (1 g coal per 1 g dissolved product). The mixture was thoroughly stirred and filtered. Each coal precipitate was washed 3x10 L with water and 200 L 15% water acetone.

Water acetone effluent from the 1-st column (187 L) was dried and gave 1034 g of bluensomycin, the second gave 777 g. The portions of antibiotic were combined and purified by chromatography. The column (high 1.2 m, volume 155 L, with sea sand, adsorbent cotton and fossil flour as the carrier) was used. It was washed with 150 L of deionized water and 300 L 10% water acetone (rate 410 ml per minute). A fraction 101-127 L water acetone gave 640 g bluensomycin after drying. The IR and UV spectra, element analysis confirmed the structure of prepared product and its purity.

References

Eble T.E., Johnson L-R, E.; D.B. Patent No. 1,183,631; July 19, 1962; the Upjion Company, Kalamazoo, Mich. (V.St. A.)

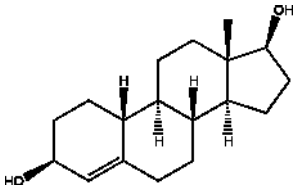
BOLANDIOL

Therapeutic Function: Anabolic

Chemical Name: (3β,17β)-Estr-4-ene-3,17-diol

Common Name: Bolandiol

Structural Formula:



Chemical Abstracts Registry No.: 19793-20-5

Trade Name	Manufacturer	Country	Year Introduced
19-Norandrostenediol	Epochem Co., Ltd.	-	-

Raw Materials

19-Nortestosterone
Lithium aluminum hydride

Manufacturing Process

To a suspension of 6 parts of lithium aluminum hydride in 2100 parts of ether there are added, with stirring, 7.2 parts of 19-nortestosterone in 700 parts of ether. The mixture is stirred with heating on the steam bath for 45 min, after which the unreacted lithium aluminum hydride is decomposed by addition of acetone. The mixture is diluted with water and the organic layer is separated and washed with water and saturated aqueous sodium chloride solution. After drying over anhydrous sodium sulfate, the ether solution is evaporated under vacuum and the residue is dissolved in benzene and thus applied to a chromatography column containing 760 parts of silica gel. The column is developed with benzene and then with 5 and 10% solutions of ethyl acetate in benzene. Further elution with a 15% solution of ethyl acetate in benzene and concentration of the eluate yields a residue which is recrystallized from acetone and water, ethyl acetate and petroleum ether, and again from acetone and water to yield the 4-estrene-3β,17β-diol, melting point 169°-172°C.

References

Colton F.B.; US Patent No. 2,843,608; July 15, 1958; Assigned: G.D. Searle and Co., Chicago, III., a corporation of Delsaware

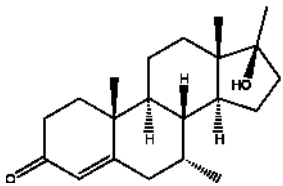
BOLASTERONE

Therapeutic Function: Anabolic

Chemical Name: Androst-4-en-3-one, 17-hydroxy-7,17-dimethyl-, (7α,17β)-

Common Name: Bolasterone; Dimethyltestosterone

Structural Formula:



Chemical Abstracts Registry No.: 1605-89-6

Trade Name	Manufacturer	Country	Year Introduced
Myagen	Upjohn	-	-
Bolasterone	ThermoLife	-	-
Methosarb	Upjohn	-	-

Raw Materials

Copper chloride
Methyl magnesium bromide
Hydrochloric acid
6-Dehydro-17-methyltestosterone
Sodium carbonate

Manufacturing Process

A mixture of 0.4 g of cuprous chloride, 20 ml of 4 M methylmagnesium bromide in ether and 60 ml of redistilled tetrahydrofuran was stirred and cooled in an ice bath during the addition of a mixture of 2.0 g of 6-dehydro-17-methyltestosterone, 60 ml of redistilled tetrahydrofuran and 0.2 g of cuprous chloride. The ice bath was removed and stirring was continued for 4 h. Ice and water were than carefully added, the solution acidified with 3 N hydrochloric acid and extracted several times with ether. The combined ether extracts were washed with a brine-sodium carbonate solution, brine and then

dried over anhydrous magnesium sulfate, filtered and then poured over a 75.0 g column of magnesium silicate (Florisil) packed wet with hexanes (Skellysolve B). The column was eluted with 250 ml of hexanes, 0.5 liter of 2% acetone, two liters of 4% acetone and 3.5 L of 6% acetone in hexanes.

The residues from fractions 8 to 16 were combined and rechromatographed over a 125.0 g column of magnesium silicate. The column was eluted with 6% acetone in hexanes. Fractions 18 to 29 were combined and dissolved in acetone, decolorized with charcoal, and recrystallized from acetone. 1.0 g of a crystalline mixture of the 7-epimers of 7,17-dimethyltestosterone was obtained melting at 120° to 140°C.

The 7α-isomer are separated according to following procedure:

To obtain the 7(α)-isomer of 7,17-dimethyltestosterone the crystalline mixture of the 7 stereoisomers of 7,17-dimethyltestosterone was refluxed in tertiary butyl alcohol with recrystallized chloranil under nitrogen. The reaction mixture was concentrated under a fast stream of nitrogen, diluted with methylene chloride and the solution washed with dilute sodium hydroxide, water and then dried, filtered and the solvent removed. The residue, was combined with the product from an identical run and chromatographed through a magnesium silicate column developed with solvent of the following composition and order: two each of hexane hydrocarbons (Skellysolve B), hexanes plus 4% acetone, hexanes plus 8% acetone, hexanes plus 12% acetone, hexanes plus 14% acetone, hexanes plus 16% acetone, hexanes plus 18% acetone, hexanes plus 20% acetone, hexanes plus 24% acetone, hexanes plus 28% acetone, and two of acetone.

The residues, eluted with mixture: water-acetone, were combined and chromatographed through a 50 g 1:1 charcoal (Darco)-diatomaceous earth (Celite) column. The column was developed with solvent of the following composition and order: methanol, a 1:1 mixture of methanol and acetone, a 1:2 mixture of methanol and acetone, acetone and a 1:4 mixture of acetone and methylene chloride. Fractions, containing 7(α)-epimer were combined, the solvent evaporated and the residue crystallized from acetone to give the 7α,17-dimethyltestosterone, melting point at 163° to 165°C.

References

Babcock J.C., Campbell J.A.; US Patent No. 3,341,557; Sept. 12, 1967; Assigned: The Upjohn Company, Kalamazoo, Mich a corporation of Delaware

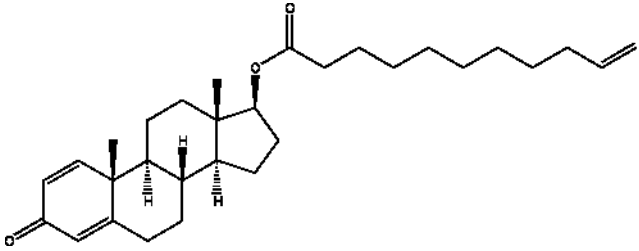
BOLDENONE UNDECYLENATE

Therapeutic Function: Anabolic

Chemical Name: Androsta-1,4-dien-3-one, 17β-hydroxy-, 10-undecenoate

Common Name: Boldenone undecylenate; Boldone; Vebonol

Structural Formula:



Chemical Abstracts Registry No.: 13103-34-9

Trade Name	Manufacturer	Country	Year Introduced
Boldenone undecylenate	Shandong Xinfa Pharmaceutical Co., Ltd.	-	-
Boldenone undecylenate	Epochem Co., Ltd.	-	-
Equipoise	Genfar	-	-
Equipoise	Squibb	-	-
Bold 200	Quality Vet	-	-
Boldane	Squibb	-	-
Vebonol	Ciba-Geigy Agrochemicals	-	-
Vebonol	Ciba-Geigy	-	-
Pace	Jurox Labs	-	-
Parenabol	Ciba	-	-

Raw Materials

L-Dehydrotestosterone
Undecylene chloride

Manufacturing Process

To a solution 5 g of L-dehydrotestosterone in 25 ml of benzene was added 3 ml of pyridine and 7.1 ml undecylene chloride. The mixture was heated for 2 heurs at 70°C. After cooling pyridine hydrochloride was filtered off. The filtrat was purified via chromatography on neutral aluminum oxide. Benzenic eluate was concentrated to obtain 1-dehydrotestosteron 17-undecylenate (boldenone undecylenate) as an oil; λ_{max} 243-244 nm.

References

Belg. Patent No. 623,277, Oct. 10, 1961; Assigned to E. Merck Aktiengesellschaft, Darmstadt, Germany

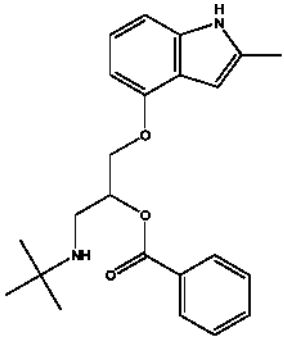
BOPINDOLOL

Therapeutic Function: Beta-adrenergic blocker

Chemical Name: 2-Propanol, 1-((1,1-dimethylethyl)amino)-3-((2-methyl-1H-indol-4-yl)oxy)-, benzoate (ester), (+/-)-

Common Name: Bopindolol; Sandonorm; Wandonorm

Structural Formula:



Chemical Abstracts Registry No.: 62658-63-3

Trade Name	Manufacturer	Country	Year Introduced
Bopindolol	Sandoz (Novartis)	-	-

Raw Materials

Benzoic acid
Hexamethylphosphoric acid triamide
1-t-Butylamino-3-(2-methyl-indole-4-yloxy)-2-propanol
Benzoic acid anhydride
Tartaric acid

Manufacturing Process

4-(2-Benzoyloxy-3-t-butylaminopropoxy)-2-methyl-indole:

26 g of benzoic acid are dissolved, while heating, in 50 ml of hexamethylphosphoric acid triamide and 3.5 g of 1-t-butylamino-3-(2-methyl-indole-4-yloxy)-2-propanol are added. After cooling, 3.0 g of benzoic acid anhydride are added and stirred for 20 hours at room temperature. The resulting clear, yellow solution is poured onto ice 0.5 liters of ether are added and stirred for 2 hours. After making the liquid alkaline with concentrated ammonia, the ether phase is separated, shaken out with tartaric acid, made alkaline with caustic soda solution while cooling with ice and extracted with methylene chloride. After evaporating the solvent, the residue is crystallized with 1 mol of fumaric acid from methanol and acetone.

References

Troxler F. et al.; US Patent No. 4,340,541; July 20, 1982; Assigned to Sandoz Ltd., Basel, Switzerland

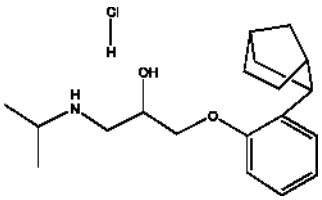
BORNAPROLOL HYDROCHLORIDE

Therapeutic Function: Beta-adrenergic blocker

Chemical Name: 1-(Isopropylamino)-3-(o-2-exo-norbornylphenoxy)-2-propanol hydrochloride

Common Name: Bornaprolol hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 66451-06-7 (Base); 69319-47-7

Trade Name	Manufacturer	Country	Year Introduced
Bornaprolol hydrochloride	Onbio Inc.	-	-

Raw Materials

2-(2-Norbornylexo)phenol
Epichlorohydrin
Sodium
Isopropylamine

Manufacturing Process

1-Isopropylamino-3-[2-(2-norbornylexo)phenoxy]propan-2-ol:

24.5 g (0.13 moles) 2-(2-norbornylexo)phenol (L. A. KHEIFITS and A. E. GOL'DOVSKII, Zh. Obshch. Khim., 1963, 33, 2048), 350 ml anhydrous toluene and 3 g (0.13 mole) metallic sodium are introduced into a three-neck flask through which a stream of nitrogen flows. The reaction mixture is refluxed until the liberation of hydrogen ceases, then the solvent is driven off under reduced pressure and the residue is taken up in 250 ml tetrahydrofuran. 24 g (0.26 mole) epichlorohydrin are then added and the mixture is heated under reflux for 6 hours. An extraction with ether is then undertaken, the organic phase is washed with water, dried and the solvent is evaporated. 25 g 2-(2-norbornylexo)-1-phenoxy-2,3-epoxypropane are thus obtained in the form of

an oil.

15 g (0.06 mole) of the preceding product are dissolved in 50 ml isopropylamine. After 4 days contact, the excess amine is evaporated under reduced pressure, then an extraction with ether is carried out. After washing with water and drying, the ethereal phase is saturated with gaseous hydrochloric acid. The precipitate formed is washed abundantly with ether then crystallized from an acetone/ethanol mixture (3/2). 16 g of the desired product in the form of the hydrochloride are thus obtained, having a melting point of 189°-191°C.

References

Mardiguuian J.; US Patent No. 4,157,400; June 5, 1979; Assigned to MARPHA, Societe d'Etude et d'Explotation de Marques, Paris, France

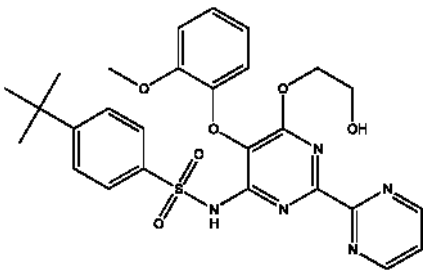
BOSENTAN

Therapeutic Function: Endothelin receptor antagonist

Chemical Name: Benzenesulfonamide, 4-(1,1-dimethylethyl)-N-(6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)(2,2'-bipyrimidin)-4-yl)-

Common Name: Bosentan; Tracleer

Structural Formula:



Chemical Abstracts Registry No.: 147536-97-8

Trade Name	Manufacturer	Country	Year Introduced
Bosentan	Roche	-	-

Raw Materials

Pyrimidine-2-carboxamidine hydrochloride
5-(2-Methoxyphenoxy)-2-(pyrimidin-2-yl)tetrahydropyrimidine-4,6-dione
4,6-Dichloro-5-(2-methoxyphenoxy)-2,2'-bipyrimidine
4-t-Butyl-N-[6-chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)-pyrimidin-4-yl]benzenesulfonamide

Sodium
Ethylene glycol
Tartaric acid

Manufacturing Process

A solution of 0.11 g of sodium in 3.0 ml of ethylene glycol and equivalent of 4-t-butyl-N-[6-chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)-pyrimidin-4-yl]benzenesulphonamide were heated to 100°C, cooled for a further 4 hours, poured on to ice and adjusted to pH 3 with 1 M tartaric acid. The suspension obtained was extracted with ethyl acetate, the organic extracts were combined, washed with water, dried with sodium sulfate and concentrated under reduced pressure. The residue was chromatographed on silica gel with CH_2Cl_2-ethyl acetate 9:1 and yielded 4-t-butyl-N-[6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)-pyrimidin-4-yl]benzenesulphonamide as a solid. Sodium salt melted at 195°-198°C.

The 4-t-butyl-N-[6-chloro-5-(2-methoxyphenoxy)-2-pyrimidin-2-yl)-pyrimidin-4-yl]benzenesulfonamide was prepared starting from pyrimidine-2-carboxamidine hydrochloride via rac-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)tetrahydropyrimidine-4,6-dione and 4,6-dichloro-5-(2-methoxyphenoxy)-2,2'-bipyrimidine.

References

Burri K. et al.; US Patent No. 5,292,740; March 8, 1994; Assigned to Hoffmann-La Roche Inc., Nutley, N.J.

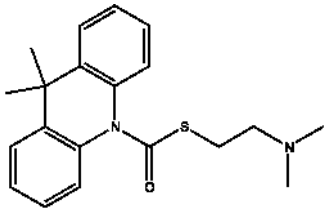
BOTIACRINE

Therapeutic Function: Antiparkinsonian

Chemical Name: 10-Acridancarbothioic acid, 9,9-dimethyl-, S-(2-(dimethylamino)ethyl) ester

Common Name: Botiacrine

Structural Formula:



Chemical Abstracts Registry No.: 4774-53-2

Trade Name	Manufacturer	Country	Year Introduced
Botiacrine	ZYF Pharm Chemical	-	-

Raw Materials

Dimethylaminoethanethiol
9,9-Dimethylacridan
Phosgene

Manufacturing Process

To 1 gramm-equivalent (g-eq) of dimethylaminoethanethiol in 150 ml of ether, a suspension of g-eq of 50% sodium hydride in 50-ml of anhydrous ether was added. After boiling for 1 hour, the reaction mixture was cooled to 0°C, whereupon g-eq of 9,9-dimethylacridan-10-carboxylic acid chloride (prepared from 9,9-dimethylacridan and phosghene - cf. Swiss Specification No. 426,821) were added and the mixture was heated for a further 6 hours to boiling temperature. After cooling to ambient temperature, the precipitated sodium chloride was filtered in a Buchner funnel fitted with a filter cell. The corresponding 9,9-dimethylacridan-10-carboxylic acid-dimethylaminoethanethiol ester was immediately precipitated out of filtrate as base, which melted at 110.5°-111°C. Ethanesulphonic acid salt melted at 147°-150°C.

References

Molnar I. et al.; US Patent No. 3,630,918; August 20, 1974; Assigned to Siegfried Aktiengesellschaft, Zofingen, Switzerland

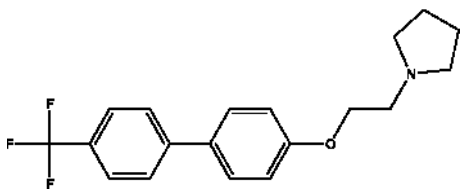
BOXIDINE

Therapeutic Function: Antihyperlipidemic

Chemical Name: Pyrrolidine, 1-(2-((4'-(trifluoromethyl)(1,1'-biphenyl)-4-yl) oxy)ethyl)-

Common Name: Boxidine

Structural Formula:



Chemical Abstracts Registry No.: 10355-14-3

Trade Name	Manufacturer	Country	Year Introduced
Boxidine	Onbio Inc.	-	-

Raw Materials

p-Iodobenzotrifluoride
Copper
2-Pyrrolidinylethyl chloride
p-Bromobenzotrifluoride
Methyl iodide
Nitrobenzene
p-Iodoanisole
Hydrobromic acid
4-Hydroxy-4'-trifluoromethylbiphenyl
4-Methoxycyclohexanone
Palladium on carbon

Manufacturing Process

The title compound may be prepared 2 ways:

1). 1-(2-[4'-(Trifluoromethyl)-4-biphenylyloxy]ethyl)pyrrolidine:

A suspension consisting of 89.8 g (0.33 mole) of p-iodobenzotrifluoride, 132.5 g (0.65 mole) of p-iodoanisole, and 322.7 g of Cu powder in DMF (175 ml) was heated (225-230°C) with stirring in a resin pot for about 5 days. After cooling, the solid reaction mass was pulverized and continuously extracted (heptane) for 2 days. Evaporation of the solvent left a dark brown residue (ca. 50 g) which was dissolved (heptane, 200 ml), decolorized (charcoal), and concentrated to 100 ml. On standing ca. 20 g of impure 4,4'-dimethoxybiphenyl were deposited as colorless crystals. Fractional crystallization was continued until the crops of crystalline material were free of impurities by TLC (80:20 heptane-ethyl acetate). Pure 4-methoxy-4'-trifluoromethylbiphenyl was isolated as colorless granules, 21.6 g (26%), MP: 124-126°C. A solution consisting of 21.6 g (0.09 moles) of 4-methoxy-4'-trifluoromethylbiphenyl dissolved in glacial acetic acid and HBr (48%) was refluxed for approximately 24 hr. After cooling the acetic reaction mixture was poured into H_2O (1.5 L) and the solid which separated was collected and air dried. 18.0 g (83%) of the crude product was isolated and taken up in Et_2O (100 ml), decolorized (charcoal), filtered, and concentrated to one-third of the original volume. The material which separated from the Et_2O solution (m.p. 147-148°C) was pure enough for the next synthetic step (structure verified by NMR). 1.5.6 g (0.06 mole) of the sodium derivative of 4-hydroxy-4'-trifluoromethylbiphenyl (prepared from 4-hydroxy-4'-trifluoromethylbiphenyl and sodium hydride) allowed to react with 8.0 g (0.06 mole) of 2-pyrrolidinylethyl chloride in refluxing DMF (100 ml) for 18 hr. The resulting suspension was cooled, filtered, and the clear filtrate was concentrated to semisolid residue. Two 100 ml portions of water were used to triturate the crude product which was then dissolved in benzene; the solution was decolorized (char coal) and dried (Na_2SO_4) and the benzene was removed. Several fractional crystallizations from acetone afforded 9.8 g (49%) of pure 1-1 2- [4'-(trifluoromethyl)-4-biphenylyloxy]ethyl)pyrrolidine MP: 109-110°C.

2). p-Bromobenzotrifluoride (1.37 g, 0.7 mole) and ca. 1.0 g of MeI dissolved in dry Et_2O (200 ml) was added to 19 g (0.8 g-atom) of 11 g suspended in Et_2O (20 ml) under the usual conditions. Addition of the aromatic halide was regulated to maintain a gentle reflux and refluxing was continued an

additional 1 hr after addition was complete. 4-Methoxycyclohexanone (64 g, 0.5 mole) dissolved in 75 ml of dry Et_2O was added to the freshly formed Grignard reagent with vigorous stirring and, after addition of the ketone was complete, the reaction mixture was refluxed with stirring for approximately 1 hr. Decomposition of the Grignard reagent-ketone addition product was achieved by adding excess cold, aqueous ammonia chloride (53 g in 1 L of H_2O), and the crude product was removed using two 100-ml portions of Et_2O. The combined extracts were decolorized (charcoal), filtered, and dried (Na_2SO_4). Removal of the Et_2O left a brown, oily residue which was distilled in vacuum affording 51.3 g (38%) of 1-(p-trifluoromethylphenyl)-4-methoxycyclohexanol, b.p. 121-122°C (0.4-0.5 mm), m.p. 53-54°C.

The 4-methoxycyclohexanol derivative (27 g, 0.1 mole), purified as described above, was added to a vigorously stirred concentrated H_2SO_2-glacial acetic acid (10:40 ml) solution. When a clear solution resulted (ca. 2 min), the reaction mixture was poured all at once into a previously cooled (5-10% mixture of H_2O (300 ml) covered with Et_2O (300 ml)). The Et_2O layer was separated, dried (Na_2SO_4), and concentrated to a brown, oily residue. Fractionation of the crude oil yielded 18.3 g (717) of 1-(p-trifluoromethylphenyl)-4-methoxycyclohexene, b.p. 104-103°C (0.3-0.4 mm).

Dehydrogenation of the purified 4-methoxycyclohexene derivative, obtained as described above, was accomplished using a modification of the method described by Anisworth (J.A.C.S., 76, 4446 (1954)). A suspension consisting of 1-(p-trifluoromethylphenyl)-4-methoxycyclohexene (500 g, 1.95 moles), 166 g of Pd/C and nitrobenzene was refluxed for 22 hr. Aliquots of the reaction mixture taken periodically and analyzed by TLC (heptane-ethyl acetate (4:1) solvent system) indicated that aromatization was complete after this period of time, Removal of the nitrobenzene under reduced pressure left 442 g (89.9%) of the crude biphenyl derivative. Two recrystallizations (petroleum ether) produced material identical with that obtained from the 1 procedure described above.

References

Bach FL et al.; J. Med. Chem.; 1968, 11, 987

BRETAZENIL

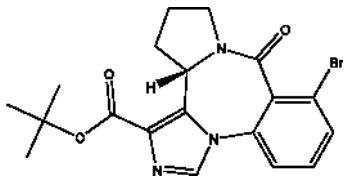
Therapeutic Function: Anxiolytic

Chemical Name: (S)-8-Bromo-11,12,13,13a-tetrahydro-9-oxo-9H-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylic acid 1,1-dimethylethyl ester

Common Name: Bretazenil

Chemical Abstracts Registry No.: 84379-13-5

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Bretazenil	Hoffman-La Roche, Inc.	-	-

Raw Materials

6-Bromoisatoic acid anhydride
Sodium hydride
Potassium t-butylate
Proline, L-
Diethylchlorophosphate
t-Butyl isocyanoacetate

Manufacturing Process

50.6 mmol of 6-bromoisatoic acid anhydride are stirred at 110°C for 2 hours with 50.6 mmol of L-proline in 80 ml of dimethyl sulphoxide. The solution is evaporated and the residue is crystallized from ethyl acetate. There is obtained (S)-6-bromo-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H)-dione.

A suspension of 29.8 mmol of sodium hydride (55 percent oil dispersion) in 40 ml of dry dimethylformamide is treated at 20-30°C with 27.1 mmol of (S)-6-bromo-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H)-dione, the mixture is stirred in the above temperature range for 45 min and then at -35°C 27.1 mmol of diethylchlorophosphate are added dropwise thereto.

Separately, 3.0 g (27.1 mmol) of potassium t-butylate are dissolved in 9.0 ml of dry dimethylformamide, cooled in an acetone/dry-ice bath, treated with 3.9 g (27.1 mmol) of t-butyl isocyanoacetate and the solution obtained is added dropwise at -15°C to the mixture obtained according to the preceding paragraph. The mixture is warmed to 15°C, neutralized with 1.5 ml of glacial acetic acid, poured into 100 ml of water and extracted four times with methylene chloride. The methylene chloride solution is washed twice with water, dried over magnesium sulfate, evaporated and the crude product obtained is chromatographed on silica gel using ethyl acetate for the elution. By recrystallization from ethyl acetate/n-hexane there is obtained t-butyl (S)-8-bromo-11,12,13,13a-tetrahydro-9-oxo-9H-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylate.

References

Hunkeler W., Kyburz E.; US Patent No. 4,353,827; October 12, 1982; Assigned to Hoffmann-La Roche Inc. (Nutley, NJ)

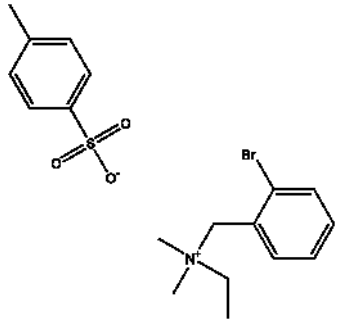
BRETYLIUM TOSYLATE

Therapeutic Function: Adrenergic blocker; 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	UK	1973
Bretylate	Wellcome	France	1974
Bretylol	Am. Crit. Care	US	1978
Critifib	Arnar-Stone	US	-
Darenthin	Burroughs-Wellcome	US	-

Raw Materials

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

Manufacturing Process

N-o-Bromobenzyl-N,N-dimethylamine (100g) 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.; US Patent 3,038,004; June 5, 1962; assigned to Burroughs Wellcome and Co.

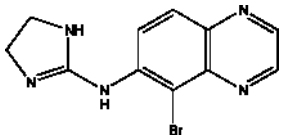
BRIMONIDINE

Therapeutic Function: Antiglaucoma

Chemical Name: 6-Quinoxalinamine, 5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-

Common Name: Brimonidine

Structural Formula:



Chemical Abstracts Registry No.: 59803-98-4

Trade Name	Manufacturer	Country	Year Introduced
Alphagan P	Allergan	Australia	-
Brimonidine	Ratiopharm	-	-

Raw Materials

6-Aminoquinoxaline
Thiophosgene
Sodium bisulfite
Bromine
Ethylenediamine

Manufacturing Process

6-Aminoquinoxaline (2.08 g, 14.4 mmol) was dissolved in 11.5 ml glacial acetic acid. The solution was cooled in water while a solution of bromine (0.74 ml, 2.3 g, 14.4 mmol) in 1.5 ml glacial acetic acid was added slowly over 15 min. After stirring for an additional 30 min. the orange red solid formed was filtered off and washed thoroughly with dry ether. The solid was dried in vacuo overnight to yield 4.44 g crude product (a yield of 100%). The compound, 6-amino-5-bromoquinoxaline hydrobromide, had no definite melting point. A

phase change (from fine powder to red crystals) was noticed at about 220°C. Decomposition was observed at about 245°C. It was used directly for the next step.

The crude 6-amino-5-bromoquinoxaline from above was dissolved in water and saturated sodium bisulfite solution was added until the resulting solution tested negative with starch-iodide paper. The solution was then basified with 2 N sodium hydroxide and extracted thoroughly with ethyl acetate. The organic extract was dried over magnesium sulfate and concentrated under reduced pressure to give the free base. The crude product was recrystallized from boiling benzene to give yellow crystals, m.p. 155°-156°C. Using various analytical procedures, the yellow crystals were determined to be 6-amino-5-bromoquinoxaline. The yield was 82%.

The crude hydrobromide product previously noted (4.27 g, 14.0 mmol) was dissolved in 60 ml of water and thiophosgene (1.28 ml, 16.8 mmol) was added in small portions with vigorous stirring. After 2 hours, the red color of the solution was discharged. The solid formed was filtered off and washed thoroughly with water. After drying in vacuo at 25°C 3.38 g (a yield of 90%) of brick red crystals was obtained, m.p. 157°-158°C. A portion of this material was further purified by column chromatography to give white crystals, m.p. 157°-158°C. Using various analytical procedures, these crystals were determined to be 5-bromo-6-isothiocyanatoquinoxaline.

A solution of the isothiocyanate (3.25 g, 12.2 mmol) in 145 ml benzene was added to a solution of ethylenediamine (5.43 g, 90.0 mmol) in 18 ml benzene at 25°C over 2 hours. After stirring for a further 30 min., the supernatant was poured off. The oil which remained was washed by swirling with dry ether three times and used directly for the next step. A portion of this product was further purified by column chromatography (SiO_2, $CHCl_3$) for characterization. A white solid was decomposed at 175°C. This white solid was determined to be 5-bromo-6-(N-2-(aminoethyl)thioureido)quinoxaline.

The crude product from above was dissolved in 100 ml dry methanol and the brown solution was refluxed for 19 hours until hydrogen sulfide gas was no longer evolved. The mixture was cooled to room temperature and concentrated to about 50 ml. The yellow solid was filtered off and dried in vacuo; weight 2.52 g (a yield of 70%), m.p. 242°-244°C. As the crude product was insoluble in most common organic solvents, initial purification was achieved by an acid-base extraction procedure. 23 g of the crude product was dissolved in 100 ml 0.5 N hydrochloric acid. The turbid yellow solution was filtered to give a clear orange yellow solution which was extracted twice with ethyl acetate (2x10 ml). The aqueous phase was cooled to 0°C and basified with 6 N sodium hydroxide, keeping the temperature of the solution below 15°C at all times. The yellow solid which precipitated was filtered off and washed thoroughly with water until the washings were neutral to pH paper. The solid was dried overnight in vacuo to give 1.97 g yellow solid, m.p. 249°-250°C. The recovery was about 88%.

Further purification was achieved by recrystallization as described below. The partially purified product from above was dissolved in N,N-dimethylformamide (about 17 ml/g) at 100°C with vigorous stirring. The solution was filtered hot and set aside to cool overnight. The bright yellow crystals were collected by filtration, m.p. 252°-253°C. Recovery was from 65-77%. Using various

analytical procedures the bright yellow solid was determined to be 5-bromo-6-(2-imidazolin-2-ylamino)quinoxaline.

References

Danielewicz J.C. et al.; US Patent No. 3,890,319; June 17, 1975; Assigned: Pfizer Inc., NewYork, N.Y.
Burke J.A. et al.; US Patent no. 5,756,503; May 26, 1998; Assigned: Allergan (Waco, TX)

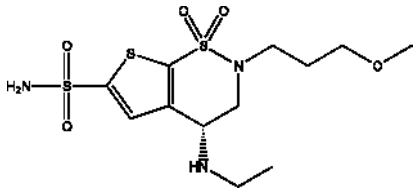
BRINZOLAMIDE

Therapeutic Function: Antiglaucoma

Chemical Name: (R)-4-Ethylamino-2-(3-methoxypropyl)-3,4-dihydro-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide

Common Name: Brinzolamide

Structural Formula:



Chemical Abstracts Registry No.: 138890-62-7

Trade Name	Manufacturer	Country	Year Introduced
Azopt	Alcon	-	-

Raw Materials

3-(2,5,5-Trimethyl-1,3-dioxane-2-yl)thiophene
2-Bromoethyl methylether
2-(Bromomethyl)ethyl methyl ether
Propylamine
Sulfur dioxide
Hydroxylamine-O-sulfonic acid
Pyridinium bromide perbromide
Sodium borohydride
Butyl lithium

Manufacturing Process

To a solution of 3-(2,5,5-trimethyl-1,3-dioxane-2-yl)thiophene (2.5 g, 11.7 mmol) in hexane (30 mL) cooled to 0°C was added via syringe n-butyl lithium in hexane (2.5 M, 10.3 mL, 25.7 mmol) over 5 min. The mixture was stirred at 0°C for 20 min, the ice bath was removed and the stirring was continued for 30 min. At this time a white precipitate formed. The mixture was cooled to

-60°C and THF (20 mL) was added. Sulfur dioxide was then passed through the surface of the mixture for 30 min. The mixture was warmed to ambient temperature and stirred for an additional 15 min. The volatiles were evaporated and to the residue was added water (50 mL) and sodium acetate trihydrate (9.55 g, 70.2 mmol). The solution was cooled on an ice bath and hydroxylamine-O-sulfonic acid (4.62 g, 40.9 mmol) was added. The mixture was stirred at ambient temperature for 1 h, extracted with ethyl acetate (3x100 mL) and the combined extracts were washed with a sodium bicarbonate solution, brine and dried over molecular sieves. Evaporation to dryness gave a viscous liquid (4.93 g), which was chromatographed (silica, eluting with 33% ethyl acetate-hexane) to give a solid 3-(2,5,5-trimethyl-1,3-dioxane-2-yl)-2-thiophenesulfonamide (2.47 g, 72%): m.p. 200°-202°C.

The last compound (9.45 g, 32.5 mmol) and 1 N HCl (100 mL) in THF (100 mL) was heated at reflux for 1 h. The THF was evaporated and the aqueous solution was made basic by the addition of sodium bicarbonate. The mixture was cooled using an ice bath and the precipitate was filtered, washed with cold water and dried in vacuo to give 5.83 g (88%) of a solid 3-acetyl-2-thiophenesulfonamide: m.p. 193°-196°C.

The last product (5.73 g, 28.0 mmol) was dissolved in hot THF (200 mL). The solution was cooled to 10°C and pyridinium bromide perbromide (10.73 g, 33.5 mmol) was added. The mixture was allowed to stir at ambient temperature for 1 h. The volatiles were evaporated and the residue was mixed with water. The precipitate was filtered, washed with cold water and dried in vacuo overnight to give 7.77 g of a solid. A portion of this solid (3.49 g, 12.3 mmol) was suspended in ethanol (100 mL) and treated with sodium borohydride (266 mg, 7.04 mmol). The suspension turned clear after 10 min and was heated at reflux for 1 h. The ethanol was evaporated and the residue was extracted with ethyl acetate, washed with brine and evaporated to give 3,4-dihydro-4-hydroxy-2H-thieno[3,2-e]-1,2-thiazine 1,1-dioxide (1.80 g, 71%): m.p. 138°-140°C.

A solution of the above product (19.2 g, 0.093 mol) in DMF (125 mL) was added to a suspension of sodium hydride (3.08 g, 80% oil dispersion, 0.103 mol) in DMF at 006. When the addition was completed the ice bath was removed and the reaction 20 mixture stirred at ambient temperature for 1 h. The reaction mixture was cooled to 0°C and 2-bromoethyl methylether (13.6 mL, 0.14 mol) was added. The reaction mixture was stirred at ambient temperature for 18 h after which time it was evaporated to dryness. The residue was suspended in brine (100 mL) and extracted with methylene chloride (4x80 mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated to a solid which was recrystallized from ethyl acetate to give the desired subject (17.4 g). Chromatography of the mother liquor (silica, 3% ethanol/methylene chloride) furnished more subject which was combined with the first batch to give a total of 19.3 g (78%) of 3,4-dihydro-4-hydroxy-2-(2-methoxy)ethyl-2H-thieno[3,2-e]-1,2-thiazine 1,1-dioxide.

3,4-Dihydro-4-hydroxy-2-(2-methoxy)ethyl-2H-thieno[3,2-e]-1,2-thiazine 1,1-dioxide (4.9 g, 50 18.6 mmol) was converted to the 4-(1-ethoxy)ethoxy-3,4-dihydro-2-(2-methoxy)ethyl-2H-thieno[3,2-e]-1,2-thiazine 1,1-dioxide (6.2 g, 99%) using the reaction with p-toluensulfonic acid and ethylvinyl ether at 0°C in tetrahydrofuran for 2 hrs.

The last one (6.2 g, 18.4 mmol) was converted into 3,4-dihydro-4-hydroxy-2-(2-methoxy)ethyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide (4.87 g, 77%) m.p. 187°C by using the reaction with n-butyl lithium in anhydrous THF at -40°C for 40 min, and then bubbling sulfur dioxide gas for 20 min after which time the mixture was warmed to room temperature. After 30 min at room temperature the mixture was concentrated the residue was dissolved in water, cooled (0°C), sodium acetate trihydrate was added followed by hydroxylamine-O-sulfonic acid. The reaction mixture was stirred at room temperature for 18 h after which time was basified with solid sodium bicarbonate and extracted with ethyl acetate.

3,4-Dihydro-2-(2-methoxy)ethyl-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride was obtained by the reaction of 3,4-dihydro-4-hydroxy-2-(2-methoxy)ethyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide in THF containing triethylamine with tosyl chloride at -16°C and the next stirring for 18 hrs at room temperature. After which time the mixture was cooled to 0°C and propylamine was added, the desired product (0.57 g, 46%) was obtained: m.p. 178°-181°C.

The desired 4-ethylamino-3,4-dihydro-2-(3-methoxy)propyl-2H-thieno[3,2-e]-1,2-thriazine-6-sulfonamide-1,1-dioxide was prepared according to described above procedure for 3,4-dihydro-4-hydroxy-2-(2-methoxy)ethyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide substituting 2-bromoethylmethylether for 2-(bromomethyl)ethyl-methylether.

References

Dean T.R. et al.; US Patent No. 5,240,923; Aug. 31, 1993; Assigned: Alcon Laboratories, Inc. (Fort Worth, TX)

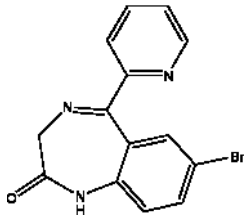
BROMAZEPAM

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	UK	1982
Compedium	Polifarma	Italy	-
Creosidin	Osiris	Argentina	-
Lectopam	Hoffmann - La Roche Inc.	US	-
Lenitin	Ikapharm	Israel	-
Lexaurin	Krka	Yugoslavia	-
Lexilium	Alkaloid	Yugoslavia	-
Normoc	Merckle	W. Germany	-

Raw Materials

2-(2-Aminobenzoyl)pyridine
Bromine
Bromoacetyl bromide
Ammonia
Acetic anhydride
Hydrogen chloride
Water

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)-pyridinein 250 cc of acetic acid. The dark solution was stirred for another 3 hours, permitted to stand over night, 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)-pyridineas yellow crystals melting at 131.5°-133°C.

20.85 grams of 2-(2-acetamido-5-bromobenzoyl)-pyridinein 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)-pyridinehydrochloride. Digestion of this

hydrochloride with 0.5liter 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)-pyridinehydrobromide 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)-pyridinewas 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 stirrind 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 and Engel p.110
DOT 9 (6) 238 (1973) and 11 (1) 31 (1975)
I.N. p. 154
REM p. 1064
Fryer, R.I., Schmidt, R.A. and Sternbach, L.H.; US Patent 3,100,770; August 13, 1963; assigned to Hoffmann-LaRoche Inc.
Fryer, R.I., Schmidt, R.A. and Sternbach, L.H.; US Patent 3,182,065; May 4, 1965; assigned to Hoffmann-LaRoche Inc.
Fryer, R.I., Schmidt, R.A. and Sternbach, L.H.; US 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	US	1962
Bromelain	Nadrol	W. Germany	1965
Resolvit	Mepha	Switz.	1965
Ananase	Rorer	Italy	1965
Ananase	Rorer	UK	1966
Extranase	Rorer	France	1969
Bromelain	Towa Yakuhin	Japan	1981
Ananase	Pharmax	UK	-
Ananase	Yamanouchi	Japan	-
Bromelain	Permicutan	W. Germany	-
Dayto Anase	Dayton	US	-
Inflamen	Hokuriku	Japan	-
Mexase	Ciba Geigy	France	-
Pinase	Dainippon	Japan	-
Proteolvis	Benvegna	Italy	-
Resolvit	Mepha	Switz.	-
Rogorin	Saba	Italy	-
Traumanase	Arznei Muller-Rorer	W. Germany	-

Raw Materials

Pineapple Juice
Acetone

Manufacturing Process

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

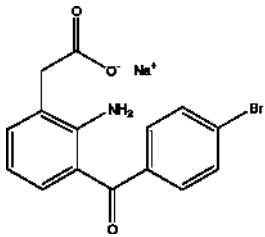
BROMFENAC SODIUM

Therapeutic Function: Analgesicá Antiinflammatory

Chemical Name: 2-Amino-3-(4-bromobenzoyl)benzeneacetic acid, sodium salt

Common Name: Bromfenac sodium

Structural Formula:



Chemical Abstracts Registry No.: 91714-93-1; 91714-94-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Duract	Wyeth-Ayerst	-	-
Xibrom	ISTA Pharmaceuticals, Inc.	-	-

Raw Materials

(2-Aminophenyl)-(4-bromophenyl)-methanone
t-Butyl hypochlorite
Methylsulfanylacetic acid ethyl ester
Nickel Raney

Manufacturing Process

Reaction of (2-aminophenyl)-(4-bromophenyl)-methanone with methylsulfanylacetic acid ethyl ester and tert-butyl hypochlorite gives a corresponding sulfonium salt. This salt was transformed to initially to the betaine. Electrocyclic rearrangement of that transient intermediate leads, after rearomatization, to the homoanthranilic acid. Internal ester-amine interchange leads then to 4-bromophenyl-(3-(methylthio)indolin-7-yl)methanone. The thiomethyl group is then removed with Raney nickel to give 4-bromophenyl-(indolin-7-yl)methanone. Saponification of this intermediate affords the (2-amino-3-(4-bromobenzoyl)-phenyl)-acetic acid (Bromfenac).

In practice it is usually used as sodium salt.

References

Merck Index, Monograph number: 1411, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Walsh D.A. et al.; J. Med. Chem.; 1984, 27, 1379
Gassman P.G. et al.; J. Amer. Chem. Soc.; 1973, 95, 6508

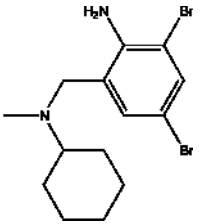
BROMHEXINE

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 salt)

Trade Name	Manufacturer	Country	Year Introduced
Bisolvon	Boehringer Ingelheim	Switz.	1963
Bisolvon	Thomae	W. Germany	1963
Bisolvon	Boehringer Ingelheim	Italy	1968
Bisolvon	Boehringer Ingelheim	UK	1968

Trade Name	Manufacturer	Country	Year Introduced
Bisolvon	Boehringer Ingelheim	France	1969
Lebelon	Towa Yakuhin	Japan	1981
L-Customed	Roha	W. Germany	1982
Aletor	Cantabria	Spain	-
Auxit	Heyden	W. Germany	-
Bendogen	Gea	Denmark	-
Bromeksin	Mulda, Yurtoglu	Turkey	-
Broncokin	Geymonat	Italy	-
Bronkese	Lennon	S. 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
Hydrazine
Cyclohexylmethylamine
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 159 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 600cc 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 and Engel p.113
OCDS Vol.2 p.96 (1980)
I.N. p. 154
Keck, J.; US Patent 3,336,308; August 15, 1967; assigned to Boehringer Ingelheim G.m.b.H.

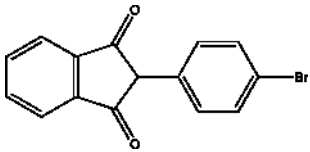
BROMINDIONE

Therapeutic Function: Anticoagulant

Chemical Name: 2-p-Bromophenylindandione

Common Name: Bromindione; Bromophenindione; Brophenadione

Structural Formula:



Chemical Abstracts Registry No.: 1146-98-1

Trade Name	Manufacturer	Country	Year Introduced
Bromindione	Chemical Formulations	-	-

Raw Materials

Sodium
Phthalide
Ethanol
p-Bromobenzaldehyde

Manufacturing Process

To a solution of 1.85 g of sodium in 40 ml of ethanol, was added 10 g of phthalide and 14.0 g of p-bromobenzaldehyde, and the reaction mixture was heated on the steam bath for one hour. Water was then added, and the alcohol was distilled off. Then after adding additional water, the reaction mixture was acidified with hydrochloric acid to precipitate the crude product, which was filtered off, dried and recrystallized from methanol. The 2-p-bromophenylindandione is in the form of dark red crystals, having a melting point of 133-135°C.

References

Merck Index, Monograph number: 1414, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Freedman L. et al.; US Patent No. 2,847,474; Aug. 12, 1958; Assigned to U.S. Vitamin Corporation, New York

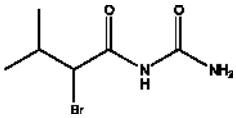
BROMISOVALUM

Therapeutic Function: Sedative, Hypnotic

Chemical Name: 2-Bromo-3-methylbutyrylurea

Common Name: Bromisoval; Bromisovalerianyl carbamidum; Bromyl; Bromovalcarbamide; Bromovalharnstoff; Bromovaluree; Bromvaletone; Bromvalerocamidum; Bromvalerylurea

Structural Formula:



Chemical Abstracts Registry No.: 496-67-3

Trade Name	Manufacturer	Country	Year Introduced
Bromisovalum	Linhai Duqiao Fine Chemical Factory	-	-
Albroman	Chinoin	-	-
Bromisoval	Slovakofarma	-	-
Milocardin	Polpharma	-	-
Sedual	Pharmed	-	-
Alluval	Berlin-Chemie	-	-
Bromural	Knoll	-	-
Bromoval	Sicomed	-	-
Calmotin	Takeda Pharmaceutical Company Ltd.	-	-
Dormigene	Pharmacobel	-	-
Isobromyl	Clin-Comar-Byla	-	-
Isoval	Mission	-	-
Pivadorm	Specia	-	-
Sedural	Rekah Pharmaceutical Industry Ltd.	-	-
Somnol	Grindex	-	-
Somnurol	Synochem	-	-
Valural	Medica	-	-

Raw Materials

2-Bromoisovalerylbromide
Urea

Manufacturing Process

A mixture of 2 kg 2-bromoisovalerylbromide and 1 kg dry urea is heated at 70°C. Then to the reaction mixture is added sodium hydrogen carbonate. 2-Bromo-3-methylbutyrylurea is recrystallized from toluene or water, melting point 149°C.

References

Merck Index, Monograph number: 1418, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
DE Patent No. 185,962; Mar 3, 1907; Assigned to Knoll and Ludwigschafen

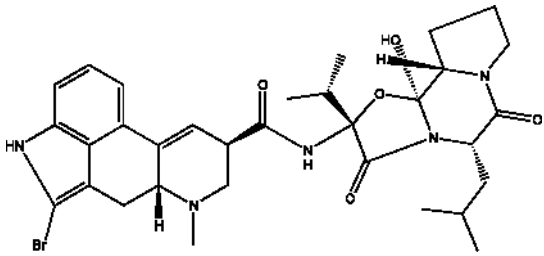
BROMOCRIPTINE

Therapeutic Function: Prolactin inhibitor

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 salt)

Trade Name	Manufacturer	Country	Year Introduced
Parlodel	Sandoz	UK	1975
Pravidel	Sandoz	W. Germany	1977
Parlodel	Sandoz	Switz.	1977
Parlodel	Sandoz	US	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 drop wise 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 afterbromination in accordance with the method described above. The fractions containing the pure heading compound are combined and crystallized from methyl ethyl ketonehopropy1 ether. Melting point 215°-218°C (decomp.), $[\alpha]_D^{20}$-195° (c = 1 in methylene chloride).

References

Merck Index 1386
Kleeman and 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.; US Patent 3,752,814; August 14, 1973; assigned to Sandoz Ltd., Switzerland
Fluckiger, E., Troxler, F. and Hofmann, A.; US Patent 3,752,888; August 14, 1973; assigned to Sandoz Ltd., Switzerland

BROMODIPHENHYDRAMINE

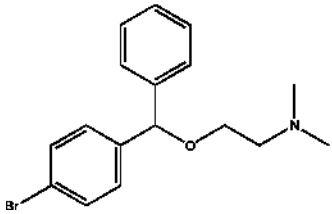
Therapeutic Function: Antihistaminic

Chemical Name: p-Bromo-α-phenylbenzyloxy-N,N-dimethylethylamine

Common Name: Bromazine; Bromdiphenhydraminum; Histabromazine; Bromodiphenhydramine

Chemical Abstracts Registry No.: 118-23-0

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Bromazine	Shanghai Lansheng Corporation	-	-
Ambodryl	Parke Davis and Co. Ltd.	-	-
Bromo-Benadryl	Parke Davis and Co. Ltd.	-	-

Raw Materials

p-Bromobenzhydrylbromide
Ethylene chlorohydrin
Calcined sodium carbonate
Dimethylethylamine

Manufacturing Process

28.1 parts of p-bromobenzhydrylbromide are heated to boiling, under reflux and with stirring, with 50 parts of ethylene chlorohydrin and 5.3 parts of calcined sodium carbonate. The reaction product is extracted with ether and the etheral solution washed with water and dilute hydrochloric acid. The residue from the solution in ether [p-bromobenzhydryl(β-chloroethyl)ether].

28.1 parts of this ether are heated with 12 parts of dimethylethylamine in a sealed tube for 4 hours at 110°C. The product of the reaction is extracted several time with dilute hydrochloric acid. The acid solution made alkaline, in the cold, with concentrated caustic soda solution, and the base which separates taken up in ether. The ether extract is washed with concentrated potassium carbonate solution, evaporated down, and the residue distilled in vacuo. Boiling point of p-bromo-α-phenylbenzyloxy)-N,N-dimethylethylamine 151-154°C under 0.3 mm.

p-Bromo-α-phenylbenzyloxy)-N,N-dimethylethylamine may be used as a hydrochloride.

References

GB Patent No. 670,622; April 23, 1952; Assigned to Parke Davis and Corporation, USA

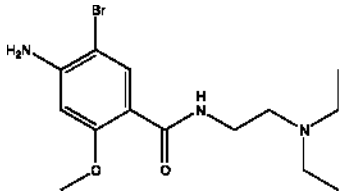
BROMOPRIDE

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
Dimethyl sulfate
Methanol
4-Aminosalicylic acid
Acetic anhydride

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 and Engel p.115
DOT 14 (5) 193 (1978)
I.N. p. 156
Thominet, M.L.; US 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 I'lle-de-France

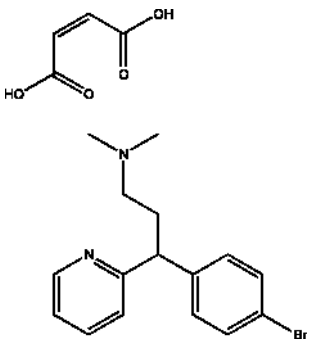
BROMPHENIRAMINE MALEATE

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

Raw Materials

Sulfuric acid
Dimethylaminoethyl chloride
2-Chloropyridine
Sodium amide
4-Bromobenzyl cyanide
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 and 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.; US Patent 2,567,245; September 11, 1951; assigned to Schering Corporation
Sperber, N., Papa, D. and Schwenk, E.; US Patent 2,676,964; April 27, 1954; assigned to Schering Corporation

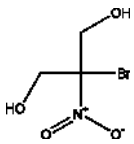
BRONOPOL

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	UK	-

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.; US Patents 3,658,921; April 25, 1972; and 3,711,561; January 16, 1973; both assigned to Henkel and Cie G.m.b.H.

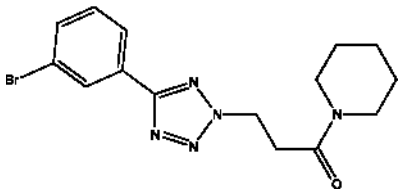
BROPERAMOLE

Therapeutic Function: Antiinflammatory

Chemical Name: Piperidine, 1-(3-(5-(3-bromophenyl)-2H-tetrazol-2-yl)-1-oxopropyl)-

Common Name: Broperamole

Structural Formula:



Chemical Abstracts Registry No.: 33144-79-5

Trade Name	Manufacturer	Country	Year Introduced
Broperamole	Onbio Inc.	-	-

Raw Materials

3-[5'-(3"-Bromophenyl)-2'H-tetrazole]propionic acid
Thionyl chloride
Piperidine

Manufacturing Process

A mixture of 32 g (0.108 mole) of 3-[5'-(3"- bromophenyl)-2'H-tetrazole]propionic acid and 80 g of thionyl chloride in 250 ml of dry chloroform was stirred under reflux for 16 hours. Evaporation of the solvent and excess reagent under reduced pressure gave a tan oil which was redissolved in 300 ml of dry tetrahydrofuran. To this was added 20 ml of redistilled piperidine in 100 ml of dry tetrahydrofuran. The mixture was stirred for 15 min at room temperature. The tetrahydrofuran was then removed under reduced pressure and the residue well triturated with one liter of 0.1 N hydrochloric acid. The resulting semi-solid was taken up in 700 ml of ether and extracted with 300 ml of 3% aqueous sodium bicarbonate solution. The ether solution was then dried over calcium chloride, filtered, and cooled in the refrigerator. This deposited 25 g (69 %) of tan needles of N-3-[5'-(3"-bromophenyl)-2'H-tetrazole]propionyl piperidine; melting point 69°C.

References

Buckler R. Th.; US Patent No. 3,681,336; Aug. 1, 1972; Assigned to Miles Laboratories, Inc., Elkhart, Ind.

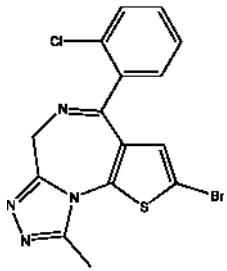
BROTIZOLAM

Therapeutic Function: Psychotropic

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 Ingelheim	Switz.	1983
Lendorm	Boehringer Ingelheim	Switz.	-

Raw Materials

7-Bromo-5-(o-chlorophenyl)-3H-[2,3-e]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 evaporation 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.; US Patent 4,094,984; June 13, 1978; assigned to Boehringer Ingelheim GmbH

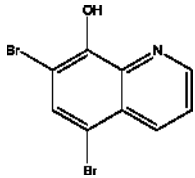
BROXYQUINOLINE

Therapeutic Function: Antibacterial

Chemical Name: 5,7-Dibromo-8-hydroxyquinoline

Common Name: Bromoxine; Broxichinolium; Broxychinolinum; Broxyquinoline; Dibromohydroxyquinoline

Structural Formula:



Chemical Abstracts Registry No.: 521-74-4

Trade Name	Manufacturer	Country	Year Introduced
Brodiar	Intervet	-	-
Colepur	Draco	-	-
Fenilor	UCB	-	-
Intensopan	Sandoz	-	-
Enterin	Leiras	-	-
Paramibe	Ucepha	-	-
Paramibe	Cid Co.	-	-
Starogyn	Oy Leiras Finland Ab	-	-

Raw Materials

8-Hydroxyquinoline
Bromine
Hydrobromic acid

Manufacturing Process

To a suspension of 14.5 g of 8-hydroxyquinoline in 400 ml of water was added dropwise a solution of 32.3 g bromine and 30 g 8% aqueous hydrobromide in 30 ml water. A temperature of reaction mixture decreased to 33°C. Stirring was continued for 30 min, a fine yellow 5,7-dibromo-8-hydroxyquinoline was collected by filtration, washed with water and dried; yield 29.8 g (98.4%), melting point 201°C.

References

Merck Index, Monograph number: 1474, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Jenkner H., DE Patent No. 2,515,476; Oct. 21, 1976; Assigned to Chemische Fabrik Kalk GmbH, 5000 Koeln

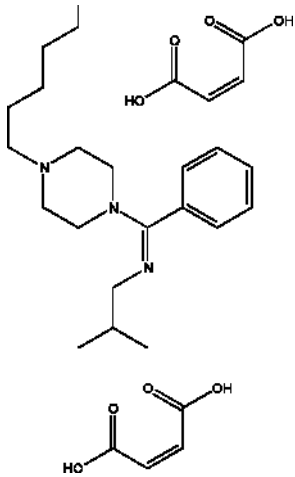
BUCAINIDE MALEATE

Therapeutic Function: Antiarrhythmic

Chemical Name: 1-Propanamine, N-((4-hexyl-1-piperazinyl) phenylmethylene)-2-methyl-, maleate (1:2)

Common Name: Bucainide maleate

Structural Formula:



Chemical Abstracts Registry No.: 51481-62-0 (Base); 51481-63-1

Trade Name	Manufacturer	Country	Year Introduced
Bucainide maleate	ZYF Pharm Chemical	-	-

Raw Materials

N-Hexylpiperazine
N-Isobutyl-benzimidoyl chloride
Maleic acid

Manufacturing Process

To a solution of 13.6 g (0.08 mol) of N-hexylpiperazine and 8.1 g (11.2 ml), (0.08 mol) of triethylamine in 120 ml toluene, was added 15.6 g (0.08 mol) of N-isobutyl-benzimidoyl chloride over a period of 15 minutes. The reaction mixture was stirred at room temperature for a period of 2 hours. The triethylamine hydrochloride was filtered off and the filtrate concentrated under vacuum. The residual oily base was washed with 20 ml water, extracted with 50 ml ether and dried over anhydrous magnesium sulfate. The dry ethereal solution was then added to a solution of 18.6 g (0.16 mol) maleic acid in 800 ml ether to obtain the dimaleate salt. Two recrystallizations from ethanol yielded 22.5 g (50.2%) of N-[(4-hexyl-1-piperazinyl)phenylmethylene]-2-methyl-1-propanamine product, M.P. 175°-176°C.

References

Shroff J.R. et al.; US Patent No. 3,793,322; February 19, 1974; Assigned to USV Pharmaceutical Corporation, Tuckahoe, N.Y.

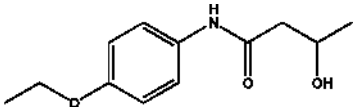
BUCETIN

Therapeutic Function: Analgesic

Chemical Name: Butanamide, N-(4-ethoxyphenyl)-3-hydroxy-

Common Name: Bucetin

Structural Formula:



Chemical Abstracts Registry No.: 1083-57-4

Trade Name	Manufacturer	Country	Year Introduced
Bucetin	ZYF Pharm Chemical	-	-

Raw Materials

Acetoacetic acid p-phenetidide
Nickel Raney
Nickel on kiesel-guhr
Aluminum amalgam

Manufacturing Process

Bucetin may be prepared from acetoacetic acid p-phenetidide as follows:

5.5 parts of acetoacetic acid p-phenetidide, suspended in 600 parts by volume of methanol, are hydrogenated at 80°-85°C with a nickel catalyst supported on kiesel-guhr. When the theoretical quantity of hydrogen has been absorbed, the solution is cooled, then filtered, and the filtrate is concentrated. The solid residue is recrystallized from six times its weight of isopropanol. β-Hydroxybutyric acid p-phenetidide is obtained in an almost quantitative yield in the form of white crystals which melt at 160°C.

55 parts of acetoacetic acid p-phenetidide, suspended in 500 parts by volume of methanol, are hydrogenated with Raney nickel at 70°C. When the theoretical quantity of hydrogen has been absorbed, the solution is cooled, then filtered, and the filtrate is concentrated. The solid residue is recrystallized from six times its weight of isopropanol. 51 parts (93 % of the theoretical yield) of β-hydroxybutyric acid p-phenetidide are obtained in the form of white crystals, which are sparingly soluble in water and melt at 160°C.

A mixture of 5 g of aluminum amalgam, 5 g of acetoacetic acid p-phenetidide and 50 ml of ethanol are gently heated for 30 minutes. After filtering off the reducing agent with suction, water is added to the filtrate, and the latter is then acidified with 2 N hydrochloric acid. β-Hydroxybutyric acid p-phenetidide melting at 160°C crystallizes in almost quantitative yield in the form of white crystals.

References

Ehrhart G. et al.; US Patent No. 2,830,087; April 8, 1975; Assigned to Farbwerke Hoechst Aktiengesellschaft vormals Meister Lucius and Bruning, Frankfurt am Main, Germany

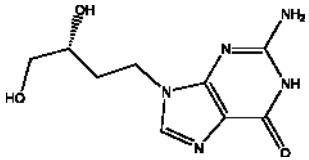
BUCICLOVIR

Therapeutic Function: Antiviral

Chemical Name: 6H-Purin-6-one, 2-amino-9-(3,4-dihydroxybutyl)-1,9-dihydro-, (R)-

Common Name: Buciclovir

Structural Formula:



Chemical Abstracts Registry No.: 86304-28-1

Trade Name	Manufacturer	Country	Year Introduced
Buciclovir	Astra Lakemedel	-	-
Buciclovir	ZYF Pharm Chemical	-	-

Raw Materials

Dimethyl maleate, R-, (+)-
Perchloric acid
N-Bromosuccinimide
Lithium aluminum hydride
Triphenylphosphine
2-Amino-6-chloropurine

Manufacturing Process

Preparation of R-(+)-9-(3,4-dihydroxybutyl)guanine:

Step A: preparation of R-(+)-1,2,4-butantriol:

R-(+)-Dimethyl maleate (1.62, 10 mmol), prepared according to Boger, D.L. and Panek, J.S., J. Org. Chem. 1981, 46, 1208-10, was dissolved in THF (10 ml) and added dropwise to a prewarmed suspension of lithium aluminium hydride (0.63 g, 16.5 mmol) in THF (15 ml). The reaction mixture was stirred overnight at 55°C. After sequential addition of water (0.62 ml), 10% sodium hydroxide (1.20 ml) and water (1.90 ml) the mixture was filtered and the solid residue was boiled twice with THF (2x20 ml) and filtered. The combined

filtrates were pooled and evaporated under reduced pressure (30°C) leaving crude 1,2,4-butantriol (0.7 g, 6.6 mmol) 66%.

Step B: preparation of R-(+)-isopropylidenbutan 1,2,4-triol:

R-(+)-1,2,4-butantriol (0.7 g, 6.6 mmol), prepared as described in step (a) above, was stirred for 1.5 hr in acetone (50 ml) containing 3 drops of conc. perchloric acid a satured solution of sodium bicarbonate in water (5 ml) was added and the stirring was continued for additional 10 min. The precipitate was filtered off and the filtrate evaporated under reduced pressure [2.7 kPa,(20 mm Hg), 30°C]. The residue was taken up in ethyl acetate, washed with satured aqueous sodium bicarbonate (5 ml) and brine (5 ml), and dried over magnesium sulfate. Evaporation of the solvent and distillation gave the title compound as a colourless oil (0.3 g, 2.05 mmol, 31%): b.p. 104°-106°C/20 mm Hg; n_D^{20}=1.4390.

Step C: preparation of R-(+)-4-bromo-isopropylidenebutan-1,2-diol:

R-(+)-Isopropylidene-butan-1,2,4-triol (0.3 g, 2.05 mmol) and triphenylphosphine (0.63 g, 2.4 mmol) were dissolved in methylene chloride (5 ml) and cooled to 0°C. N-Bromosuccinimide (0.38 g, 2.16 mmol) was added in small portions with stirring at 0°C. After additional 1 hr of stirring at 0°C hexane (15 ml) was added and the resulting precipitate was removed by filtration and washed twice with hexane (2x5 ml). The combined hexane solution was passed through a short column of silica gel (5 g). Elution with hexane (15 ml) gave after evaporation and distillation the title compound as a colorless oil (0.2 g, 0.96 mmol, 47%): b.p. 74°-76°C/20 mm Hg, n_D^{20}=1.4630. $[\alpha]_D^{20}$=+27.7° (C=20, $CHCl_3$).

Step D: preparation of R(+)-4-(2-amino-6-chloropurin-9-yl)isopropylidene-butane-1,2-diol:

2-Amino-6-chloropurin (162 mg, 0.96 mmol), R-(+)-4-bromo-isopropylidene-butandiol (200 mg, 0.96 mmol) and potassium carbonate (132 mg) was mixed in DMF (10 ml). After stirring for 16 hr the reaction mixture was filtered through celite and the solvent evaporated under reduced pressure [13 Pa (0.1 mm Hg), 50°C]. The residue was triturated with warm chloroform (5 ml) and undissolved material was filtered off. Evaporation of the solvent gave a pale yellow crystalline solid consisting mainly of the 9- and 7-isomers. These were separated by silica gel flash chromatography. Elution with chloroform/methanol (15:1) gave the title compound in pure form (106 mg, 0.36 mmol, 37%): MP: 129°-130°C, $[\alpha]_D^{21}$ =+57.5° (C=6.97, $CHCl_3$).

Step E: preparation of R-(+)-9-(3,4-dihydroxybutyl)guanine:

R-(+)-4-(2-Amino-6-chloropurin-9-yl)isopropylidene-butane-1,2-diol (100 mg, 0.33 mmol) prepared according to step (d) above was dissolved in hydrochloric acid (1 mol/L) and refluxed for 1 hr. The solution was concentrated in vacuum and the residue dissolved in water (5 ml) and made alkaline by addition of aqueous ammonium hydroxide. After evaporation the solid residue was recrystallized from water giving the title compound as white needles (40 mg, 0.17 mmol, 51%). $[\alpha]_D^{21}$=+30.8° (C=0.25, water). (+/-)-Form had MP: 260°-261°C.

References

Hugberg C-E. et al.; January 22, 1985; Assigned to Astra Lakemedel Aktiebolag, Sodertalje, Sweden

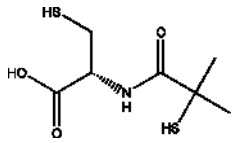
BUCILLAMINE

Therapeutic Function: Antirheumatic, Immunomodulator

Chemical Name: L-Cysteine, N-(2-mercapto-2-methyl-1-oxopropyl)-

Common Name: Bucillamine; Tiobutarit

Structural Formula:



Chemical Abstracts Registry No.: 65002-17-7

Trade Name	Manufacturer	Country	Year Introduced
Bucillamine	ZYF Pharm Chemical	-	-
Bucillamine	Bioray Pharma LLC	-	-
Rimatil	Santen Pharmaceutical Co., Ltd.	-	-

Raw Materials

S-Benzyl-L-cysteine
Thionyl chloride
Sodium
2-Benzylmercaptoisobutyric acid
Ammonia

Manufacturing Process

Preparation of N-(2-benzylmercaptoisobutyryl)-S-benzyl-L-cysteine:

1). 73.9 g of S-benzyl-L-cysteine were dissolved in 700 ml of 1 N sodium hydroxide solution. The solution was cooled in an ice bath and stirred. 2-Benzylmercaptoisobutyryl chloride, which was obtained by reacting 63.1 g of 2-benzylmercaptoisobutyric acid with 39.3 g of thionyl chloride, was added dropwise to this solution. The resulting mixture was then stirred for one hour, acidified with hydrochloric acid and extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate and evaporated to dryness. The residue was chromatographed on silica gel with benzene/ethylacetate (1:1) as an eluant. The eluate was evaporated to dryness and an oily residue

weighing 46.9 g, representing a yield of 74%, was obtained.

2). The obtained in (1) above were dissolved in 500 ml of liquid ammonia and 21.1 g of metallic sodium were added slowly with stirring. After completion of reaction, 59.4 g of ammonium chloride were added and thereafter the ammonia was removed by distillation. Water was added to the residue to dissolve the solid. The resulting water layer was separated, washed with ethyl acetate, and acidified with hydrochloric acid under cooling. The precipitates thus obtained were extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate and evaporated to dryness. The product weighed 43.6 g, representing a yield of 88%. After recrystallization from ethyl acetate, the desired compound, melting at 139°-140°C, was obtained. $[\alpha]_D^{25}$=+32.3° (c=1.0, ethanol).

References

Fujita T. et al.; US Patent No. 4,305,958; December 15, 1981; Assigned to Santen Pharmaceutical Co., Ltd., Osaka, Japan

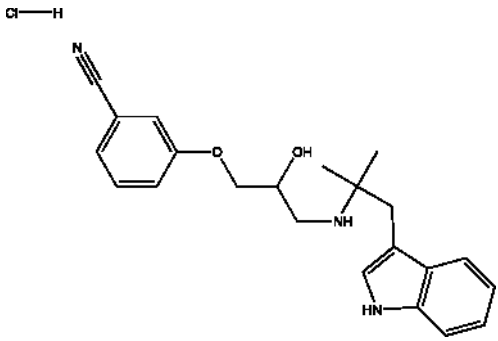
BUCINDOLOL HYDROCHLORIDE

Therapeutic Function: Antihypertensive

Chemical Name: Benzonitrile, 3-(2-hydroxy-3-((2-(1H-indol-3-yl)-1,1-dimethylethyl)amino)propoxy)- monohydrochloride

Common Name: Bucindolol hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 70369-47-0

Trade Name	Manufacturer	Country	Year Introduced
Bucindolol hydrochloride	Bristol Myers (BMS)	-	-

Raw Materials

2-Cyanophenol	Epichlorohydrin
Sodium hydroxide	Gramine
2-Nitropropane	Acetic acid
Nickel Raney	Hydrazine hydrate

Manufacturing Process

A solution of 2-cyanophenol (25.0 g, 0.21 mole), epichlorohydrin (117.0 g, 1.26 mole), and piperidine (10 drops) was stirred and heated at 115-120°C in an oil bath for 2 h. The reaction mixture was then concentrated (90/30 mm) to remove unreacted epichlorohydrin. The residue was diluted with toluene and taken to dryness twice to help remove the last traces of volatile material. The residual oil was dissolved in 263 ml of THF, and the solution stirred at 40-50°C for 1 h with 263 ml of 1 N NaOH. The organic layer was separated and concentrated to give an oil which was combined with the aqueous phase. The mixture was extracted with CH_2Cl_2 and the extract dried ($MgSO_4$) and concentrated to give 36.6 g (100%) of 2-[(2,3-epoxy)propoxy]benzonitrile as oil, which slowly crystallized to a waxy solid.

A mixture of gramine (120.0 g, 0.69 mole), 2-nitropropane (443 ml), and NaOH (28.8 g, 0.72 mole) was stirred and gradually heated to reflux under N_2. After a 6.5 h reflux period, the reaction mixture was allowed to stand at room temperature overnight, and then diluted with 600 ml of 10% aqueous AcOH. The mixture was extracted with 1.5 l of Et_2O and the organic layer washed with H_2O (4x 500 ml). Concentration of the Et_2O solution in vacuum gave an oil which was dissolved in 500 ml of 95% EtOH. This solution was diluted with 300 ml of H_2O. After cooling, the yellow solid was collected on a filter to give 105.0 g (70%) of nitro intermediate, melting point 72-74°C. The nitro compound was dissolved in 1.3 L of 95% EtOH, and Raney nickel (70.0 g, EtOH-washed) and added. The mixture was heated to reflux, and a solution of 85% hydrazine hydrate (116.0 g, 2.3 mole) in 95% EtOH (110 ml) was added dropwise at a rate to maintain gentle reflux. The mixture was then heated at reflux for an additional 1.5 h, cooled, and filtered. Concentration of the filtrate gave crude product as a solid. A solution of the solid in 400 ml of EtOAc was diluted with 500 ml of $(i\text{-}Pr)_2O$ and cooled. The white, cottony solid which separated was collected on a filter to give 91.0 g (100%) of 2-(3-indolyl)-1,1-dimethylethylamine, melting point 122-126°C.

A solution of 2-[(2,3-epoxy)propoxy]benzonitrile (18.3 g, 0.10 mole) and 2-(3-indolyl)-1,1-dimethylethylamine (15.2 g, 0.08 mole), in 500 ml of abs. EtOH was stirred at reflux overnight. After concentration of the reaction mixture to approximately 200 ml and seeding, crude product began to precipitate. The mixture was then cooled and the precipitate separated by filtration to give 24.8 g of the free base form of the product, white solid, melting point 120-123°C. The crude solid was dissolved in 400 ml of boiling MeOH, and the solution was cooled with stirring, as a by-product 1,1'-[[1,1-dimethyl-2-(1H-indol-3-yl]ethyl]imino]bis-[3-(2-cyanophenoxy)-2-propanol] precipitated. The by-product was collected on a filter and air dried to give 2.2 g, of 2-[2-hydroxy-3-[[2-(3-indolyl)-1,1-dimethylethyl]amino]propoxy] benzonitrile, melting point 180-187°C.

In practice it is usually used as hydrochloride.

References

Kreighbaum W.E., Comer W.T.; US Patent No. 4,234,595; November 18, 1980; Assigned: Mead Johnson and Company, Evansville

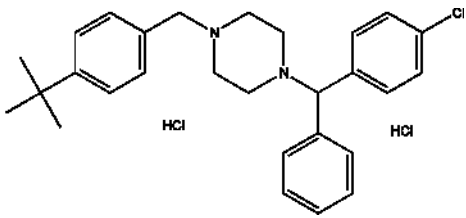
BUCLIZINE HYDROCHLORIDE

Therapeutic Function: Antihistaminic, Antiallergic, Antinauseant, Tranquilizer, Appetite stimulant

Chemical Name: Piperazine, 1-((4-chlorophenyl)phenylmethyl)-4-((4-(1,1-dimethylethyl)phenyl)methyl)-, hydrochloride

Common Name: Buclizine hydrochloride; Histabutazine; Histabutizine

Structural Formula:



Chemical Abstracts Registry No.: 129-74-8; 82-95-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Longifine	UCB	-	-
Longifene	Bios-Coutelier	-	-
Buclina	Sanofi Winthrop	-	-
Posdel	UCB	-	-
Postafen	Rhodia	-	-
Vibazine	Pfizer	-	-
Bucladin-S	Stuart Pharms	-	-
Buclizine Dihydrochloride	Toronto Research Chemicals Inc. (TRC)	-	-
Aphilan R	UCB Pharma	-	-
Histalon	Majer-Meyer	-	-
Postafeno	GSK	-	-
Quantum	Andromaco	-	-

Raw Materials

4-Chlorobenzhydryl chloride
Piperazine 1-carboxylic acid ethyl ester
4-tert-Butylbenzyl chloride

Manufacturing Process

1 mol 4-chlorobenzhydril chloride was heated in toluene to reflux with 1 mol ethyl ester of piperazine 1-carboxylic acid at about 150°C in a presence of an excess of triethyl amine. On cooling the triethyl amine hydrochloride was filtered off, a solvent was removed in vacuum and the residue [(4-chloro-phenyl)-phenyl-methyl]piperazine carboxylic acid ethyl ester was boiled straight away with potassium hydroxide in ethanol for 48 hours. After removing ethanol in vacuum to dryness, the residue was dissolved in benzene and washed with water. The benzene solution was dried, benzene removed in vacuum. The residue was distilled to give 4-chlorobezhydryl-piperazine. It had given the desired 1-(p-tert-butylbenzyl)-4-(p-chloro-α-phenylbenzyl)-piperazine, buclizine, by a reaction with 4-tert-butylbenzyl chloride in the presence of any halogen hydrochloride acceptor (triethyl amine, sodium or potassium carbonate and so on). The obtained product had BP: 230°-240°C/0.001 mm Hg.

References

Morren H.; DB Patent No. 964048; Feb. 15, 1951; Forest-Brussel (Belgium)

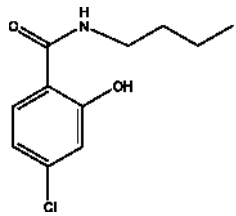
BUCLOSAMIDE

Therapeutic Function: Antifungal

Chemical Name: N-Butyl-4-chlorosalicylamide

Common Name: Buclosamide

Structural Formula:



Chemical Abstracts Registry No.: 575-74-6

Trade Name	Manufacturer	Country	Year Introduced
Fungit	Dragon	-	-
Jadit	Hoechst	-	-

Raw Materials

4-Chloro-2-hydroxy-benzoic acid n-butyl-ester
n-Butylamine

Manufacturing Process

4-Chloro-2-hydroxy-benzoic acid n-butyl-amide

A mixture consisting of 114 g of 4-chloro-2-hydroxy-benzoic acid n-butyl-ester, 64 grams of methanol and 130 g of n-butyl-amine is heated for 22 hours at 80°C; then the parts volatile up to 130°C are distilled off under reduced pressure. The residue crystallizing in the cold is dissolved in 200 ml of methanol and the solution obtained is slowly added dropwise and while stirring into dilute hydrochloric acid, if necessary, after treatment with animal charcoal. The precipitate which is at first semi-solid soon crystallizes completely. It is filtered with suction, washed with dilute hydrochloric acid, then thoroughly washed again with water, and the product obtained in good yield is dried in the air. After having been recrystallized twice from carbon tetrachloride the 4-chloro-2-hydroxybenzene acid n-butylamide melts at 90-92°C.

References

Merck Index, Monograph number: 1485, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Ruschig H. et al.; US Patent No. 2,923,737; Feb. 2, 1960; Assigned to Farbwerke Hoechst Aktiengesellschaft vormais Meister Lucius and Bruning, Frankfurt am Main, Germany

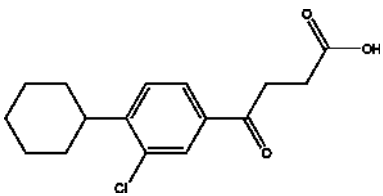
BUCLOXIC ACID

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 anhydride
Chlorine

Manufacturing Process

Phenylcyclohexane and succinic acid (Bernstein Acid) anhydride are reacted in the presence of AlCl3to 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. 33.2ml 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 and 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

BUCROMARONE

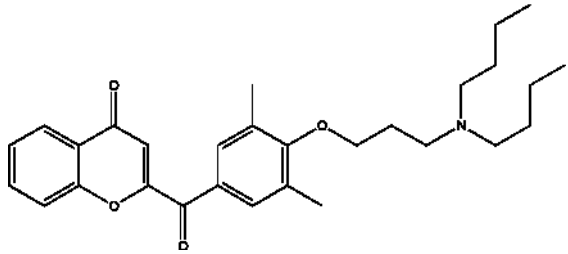
Therapeutic Function: Antiarrhythmic, Coronary vasodilator

Chemical Name: 4H-1-Benzopyran-4-one, 2-(4-(3-(dibutylamino)propoxy)-3,5-dimethylbenzoyl)-

Common Name: Bucromarone

Chemical Abstracts Registry No.: 78371-66-1

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Bucromarone	Transphyto	-	-

Raw Materials

Aluminum chloride	2,6-Dimethylphenol
Hydrochloric acid	2-Carboxylic chromone acid chloride
Potassium carbonate	3-N,N-Dibutylamino-1-chloropropane

Manufacturing Process

1.2 mol of an electrophilic catalyst, advantageously aluminum chloride, was slowly added to a solution of 48.8 g (0.4 mol) of 2,6-dimethyl phenol in 400 ml of dichloroethane and agitated at room temperature for an hour. The mixture was cooled to 0°C and a solution of 84.0 g (0.4 mol) of 2-carboxylic chromone acid chloride in 400 ml of a dichloroethane, was slowly added. Agitation was continued at 0°C for 5 h and then at room temperature for 4 days. The reaction mixture was poured into 1.6 L of iced 50% hydrochloric acid. The resulting precipitate was filtered, washed with water, dried and 106.0 g (72% yield) of 2-(3,5-dimethyl-4-hydroxybenzoyl)chromone, melting point 216°C (recrystallised from dioxane) were obtained.

6.9 g (0.05 mol) of potassium carbonate was added to a solution of 29.4 g (0.1 mol) of 2-(3,5-dimethyl-4-hydroxybenzoyl)chromone in 250 ml of dimethyl formamide and kept at 100°C for an hour. A solution of 20.5 g (0.1 mol) of 3-N,N-dibutylamino-1-chloropropane in 100 ml of diethyl formamide was then added and the resulting solution heated to 130°C for 3 h. The solution was filtered, the dimethyl formamide was concentrated, dissolved in 300 ml water and extracted twice with 200 ml of benzene. The organic phase was dried on magnesium sulfate and the hydrochloride was precipitated by adding hydrochloric ether. 40.0 g (yield 80%) of 2-[4-(3-N,N-dibutylamino-propoxy)-3,5-dimethylbenzoyl]chromone were obtained (recrystallised from an acetone/ether mixture).

References

Chibret H.; US Patent No. 4,220,645; September 2, 1980; Assigned: Thea (Therapeutique et Applications) SA, France

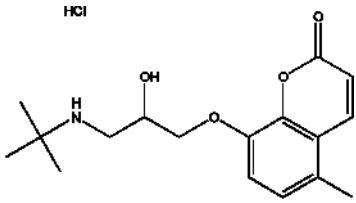
BUCUMOLOL HYDROCHLORIDE

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).

In practice it is usually used as hydrochloride.

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.; US Patent 3,663,570; May 16, 1972; assigned to Sankyo Co., Ltd.

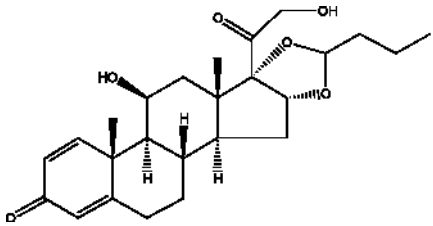
BUDESONIDE

Therapeutic Function: Corticosteroid

Chemical Name: Pregna-1,4-diene-3,20-dione, 16,17-(butylidenebis(oxy))-11,21-dihydroxy-, (11β,16α)-

Common Name: Budesonide

Structural Formula:



Chemical Abstracts Registry No.: 51333-22-3

Trade Name	Manufacturer	Country	Year Introduced
Budecort	AstraZeneca	-	-
Budesonide	Genpharm Inc.	-	-
Busonid	Biosintetica	-	-
Entocort EC	AstraZeneca	-	-
Pulmicort Respules	AstraZeneca	-	-
Ribujet	Chiesi Wasserman	-	-

Raw Materials

Desonide (16α-hydroxyprednisolone-16,17-acetonide)
Butyraldehyde
Hydrofluoric acid

Manufacturing Process

50 grams of desonide (16α-hydroxyprednisolone-16,17-acetonide) and immediately thereafter 12.5 ml of butyraldehyde were added to 500 ml of 70% hydrofluoric acid solution at -5°C, and the mixture was stirred at 0°C one hour and then poured into 5 liters of demineralized water at 0°C. The precipitate was filtered, washed to neutrality with water and dried under vacuum to give 51 g of pure budesonide with an A/B epimer ratio of 9/91.

References

Brattsand R.L. et al.; US Patent No. 3,983,233; Sept. 28, 1976; Assigned: AB Bofors (Bofors, SW)

Brattsand R.L. et al.; US Patent No. 3,929,768; Dec., 30, 1975; Assigned: AB Bofors, Bofors, Sweden

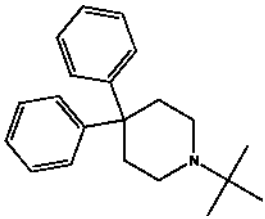
BUDIPINE

Therapeutic Function: Antiparkinsonian, Antidepressant

Chemical Name: Piperidine, 1-(1,1-dimethylethyl)-4,4-diphenyl-

Common Name: Budipine

Structural Formula:



Chemical Abstracts Registry No.: 57982-78-28

Trade Name	Manufacturer	Country	Year Introduced
Budipine	Byk Gulden (Altana)	-	-
Parkinsan	Promonta	-	-

Raw Materials

1-(tertiary Butyl)-4-hydroxy-4-phenylpiperidine
Aluminum chloride
Sodium hydroxide

Manufacturing Process

24.4 g of 1-(t-butyl)-4-hydroxy-4-phenylpiperidine are suspended in 150 ml of anhydrous benzene. 61.5 g of finely pulverized anhydrous aluminum chloride are added in portions thereto within 25 min while stirring. The reaction temperature increases on starting addition of aluminum chloride to about 45°C. After about 20 min the temperature is increased to and maintained at about 50° to 55°C for about 1 hour. The resulting reaction solution is cooled to about 20°C and is poured into a mixture of ice and concentrated hydrochloric acid. After warming the mixture to room temperature, the hydrochloric acid layer together with the dark oil formed on decomposition is separated from the benzene layer and is washed with benzene. Water is added to said hydrochloric acid -oil phase, while stirring, in portions and in an amount sufficient to produce an almost clear solution. Said acid solution is rendered alkaline by the addition of 40% sodium hydroxide solution whereby

the mixture is well cooled. The alkalized mixture is repeatedly extracted with ether. The combined ether extracts are dried over anhydrous potassium carbonate and are concentrated by evaporation of the ether. 24 g of the crude base are obtained as residue in the form of yellowish oil. A water clear oil boiling at 129-131°C/0.005 mm Hg is recovered by distillation of said crude oil in a high vacuum. The oil solidifies to crystals on standing for a short period of time. After recrystallization from aqueous dimethylformamide, the resulting 1-methyl-4,4-diphenylpiperidine has a melting point of 72-74°C.

Its hydrochloride is produced by dissolving the base in acetic acid ethyl ester and adding an ethereal hydrochloric acid solution thereto. After recrystallization from acetic acid ethyl ester, the melting point of the hydrochloride is 152-154°C.

References

Menge Heinz Gunter, Klosa Josef; US Patent No. 4,016,280; April 5, 1977; Assigned to Byk Gulden Lomberg Chemische Fabrik GmbH (DT)

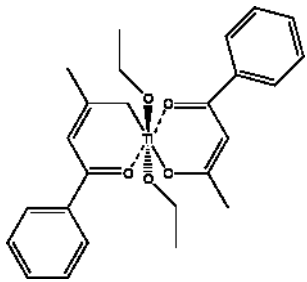
BUDOTITANE

Therapeutic Function: Antineoplastic

Chemical Name: Diethoxybis(1-phenyl-1,3-butanedionato-O,O')titanium

Common Name: Budotitane

Structural Formula:



Chemical Abstracts Registry No.: 85969-07-9

Trade Name	Manufacturer	Country	Year Introduced
Budotitane	ZYF Pharm Chemical	-	-

Raw Materials

Titantetraethoxid
Benzoylaceton

Manufacturing Process

11.4 g (0.05 mol) of titantetraethoxid were mixed with solution of 15.8 g (0.097mol) of benzoylaceton in 200 ml n-hexan. Reaction mixture was mixed for 2 h at heating in N_2 atmosphere. The precipitate obtained was filtered, then the product was washed with hexan also and filtered. So there was obtained the diethoxybis-(1-phenyl-1,3-butandionato)-titan, melting point 110°C.

References

Keller H.J. et al.; WO Patent 84/03042; February 9, 1983; Assigned: BYK GULDEN LOMBERG CHEMISCHE FABRIK GESELLSCHAFT MIT BESCHRaNKTER HAFTUNG [DE/DE]; Byk-Gulden-Strasse 2, D-7750 Konstanz (DE)

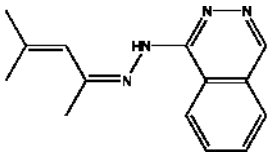
BUDRALAZINE

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 (isoproplyideneacetone) 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 neutralized 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) and 19 (10) 582 (1983)
Ueno, K., Miyazaki, S. and Akashi, A.; US Patent 3,840,539; October 8, 1974; assigned to Daiichi Seiyaku Co., Ltd.

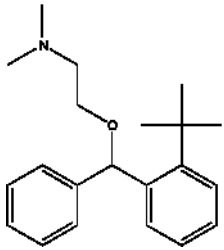
BUFENADRINE

Therapeutic Function: Antiemetic, Antihistaminic, Antiparkinsonian

Chemical Name: 2-[[2-(1,1-Dimethylethyl)phenyl]phenylmethoxy]-N,N-dimethylethanamine

Common Name: Bufenadinum; Bufenadrine

Structural Formula:



Chemical Abstracts Registry No.: 604-74-0

Trade Name	Manufacturer	Country	Year Introduced
Bufenadrine	Onbio Inc.	-	-

Raw Materials

o-t-Butyl-α-phenylbenzyl alcohol
Sodium hydride
N,N-Dimethylmonochloroacetamide
Lithium aluminum hydride

Manufacturing Process

The o-t-butyl-α-phenylbenzyl alcohol and N,N-dimethylmonochloroacetamide are dissolved in anhydrous diethyl ether. Portionwise 50% sodium hydride in the form of an oily suspension is added to the solution with stirring. After all the sodium hydride is added, the mixture is stirred at room temperature for another 3 h and then water is added to decompose excess sodium hydride. The ethereal layer is separated, dried with sodium sulfate, filtered and concentrated by removal of the solvent. The residue crystallizes upon addition of petroleum ether (boiling range 80-100°C) to which some diethyl ether is added. There is obtained 2-[o-t-butyl-α-phenylbenzyl)oxy]-N,N-dimethyl acetamide, melting point 90-91°C (81% yield).

To a solution of 2-[o-t-butyl-α-phenylbenzyl)oxy]-N,N-dimethyl acetamide in anhydrous diethyl ether is added portionwise with stirring and while refiuxing lithium aluminum hydride. After the addition is completed, refluxing is continued overnight. The reaction mixture still contains some lithium aluminum hydride which is decomposed by the addition of water. The mixture is filtered, the ethereal solution separated and dried over sodium sulfate. Diethyl ether is removed from the ethereal solution by distillation. There is obtained 2-[(o-t-butyl-α-phenylbenzyl)oxy]-N,N-dimethylethylamine.

References

Stelt C.; US Patent No. 3,463,815; August 26, 1969; Assigned: N.V. Koninklijke Pharmaceutische Fabrieken v/h Brocades-Stheeman and Pharmacia Amsterdam, Netherlands, a corporation of the Netherlands

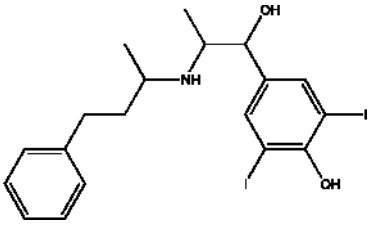
BUFENIODE

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
Hydrogen
Bromide
3-Butyl-1-phenylamine
Benzyl chloride
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 and Engel p.119
DOT 7 (2) 52 (1971) and 11 (8) 306 (1975)
I.N. p.161
South African Patent 680,046; January 3, 1968; assigned to Laboratoires Houde, France

BUFETOLOL HYDROCHLORIDE

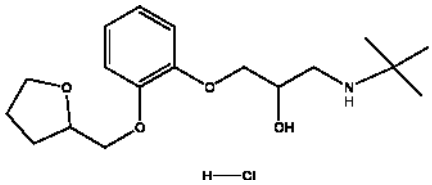
Therapeutic Function: Antiarrhythmic, Beta-adrenergic blocker

Chemical Name: Propanol, 1-(1,1-(dimethylethyl)amino)-3-(2-((tetrahydro-2-furanyl)methoxy)phenoxy)-, hydrochloride

Common Name: Bufetolol hydrochloride; Bufuronol hydrochloride

Chemical Abstracts Registry No.: 35108-88-4

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Bufetolol hydrochloride	ZYF Pharm Chemical	-	-

Raw Materials

1-Bromo-3-[2-(tetrahydro-furan-2-yloxy)phenoxy]propan-2-ol
t-Butylamine
Fumaric acid

Manufacturing Process

To a solution of 1 gramm equivalent (g-eq.) of 1-bromo-3-[2-(tetrahydrofuran-2-yloxy)phenoxy]propan-2-ol in 30 ml of ethanol is added 1 g-eq. of t-butylamine, the mixture is refluxed for 6 hours, and then the ethanol is distilled off. The residue is dissolved in benzene and the solution is extracted twice with 5% oxalic acid. The aqueous extract is made alkaline with potassium hydroxide and the isolated oil is extracted with benzene. The benzene extract is dried over potassium carbonate and the benzene is distilled off to give of oily 1-(t-butylamino)-3-(o-((tetrahydrofurfuryl)oxy)phenoxy)-2-propanol. The corresponding acid fumarate melts at 128°-132°C.

References

Nakanishi M. et al.; US Patent No. 3,723,476; March 27, 1973; Assigned to Yoshitomi Pharmaceutical Industries Ltd., Osaka, Japan

BUFETROL

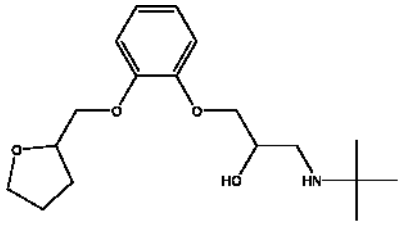
Therapeutic Function: Antiarrhythmic

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

Common Name: Bufetolol

Chemical Abstracts Registry No.: 53684-49-4

Structural Formula:



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

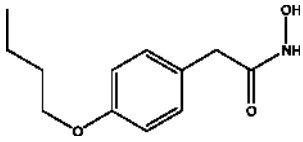
BUFEXAMAC

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	UK	1973
Feximac Cream	Nicholas	UK	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
Sodium hydroxide
Butyl bromide
Ethanol
Sulfur
Hydroxylamine hydrochloride
Morpholine

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-butyloxyacetophenone 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-butyloxyphenylecetate 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 and 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.; US Patent 3,479,396; November 18, 1969; assigned to Madan A.D.

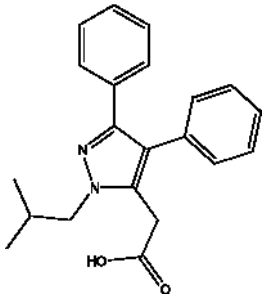
BUFEZOLAC

Therapeutic Function: Antiinflammatory

Chemical Name: 1-(2-Methylpropyl)-3,4-diphenyl-1H-pyrazole-5-acetic acid

Common Name: Bufezolac; LM 22070

Structural Formula:



Chemical Abstracts Registry No.: 50270-32-1

Trade Name	Manufacturer	Country	Year Introduced
Bufezolac	Onbio Inc.	-	-

Raw Materials

Maleic anhydride
Isobutylamine
Sodium nitrite
Perchloric acid
Sodium carbonate
Triethylamine
Hydrochloric acid
Acetic anhydride
Diphenylacetylene

Manufacturing Process

50.0 g of maleic anhydride and 180 ml of methanol are heated for 1 h under reflux while stirring. The reaction mixture is cooled to room temperature and the excess methanol is evaporated under reduced pressure. 67.0 g of monomethyl maleate are obtained. The monomethyl maleate is then cooled to 0°C after which 90 ml of triethylamine and then 34.0 g of isobutylamine are introduced over a period of 1 h. The reaction mixture is heated under reflux for 1 h, then cooled to 50°C and 200 ml of acetone added; as a result of filtering off the crystals which separate there are obtained 73.7 g of methyl N-isobutyl-β-aspartate, melting point 250°C.

Over a period of 10 min 860 ml of concentrated hydrochloric acid are added to a suspension of 340.0 g of methyl N-isobutyl-β-aspartate in 860 ml of water whilst stirring. The solution is cooled to 0°C and 128.0 g of sodium nitrite dissolved in 280 ml of water are introduced over a period of 1 h 20 min. The reaction mixture is stirred for 2 h at 0°C and extraction is then carried out thrice with a total of 3000 ml of diethyl ether. The organic phase is thrice washed with a total of 1500 ml of water, dried over magnesium sulfate and the ether evaporated under reduced pressure. The residue, when dissolved in a mixture of 1400 ml of petroleum ether and 230 ml of ether, gives, after cooling to 3°C, 325.0 g of methyl N-isobutyl-N-nitroso-β-aspartate, melting point 95°C.

Over a period of 15 min and whilst stirring 158.0 g of methyl N-isobutyl-N-nitroso-β-aspartate are added to 340 ml of acetic anhydride and then, drop by drop, 0.95 ml of 70% perchloric acid. The reaction mixture is then stirred for 2 h at room temperature. The acetic anhydride is evaporated under reduced pressure, and the residue is then successively dissolved once in 100 ml of chloroform, thrice in 100 ml of benzene each time and twice in 100 ml of diethyl ether each time, the solvent being evaporated each time under reduced pressure. 155.0 g of red oil are obtained which are dissolved in 2 volumes of hot di-isopropyl ether and cooled. After 1 min at 3°C the crystals which separate are filtered and there are thus obtained 78.0 g of methyl 3-isobutyl-4-sydnonyl acetate, melting point 39°C.

120.0 g of methyl 3-isobutyl-4-sydnonylacetate and 110.0 g of diphenyl-acetylene dissolved in 600 ml of xylene are heated under reflux whilst being stirred for 70 h. The solution is cooled to room temperature and the xylene is evaporated under reduced pressure. The residue is dissolved in a mixture of 800 ml of 1 N sodium carbonate and 800 ml of acetone. The resulting solution is heated under reflux for 4 h whilst stirring and is then cooled to room temperature and separated. The aqueous phase has 1000 ml of water added thereto and is then extracted thrice with a total of 900 ml of benzene. The aqueous phase is then made acid by the addition of 68 ml of concentrated hydrochloric acid. The oil which separates from the acidified mixture is extracted using a total of 1000 ml of chloroform in five extractions. The combined chloroform extracts are dried over magnesium sulfate and the chloroform is evaporated under reduced pressure. 78.0 g of a brown oil are obtained which are submitted to chromatography upon silica gel using a mixture of chloroform-methanol 99:1 parts. So the 1-isobutyl-3,4-diphenylpyrazolyl-5-acetic acid, melting point 181°C (recrystallisation from acetonitrile) is obtained.

References

Gueremy C., Renault C.; GB Patent No. 1,387,306; March 12, 1975; Aassigned: SOCIETE GENERALE DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES SOGERAS, a Franch Body Corporate of 10, Rue Clement Marot, 75008 Paris, France

BUFLOMEDIL

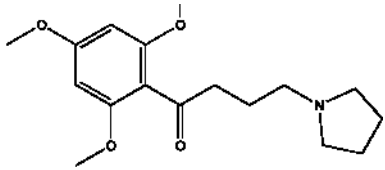
Therapeutic Function: Vasodilator

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

Common Name: -

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

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Fonzylane	Lafon	France	1976
Loftyl	Abbott	Italy	1981
Bufedil	Abbott	W. Germany	1982
Loftyl	Abbott	Switz.	1983
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 5N 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 and Engel p.121
DOT 11 (9) 339 (1975)
I.N. p. 161
Lafon, L: US Patent 3,895,030; July 15, 1975; assigned to Orsymonde

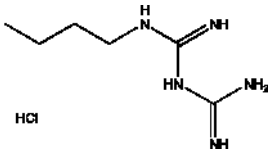
BUFORMIN HYDROCHLORIDE

Therapeutic Function: Antidiabetic

Chemical Name: N-Butylimidodicarbonimidic diamide hydrochloride

Common Name: Butyldiguanide

Structural Formula:



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

Trade Name	Manufacturer	Country	Year Introduced
Silubin	Protochemie	Switz.	-
Sindiatil	Bayer	Italy	1979
Adebit	Chinoin	Hungary	-
Andere	Toyama	Japan	-
Biforon	Meiji	Japan	-
Bigunal	Nikken	Japan	-
Bufonamin	Kaken	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.; US Patent 2,961,377; November 22, 1960; assigned to US Vitamin and Pharmaceutical Corp.

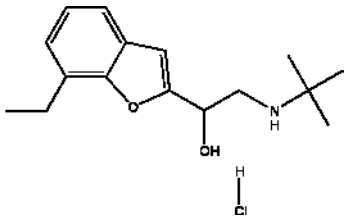
BUFURALOL HYDROCHLORIDE

Therapeutic Function: Beta-adrenergic blocker

Chemical Name: α-[[(1,1-Dimethylethyl)amino]methyl]-7-ethyl-2-benzofuranmethanol hydrochloride

Common Name: Bufuralol hydrochloride; Angium

Structural Formula:



Chemical Abstracts Registry No.: 54340-62-4 (Base); 59652-29-8

Trade Name	Manufacturer	Country	Year Introduced
Bururalol hydrochloride	Onbio Inc.	-	-

Raw Materials

Trimethyl-phenyl-ammonium perbromide
5-Bromo-2-acetyl-7-ethylbenzofuran
2-Propanamine, 2-methyl-
Palladium on carbon
Sodium borohydride
Hydrochloric acid
Sodium hydroxide
Hydrogen

Manufacturing Process

68.3 g (0.182 mol) of trimethyl-phenyl-ammonium perbromide were added in a single portion at 20°C to a stirred solution of 48.5 g (0.182 mol) of 5-bromo-2-acetyl-7-ethylbenzofuran in 400 ml of dry tetrahydro-furan. The

resulting mixture was stirred at 20°C for 3 h, during which time trimethyl-phenyl-ammonium bromide precipitated out. The mixture was then poured into water and extracted 3 times with ether. The combined ether extracts were washed successively with water, saturated sodium bicarbonate solution, water and saturated brine, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The solid residue was recrystallized from ethanol to yield 43.1 g of 5-bromo-2-bromoacetyl-7-ethylbenzofuran as yellow crystals, melting point 101-102°C.

1.35 g of sodium borohydride were added portion-wise at room temperature over a period of 20 min to a stirred solution of 17.3 g (0.05 mol) of 5-bromo-2-bromoacetyl-7-ethylbenzofuran in 100 ml of dioxane and 25 ml of water. The mixture was stirred at room temperature for 3 h, then dioxane was removed by evaporation at 40°C under reduced pressure and the residue was diluted with water and extracted 3 times with ether. The combined ether extracts were worked up in the usual manner to yield 16.0 g of crude 5-bromo-2-(2-bromo-1-hydroxyethyl)-7-ethyl-benzofuran as a viscous oil.

16.0 g of crude 5-bromo-2-(2-bromo-1-hydroxyethyl)-7-ethylbenzofuran and 37.0 g of t-butylamine were heated at 100°C in a sealed autoclave for 24 h. After cooling, excess t-butylamine was evaporated off and the residue was taken up in dilute aqueous hydrochloric acid. The aqueous solution was washed twice with ether, basified with dilute aqueous sodium hydroxide solution and extracted twice with ether. The combined ether extracts were washed with water and with brine, dried over anhydrous sodium sulfate, filtered and evaporated. The solid residue was crystallized from petroleum ether (boiling point 60-80°C) to yield 4.7 g of 5-bromo-2-(2-t-butylamino-1-hydroxyethyl)-7-ethylbenzofuran as buff crystals, melting point 101-103°C.

4.8 g of 5-bromo-2-(2-t-butylamino-1-hydroxyethyl)-7-ethylbenzofuran in 50 ml of ethanol were hydrogenated at room temperature and atmospheric pressure in the presence of 0.3 g of 5% palladium-on-carbon catalyst. After the uptake of one equivalent of hydrogen, the hydrogenation was terminated, catalyst was filtered off and the filtrate was evaporated to dryness. The residue was basified and extracted twice with ether. The combined ether extracts were worked up in the usual manner to give 2-(2-t-butylamino-1-hydroxyethyl)-7-ethylbenzofuran in the form of an oil.

In practice it is usually used as hydrochloride.

References

Fothergill G.A. et al.; US Patent No. 3,929,836; December 30, 1975; Assigned: Hoffmann-La Roche Inc., Nutley, N.J.

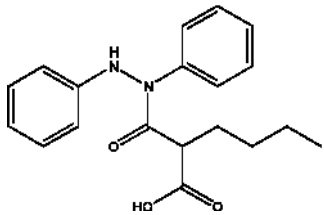
BUMADIZON

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
Eumotol	Valpan	France	1976
Eumotol	Byk Gulden	Italy	1976
Dibilan	Byk Gulden	-	-
Rheumatol	Tosse	W. Germany	-

Raw Materials

Dicyclohexylcarbodiimide
n-Butylmalonic 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-butylmalonic 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-butylmalonic acid-N,N'-diphenylhydrazide is obtained in the form of short needles which melt at 116°-118°C.

References

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

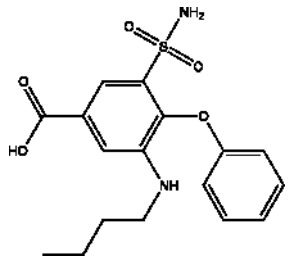
BUMETANIDE

Therapeutic Function: Diuretic

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

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 28395-03-1

Raw Materials

Sodium bicarbonate
Hydrogen
Phenol
4-Chloro-3-nitro-5-sulfamyl benzoic acid
n-Butanol

Trade Name	Manufacturer	Country	Year Introduced
Burinex	Leo	UK	1973
Fordiuran	Thomae	W. Germany	1976
Lunetoron	Sankyo	Japan	1976
Burinex	Sigma Tau	Italy	1977
Lixil	Leo	France	1978
Fontego	Polifarma	Italy	1979
Bumex	Hoffmann - La Roche Inc.	US	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	-

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 4N 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 1N 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 4N 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-sulfamyibenzoic 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 mixture 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), 1N 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 and Engel p.121
PDR p.1479
OCDS Vol.2 p.87 (1980)
DOT 8 (6) 238 (1972) and 9 (11) 449 (1973)
I.N. p.162
Felt, P.W.; US Patent 3,634,583; January 11, 1972; assigned to Lovens Kemiske Fabrik Produktionsaktieselskab. Denmark

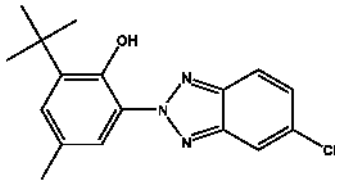
BUMETRIZOLE

Therapeutic Function: Sunscreen agent

Chemical Name: Phenol, 2-(5-chloro-2H-benzotriazol-2-yl)-6-(1,1-dimethylethyl)-4-methyl-

Common Name: Bumetrizole

Structural Formula:



Chemical Abstracts Registry No.: 3896-11-5

Trade Name	Manufacturer	Country	Year Introduced
Bumetrizole	Onbio Inc.	-	-

Raw Materials

2'-Hydroxy-3'-t-butyl-5'-methyl-5-chloro-2-nitroazobenzene
Sodium hydroxide
Zinc
Hydrochloric acid

Manufacturing Process

To a 2000 ml 3-necked, round-bottomed flask equipped with an agitator, reflux condenser, nitrogen inlet and thermometer were charged 140.5 g of 2'-hydroxy-3'-t-butyl-5'-methyl-5-chloro-2-nitroazobenzene, 119 g of isopropanol and 80 g of Amsco mineral spirits. A stream of nitrogen was introduced over the surface of the contents of the flask and the nitrogen atmosphere was then maintained throughout the remainder of the reduction process. 13.7 g of 50% aqueous sodium hydroxide solution and 222 g of water were added and the temperature of the contents of the flask were adjusted to 55°C. The ratio of the moles of alkali to moles of o-nitroazobenzene intermediate used was is 0.848/1. 104 g of zinc dust was added in 5 portions over a 2 hours period with the temperature of the flask being held at 55-60°C with some slight external cooling. The total concentration of iron impurities from all reactants less than 150 ppm based on zinc used. After all the zinc was added, the temperature was raised to 60°C and held at this temperature until a spot test indicated no more o-nitroazobenzene intermediate was present. The temperature was then raised to 65°C and held there for 4 to 5 hours or until TLC analysis indicated that no more of the N-oxy-intermediate was present. 62.6 g of anhydrous sodium sulfate and 35.6 g of water were then added, the batch was heated to 70°C and stirred for 15 min. The material was then allowed to stand and separate into three liquid phases plus unreacted zinc dust. The top two layers containing the desired product were transferred to another flask. The remaining aqueous zinc slurry was washed at 65-70°C with three successive 16 g portions of Amsco mineral spirits: isopropanol 50:50. The combined product layers and wash liquids were then washed once at 70°C with an aqueous hydrochloric acid solution made from 130 g of water and 40 g of 32% hydrochloric acid to remove cleavage amine by-products. A second and third wash followed at 70°C with aqueous hydrochloric acid solutions made each from 65 g of water and 20 g of 32% hydrochloric acid. The last wash was essentially colorless. 14 g of 32% hydrochloric acid and 220 g of isopropanol were added to the solution of the product. The batch was allowed to crystallize slowly. The solid product form was filtered and washed with isopropanol at 0°C to give 110 g of 5-chloro-2-(2-hydroxy-3-t-butyl-5-methylphenyl)-2H-benzotriazole with a melting point of 140-141°C.

References

White Howard L.; US Patent No. 4,041,044; August 9, 1977; Assigned to Ciba-Geig Corporation (Ardsley, NY)

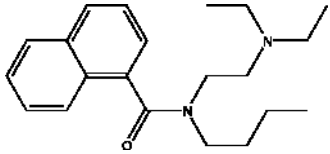
BUNAFTINE

Therapeutic Function: Antiarrhythmic

Chemical Name: N-Butyl-N-[2-(diethylamino)ethyl]-1-naphthalenecarboxamide

Common Name: Bunaftine; Bunaphtide; Meregon

Structural Formula:



Chemical Abstracts Registry No.: 32421-46-8

Trade Name	Manufacturer	Country	Year Introduced
Bunaftine	Malesci	-	-

Raw Materials

1-Naphthoic acid chloride
N,N-2-Diethylamine-ethyl-N'-(n-butyl)amine
Hydrochloric acid
Potassium carbonate

Manufacturing Process

Into a solution containing α-naphthoic acid chloride in benzene with agitation and cooling for 0.5 h a benzene solution of N,N-diethylamine-ethyl-N'-(n-butyl)amine is dropped. As the dropping is ended, the solution is kept under agitation in a water bath for 3 h.

After cooling the benzene solution is extracted with 10% hydrochloric acid; then the aqueous solution is saturated with potassium carbonate. The separated oil is extracted with ether and, after drying on sodium sulfate, the solvent is removed and the residue is vacuum distilled. So the N-(2-diethylamino-ethyl)-N-(n-butyl)-1-naphthalenecarboxamide, boiling point 178°C/0.1 mm/Hg.

References

Giannini M.; US Patent No. 3,704,322; November 28, 1972; Assigned: Malesci S.A.S. Istituto Farmacobiologico, Florence, Italy

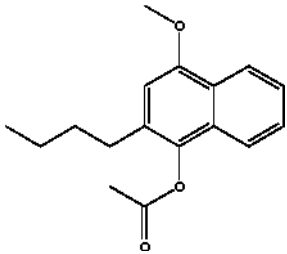
BUNAPROLAST

Therapeutic Function: Anti-asthmatic

Chemical Name: 1-Naphthalenol, 2-butyl-4-methoxy-, acetate

Common Name: Bunaprolast

Structural Formula:



Chemical Abstracts Registry No.: 99107-52-5

Trade Name	Manufacturer	Country	Year Introduced
Bunaprolast	ZYF Pharm Chemical	-	-

Raw Materials

Chromium hexacarbonyl
Phenyl lithium
Acetic anhydride
Triethylamine
Trimethyloxonium tetrafluoroborate(1-)
1-Hexyne
Acetylene

Manufacturing Process

Preparation of pentacarbonyl[phenyl(methoxy)carbene]chromium:

To a suspension of 22 g (0.1 mole) of chromium hexacarbonyl in ether is slowly added phenyllithium (51 ml, 0.1 mole, cyclohexane/ether solution) via syringe over a period of 15-20 minutes under argon at room temperature, and the resulting deep red solution is stirred at room temperature for 1 hour. The solvent is removed under reduced pressure (bath temperature should be below 40°C), and the black residue is dissolved in 200 ml water. $(CH_3)_3O{\cdot}BF_4$ (about 15 g) is added portionwise to the solution until it becomes slightly acidic (pH 5.5). The aqueous layer is extracted three times with 200 ml of ether, and the combined etheral extracts are washed once with 300 ml of saturated brine solution, once with 300 ml of saturated sodium carbonate solution, and three times with 300 ml of saturated brine solution, dried over anhydrous sodium sulfate and filtered. The solvent is removed using a rotary evaporator. The deep red tarry residue is purified using flash chromatography by a silica gel column (200 g). Elution by 10% ether in n-hexane gives a deep red syrup, which is solidified upon cooling. Recrystallization from pet-ether at -70°C gives 25.12 g (80.5%) of pentacarbonyl[phenyl(methoxy)carbene] chromium as deep red crystalline. The physical properties of the product are consistent with those described in the literature.

2-Butyl-4-methoxy-1-naphthalenol, acetate:

Reaction of pentacarbonyl[phenyl(methoxy)carbene]chromium with 1-hexyne:

Part A.

A mixture of the carbene complex (1.0 g, 3.2 mmole), 1-hexyne (2.6 equivalents), acetic anhydride (1.0 eq.) and triethylamine (1.0 eq.) in tetrahydrofuran (90 ml) is heated at 65°C under an argon atmosphere for 1 hour. The solution is cooled and concentrated to give a black residue, which is chromatographed through a silica gel (200 g) column using a flash chromatography. Elution by10% ether in n-hexane gives 71 5 mg (82.2%) of the title product, which solidified. Recrystallization from pet-ether gave white crystals of 2-butyl-4-methoxy-1-naphthalenol acetate; MP: 49°C.

Part B.

Alternatively, a mixture of 2.0 g (6.4 mmole) of the carbene complex, acetylene (2.6 eq.) and acetic acid in tetrahydrofuran is heated at 65°C for 2 hours under argon atmosphere. After cooling the reaction solution is concentrated and the black residue is loaded on a silica gel (200 g) column for a flash chromatography. Elution by 10% ether in n-hexane gives 895 mg (51.4%) of the title product.

References

Yamashita A.; European Patent No. 0,146,348; December 13, 1984; The Upjohn Company, Michigan, USA

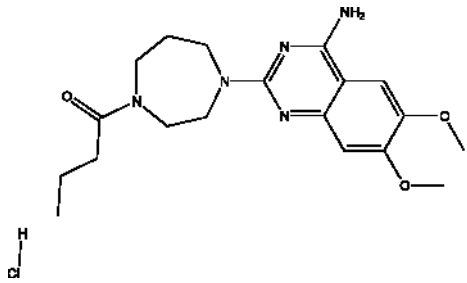
BUNAZOSIN HYDROCHLORIDE

Therapeutic Function: Antihypertensive

Chemical Name: 1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)hexahydro-4-(1-oxobutyl)-1H-1,4-diazepine monohydrochloride

Common Name: Bunazosin hydrochloride; Andante; Bunatenon

Structural Formula:



Chemical Abstracts Registry No.: 52712-76-2

Trade Name	Manufacturer	Country	Year Introduced
Andante	Boehringer-Ingelh.	-	-
Bunazosin hydrochloride	Eisai	-	-

Raw Materials

2-Chloro-4-amino-6,7-dimethoxyquinazoline
N-Formylhomopiperazine
2-Butylcarboxylic acid chloride

Manufacturing Process

17.0 g of 2-chloro-4-amino-6,7-dimethoxyquinazoline and 18.2 g of N-formylhomopiperazine are added to 170 ml of butanol and the whole is refluxed with stirring for 3 h. After completion of the reaction, the mixture is cooled, and the crystals thus precipitated are filtered out, washed with a small quantity of ethanol and air-dried. 25.0 g of crude 2-homopiperazino-4-amino-6,7-dimethoxyquinazoline are obtained.

A solution of 2-homopiperazino-4-amino-6,7-dimethoxyquinazoline in 60 ml of acetone is added dropwise to a solution of 2-butylcarboxylic acid chloride in acetone under stirring and ice-cooling. After completion of the addition, the stirring is continued for additional 1 h to complete the reaction. The crystals thus precipitated are filtered out and the 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)hexahydro-4-(1-oxobutyl)-1H-1,4-diazepine, melting point 280-282°C (recrystallized from a mixture of methanol-ethanol) is obtained.

References

Takahashy T., Sugimoto H.; US Patent No. 3,920,636; November 18, 1975; Assigned: Eisai Co., Ltd., Tokyo, Japan

BUNITROLOL

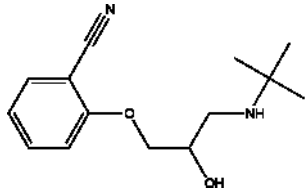
Therapeutic Function: Antianginal

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

Common Name: -

Chemical Abstracts Registry No.: 34915-68-9

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
St resson	Boehringer Ingelheim	W. Germany	1976
Betriol	Boehringer Ingelheim	Italy	1981
Betrilol	Boehringer Ingelheim	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 there from in crystalline form which after recrystallization from ethanol with an addition of ether gave9.8 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 and 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.; US 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

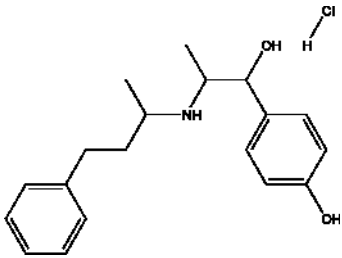
BUPHENINE HYDROCHLORIDE

Therapeutic Function: Vasodilator

Chemical Name: 4-Hydroxy-α-[1-[(1-methyl-3-phenylpropyl)amino]ethyl] benzenemethanol hydrochloride

Common Name: Buphenine hydrochloride; Nylidrine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 849-55-8

Trade Name	Manufacturer	Country	Year Introduced
Buphenine hydrochloride	Troponwerke	-	-
Opino	Bayropharm	-	-
Pervadil	Empire	-	-
Verina	Daiichi	-	-

Raw Materials

1-Phenyl-3-aminobutane
Hydrogen
Acetic acid
p-Benzoxy-α-bromopropiophenone
Palladium hydroxide on barium sulfate

Manufacturing Process

The p-benzoxy-α-bromopropiophenone and 1-phenyl-3-amino-butane were heating for an hour on the water bath in the absence of solvents. A solid crystalline cake was obtained. After being extracted with boiling acetic acid, the hydrobromide of 1-(p-hydroxyphenyl)-2-(β-phenylbutylamino)propanone-1 was obtained.

The hydrobromide of 1-(p-hydroxyphenyl)-2-(β-phenylbutylamino)propanone-1 was suspended in very pure methanol and shaken with a 10% palladium hydroxide barium sulfate catalyst in contact with, hydrogen. After rather more than 2 mols of hydrogen had been taken-up the hydrogenation stopped. The 1-(p-hydroxyphenyl)-2-(3-phenylbutylamino)propanol-1, was filtered, washed with methanol and evaporated, melting point 110-111°C.

References

Kulz F. et al.; US Patent No. 2,661,373; December 1, 1953; Assigned: Fritz Kulz, and Clemens Schopf, Darmstadt, Germany

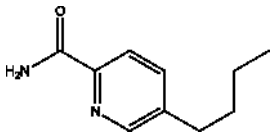
BUPICOMIDE

Therapeutic Function: Antihypertensive

Chemical Name: 5-Butyl-2-pyridinecarboxamide

Common Name: Bupicomide

Structural Formula:



Chemical Abstracts Registry No.: 22632-06-0

Trade Name	Manufacturer	Country	Year Introduced
Bupicomide	ZYF Pharm Chemical	-	-

Raw Materials

Methyl vinylketone
Hydroxylamine
Thionyl chloride
Potassium carbonate
Acetic acid
Selenium dioxide
Ammonia

Manufacturing Process

3-n-Butyl-6-methyl-3,4-dihydro-1,2-pyran was obtained and isolated from the reaction mixture by fractional distillation in vacuum to separate a by-product formed by cyclodimerisation of methyl vinylketone. The yield of the3-n-butyl-6-methyl-3,4-dihydro-1,2-pyran was 47% (boiling point 106-107°C.

The saponification of the 3-n-butyl-6-methyl-3,4-dihydro-1,2-pyran was accomplished by heating for 0.5 h in a mixture with acetic acid. The 1-methyl-4-n-butyl-1,5-dicarbonyl acid formed not isolated from the reaction mixture was added to hydroxylamine. The reaction with hydroxylamine was carried out by gradual addition of acetic acid solution of 1,5-dicarbonyl compound to the stirring refluxing suspension of hydroxylamine in glacial acetic acid. By usual treatment was fractionned in vacuum to yield 37.5% of 2-methyl-5-n-butylpyridine, boiling point 105°C.

The 2-methyl-5-n-butylpyridine was oxidated by selenium dioxide in pyridine to 5-n-butyl-2-pyridine carboxylic (fusarinic) acid, melting point 100-101°C.

25.0 g of the 5-n-butyl-2-pyridine carboxylic (fusarinic) acid and 25 ml of thionyl chloride were mixed; after all of the acid is dissolved, concentrate (in vacuo) the mixture and take up the mixture in 500 ml of anhydrous benzene; with cooling add the mixture to a solution of excess ammonia in 1 l of benzene, concentrate (in vacuo) the resulting mixture; add water and potassium carbonate and extract the amide with ether; dry and concentrate the ether extract and 5-n-butyl-2-pyridine carboxamide was obtained (recrystallize from acetonitrile).

References

Symchowicz S., Sherlock M.H.; US Patent No. 3,519,717; July 7, 1970; Assigned: Schering Corporation, Bloomfield, N.J.., a corporation of a New Jersey
Chumakov Yu.I., Sherstyuk V.P.; Tetrahedron Letters N 2, pp.129-135, 1965

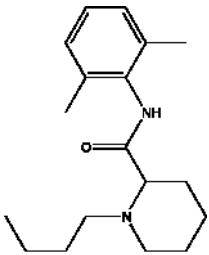
BUPIVACAINE

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 salt)

Raw Materials

2,6-Dimethylaniline	Nitrosyl chloride
Formic acid	Diethyl malonate
Zinc	n-Butyl bromide

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

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 steamdistilled 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 and 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 Egner, B.P.H.; US Patent 2,792,399; May 14, 1957; assigned to AB Bofors, Sweden
Thuresson, B. and Pettersson, B.G.; US Patent 2,955,111; October 4, 1960; assigned to AB Bofors, Sweden

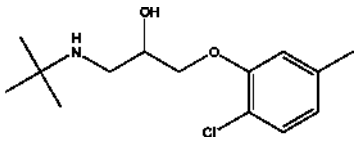
BUPRANOLOL

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 salt)

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 and Engel p.125
I.N. p.164
Kunz, W., Jacobi, H., Koch, C. and Geus, R.J.; US Patent 3,309,406; March 14, 1967

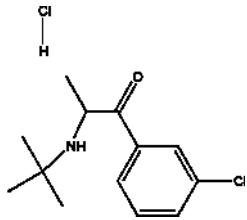
BUPROPION HYDROCHLORIDE

Therapeutic Function: Antidepressant; Smoking cessation aid

Chemical Name: 1-Propanone, 1-(3-chlorophenyl)-2-((1,1-dimethylethyl) amino)-, (+/-)-, hydrochloride

Common Name: Amfebutamone hydrochloride; Bupropion hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 34911-55-2 (Base); 31677-93-7

Trade Name	Manufacturer	Country	Year Introduced
Bupropion hydrochloride	AroKor Holdings Inc.	-	-
Wellbutrin	Glaxo-Wellcome	-	-
Zyban	Glaxo-Wellcome	-	-
Bupropion hydrochloride	Shanghai BR Chemical Co., Ltd.	-	-

Raw Materials

Ethyl magnesium bromide	m-Chlorobenzonitrile
Hydrochloric acid	Bromine
t-Butylamine	Sodium hydroxide

Manufacturing Process

To ethyl magnesium bromide (2 L, 3 M) was added over 45 min with stirring and cooling m-chlorobenzonitrile (688.0 g, 5 mole) in ether (2.5 L). The resultant solution was heated under gentle reflux for 5 h. The reaction mixture was hydrolyzed with cold dilute hydrochloric acid, the ether was distilled off, and the aqueous solution was heated at 90°C for 1 h. The flask was then cooled. The solid ketone that separated was washed with cold water and recrystallized from methanol. The recrystallized m-chloropropiophenone, melting point 39°-40°C, weighed 750.0 g.

In methylene chloride (3 L) was dissolved m-chloropropiophenone (698.0 g; 4.15 mole). The solution was stirred with charcoal (Darco) and magnesium sulfate for 2 h and filtered. To it was added with stirring (662.0 g) of bromine in methylene chloride (1 L). When the bromine color had faded completely, the solvent was evaporated in vacuum and m-chloro-α-bromopropiophenone was obtained as oil.

The m-chloro-α-bromopropiophenone was dissolved in acetonitrile (1300 ml). To this, t-butylamine (733.0 g) in acetonitrile (1300 ml) was added while keeping the temperature below 32°C. The reaction mixture was allowed to stand over night. It was then partitioned between water (4200 ml) and ether (2700 ml). The aqueous layer was extracted with a further portion of ether (1300 ml). The combined ethereal layers were then washed with water (4200 ml) to which hydrochloric acid was added until the pH of the aqueous layer was 9. The aqueous layer was separated and washed with ether (500 ml) and then discarded. The combined ethereal layers were then stirred with ice (560.0 g) and concentrated hydrochloric acid (324 ml). The ethereal layer was separated and again washed with water (200 ml) and concentrated hydrochloric acid (50 ml). These last two acid layers were combined and concentrated in vacuum until crystals appeared. The solution was then chilled to 5°C and filtered. The product was sucked dry, washed with acetone and recrystallized from a mixture of isopropanol (3 L) and absolute ethanol (800 ml). The DL-m-chloro-α-t-butylaminopropiophenone hydrochloride so was obtained, melting point 233°-234°C.

The DL-m-chloro-α-t-butylaminopropiophenone was obtained by treatment of DL-m-chloro-α-t-butylaminopropiophenone hydrochloride with sodium hydroxide.

References

Nariman B.M.; US Patent No. 3,819,706; June 25, 1974; Assigned: Burroughs Wellcome Co., Research Triangle Park, N.C.

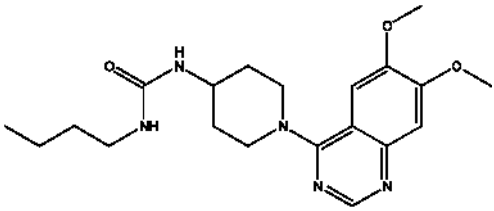
BUQUINERAN

Therapeutic Function: Coronary vasodilator

Chemical Name: N-Butyl-N'-[1-(6,7-dimethoxy-4-quinazolinyl)-4-piperidinyl] urea

Common Name: Buquineran; BDPU

Structural Formula:



Chemical Abstracts Registry No.: 59184-78-0

Trade Name	Manufacturer	Country	Year Introduced
Buquineran	Pfizer Central Research	-	-

Raw Materials

Triethylamine
4-Chloro-6,7-dimethoxyquinazoline
Sodium hydroxide
4-(3-n-Butylureido)piperidine hydrochloride

Manufacturing Process

4-Chloro-6,7-dimethoxyquinazoline (45.0 g), 4-(3-n-butylureido)piperidine monhydrochloride (80.0 g) and triethylamine (140 ml) were refluxed in ethanol (450 ml) for 1.25 h. The mixture was then concentrated in vacuo and the resultant solid was stirred in water which was then basified to pH 11 with 5 N NaOH solution. The suspension was shaken with chloroform and the organic layer was separated, dried (Na_2CO_3) and evaporated to dryness in vacuo to give a yellow oily solid. Trituration with ether followed by recrystallization from ethanol gave the product (37.0 g) with small traces of impurities, wich were removed by running a chloroform solution of it down a glass column packed with "Florisil" and eluting with 10% isopropanol in chloroform.

After evaporation, appropriate fractions were bulked to give a pure 4-(4-[3-n-butylureido]piperidino)-6,7-dimethoxyquinazoline, melting point 204-205°C (21.0 g; recrystallized from ethanol).

References

Danilewicz J.C. et al.; US Patent No. 4,001,422; January 4, 1977; Assigned: Pfizer Inc., New York, N.Y.

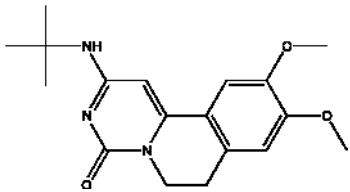
BUQUITERINE

Therapeutic Function: Bronchodilator

Chemical Name: 2-[(1,1-Dimethylethyl)amino]-6,7-dihydro-9,10-dimethoxy-4H-pyrimido[6,1-a]isoquinolin-4-one

Common Name: Buquiterine

Structural Formula:



Chemical Abstracts Registry No.: 76536-74-8

Trade Name	Manufacturer	Country	Year Introduced
Buquiterine	ZYF Pharm Chemical	-	-

Raw Materials

Sodium hydroxide
t-Butylamine
9,10-Dimethoxy-2-chloro-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-4-one

Manufacturing Process

A solution of 9,10-dimethoxy-2-chloro-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-4-one (3.0 g) and t-butylamine (10 ml) in chloroform (75 ml) is heated under reflux for 16 h. The solvent is evaporated under reduced pressure and the residue triturated with a dilute solution of sodium hydroxide to give a white precipitate of 9,10-dimethoxy-2-t-butylamino-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-4-one.

References

Lal B., et al.; US Patent No. 4,482,556; November 13, 1984; Assigned: Hoechst Aktiengesellschaft, Frankfurt am Main, Fed. Rep. of Germany

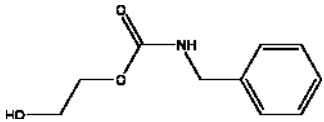
BURAMATE

Therapeutic Function: Anticonvulsant, Tranquilizer

Chemical Name: (Phenylmethyl)carbamic acid 2-hydroxyethyl ester

Common Name: Buramate; Hyamate

Structural Formula:



Chemical Abstracts Registry No.: 4663-83-6

Trade Name	Manufacturer	Country	Year Introduced
Buramate	Chauny and Cirey	-	-

Raw Materials

Cyclic carbonate of glycol
Benzylamine

Manufacturing Process

Into a vessel provided with efficient stirring means there are gradually introduced, while maintaining the temperature at 40°C, 535.0 g of benzylamine and 440.0 g of cyclic carbonate of glycol. The mass obtained is maintained at a temperature 40-50°C for about 12 h. Upon cooling, there is obtained a glycol benzylcarbamate as a white crystalline, melting point at 40°C, yield 92%.

References

GB Patent No. 689,705; April 1, 1953; Assigned: Societe Anonyme des Manufactures des Glaces et Produits Chimiques de Saint-Gobain, Chauny et Cirey, a Company organized under the laws of the French Republic, of 1 bis Place des saussaies, Paris VIIIe, Franc

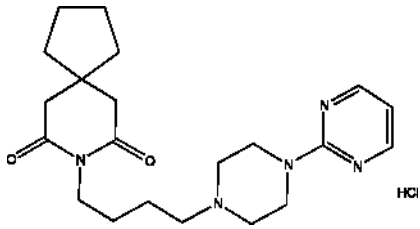
BUSPIRONE HYDROCHLORIDE

Therapeutic Function: Anxiolytic

Chemical Name: 8-Azaspiro[4.5]decane-7,9-dione, 8-(4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl), monohydrochloride

Common Name: Buspirone hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 33386-08-2

Trade Name	Manufacturer	Country	Year Introduced
Ansial	Bristol-Myers Squibb	-	-
Anxiolan	Medochemie Ltd.	-	-
Bespar	Bristol-Myers Squibb	-	-
Buspar	Bristol-Myers Squibb	-	-
Buspirone hydrochloride	Alexis Biochemicals	-	-
Busirone	Bristol-Myers Squibb	-	-

Raw Materials

3-Chloropropionitrile
Cyclohexane
Nickel Raney
3,3-Tetramethyleneglutaric anhydride
1-(2-Pyrimidinyl)piperazine
Hydrazine hydrate

Manufacturing Process

There is the 3 methods for preparing of 8-azaspiro(4.5)decane-7,9-dione, 8-(4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl) monohydrochloride (U.S. Patent 3,717,634). One of them is follows: a mixture of 0.1 mole of the substituted glutaric anhydride, 0.1 mole of l-(4-aminobutyl)-4-(2-pyrimidinyl)piperazine (U.S. Pat. 3,398151), and 300 ml of pyridine was refluxed until imide formation was completed. The degree of reaction was readily followed by taking an aliquot portion of the reaction mixture, removing the solvent, and obtaining the infrared absorption spectrum of the residue. When reaction is complete, the spectrum exhibited typical infrared imide bands at 1701 and 1710 cm^{-1} whereas if incomplete, the infrared spectrum contains amide and carboxyl absorption bands at 1680, 1760 and 3300 cm^{-1}.

1-(3-Cyanopropyl)-4-(2-pyrimidinyl)-piperazine. A mixture of 1-(2-pyrimidinyl)piperazine (6.0 g, 0.04 mole), 4.6 g (0.044 mole) of 3-chloropropionitrile and sodium carbonate (4.24 g, 0.04 mole) in 50 ml of n-butanol was gently refluxed for 16 hours. The reaction mixture was concentrated in vacuo and the residual oil dissolved in about 100 ml of cyclohexane. On standing a white crystalline material separated which was crystallized from cyclohexane to provide 6.5 g (yield 70%) of the cyano

intermediate, m.p. 56.6-58°C. A solution of 11.5 g (0.05 mole) of 1-(3-cyanopropyl)-4-(2-pyrimidinyl)piperazine in 150 ml of absolute ethanol was saturated with ammonia. W-6 Raney nickel catalyst was added and the mixture hydrogenated under 1200 p.s.i. When the hydrogenation was completed the mixture was filtered and the residual oil distilled under reduced pressure to provide 8.2 g (70%) of 1-(4-aminobutyl)-4-(2-pyrimidinyl)piperazine, b.p. 143-146°C at 0.1 mm. (n_D^{26} = 1.5582).

The azospiroalkenedione 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro[4.5]decane-7,9-dione was purified as free base by stripping off the pyridine solvent and crystallizing the residue from a suitable solvent or by vacuum distillation thereof hydrochloric salt of it was prepared by treating of an ethanol solution of free base with equimolar amount of HCl.

References

Yao Hua Wu et al.; US Patent No. 3,717,634; Feb. 20, 1973; Assigned: Mead Johnson and Company (Evansville, IN)
Yao Hua Wu et al.; US Patent No. 3,976,776; Aug. 24, 1976; Assigned: Mead Johnson and Company (Evansville, IN)

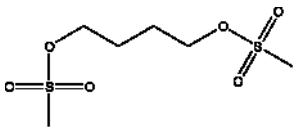
BUSULFAN

Therapeutic Function: Antineoplastic

Chemical Name: 1,4-Butanediol dimethanesulfonate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 55-98-1

Trade Name	Manufacturer	Country	Year Introduced
Myleran	Burroughs-Wellcome	US	1954
Misulban	Techni-Pharma	France	1955
Myleran	Wellcome	Switz.	1955
Myleran	Wellcome	W. Germany	1955
Mablin	Takeda	Japan	-
Mielucin	Farmasimes	Spain	-
Myeleukon	Arzneimittelwerk Dresden	E. Germany	-
Mylecytan	Spofa	Czechoslovakia	-

Raw Materials

1,4-Butanediol
Methanesulfonyl 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 to; 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 and Engel p.125
PDR p.754
I.N. p.165
REM p.1144
Timmis, G.M.; US Patent 2,917,432; December 15, 1959; assigned to Burroughs Wellcome and Co., Inc.

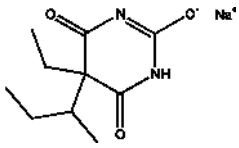
BUTABARBITAL SODIUM

Therapeutic Function: Hypnotic

Chemical Name: Barbituric acid, 5-sec-butyl-5-ethyl-, sodium salt

Common Name: Butabarbital sodium; Butabarbitone sodium; Secbutabarbital sodium; Secbutobarbitone sodium

Structural Formula:



Chemical Abstracts Registry No.: 143-81-7

Trade Name	Manufacturer	Country	Year Introduced
Butisol sodium	Wallace Labs	USA	-
Butisol sodium	Acura Pharmaceuticals, Inc.	-	-

Raw Materials

Diethyl ester of malonic acid
Sodium ethylate
Urea
Ethyl bromide
2-Butyl bromide

Manufacturing Process

5-sec-Butyl-5-ethylbarbituric acid was prepared from diethyl ester of malonic acid in 3 steps. At the above malonic ester was reacted with C_2H_5Br and sodium ethylate producing the diethyl ester of ethylmalonic acid, which after a reaction with sodium ethylate and 2-butylbromide gave the ethyl-(2-butyl)-malonic acid diethyl ester. The last one produced the 5-sec-butyl-5-ethyl-barbituric acid after a reaction with urea and sodium ethylate.

23 g sodium (1 mol) was dissolved in 300 ml alcohol. To this solution was added a solution of 5-sec-butyl-5-ethyl-barbituric acid (1 mol) in 800 ml alcohol. To a mixture was added 1000 ml benzene, which precipitated the sodium salt of the barbituric acid (butabarbital sodium). The product was filtered and dried.

References

Whitmore F.C. et al.; US Patent No. 2,161,212; June 6, 1939
Shonle H.A. et al.; US Patent No. 1,856,792; May 3, 1932
Pharmazeitishe Wirkstoffe, A. Kleeman und J. Engel, N.I. 1982

BUTACAINE

Therapeutic Function: Local anesthetic

Chemical Name: 1-Propanol, 3-(dibutylamino)-, p-aminobenzoate (ester)

Common Name: Butacaine; Butaprobenz; Butocaina

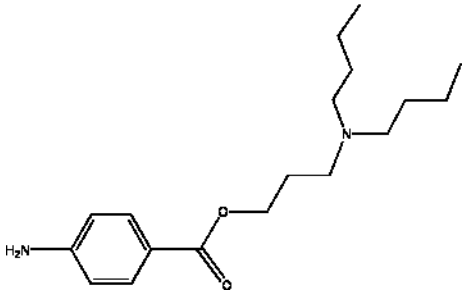
Chemical Abstracts Registry No.: 149-16-6

Trade Name	Manufacturer	Country	Year Introduced
Butelline	ALK-Abello	-	-
Butyn Dental	Abbott	-	-

Raw Materials

p-Nitro-gamma-bromo-propylbenzoate
Hydrochloric acid
Dibutylamine
Iron filings

Structural Formula:



Manufacturing Process

40 g p-nitro-gamma-bromo-propylbenzoate and 40 g dibutylamine are heated together at 60°C, for four hours. The excess dibutyl amine is removed by washing the product with water and then steam distilling the residue. The material remaining in the flask is taken up in benzene and treated with aqueous hydrochloric acid. Part of the p-nitrobenzoyl-gamma-di-n-butylamminopropanol hydrochloride thus formed goes into the water layer, while most of it separates as a heavy oily layer. This, together with the water layer, is separated from the benzene layer, made alkaline, and the resulting base taken up in benzene. Upon removal of the solvent, the desired p-nitrobenzoyl-gamma-di-n-butylamminopropanol is obtained.

The p-nitrobenzoyl-gamma-di-n-butylamminopropanol is reduced by warming to about 60°C with an excess of iron filings and a small amount of hydrochloric acid for four hours. The material is then allowed to cool, neutralized with dilute sodium hydroxide solution, and extracted with ether. Upon the removal of the ether, the free base, para-aminobenzoyl-gamma-di-n-butylaminopropanol, remains behind as an oil. It is exactly neutralized with aqueous hydrochloric acid and the resulting solid salt purified by recrystallization from water or a suitable organic solvent. It melts at 151°-152°C (corr.) after drying at 100°C.

References

Merck Index, Monograph number: 1531, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Adams R., Volwiler E.H.; US Patent No. 1,358,751; Nov. 16, 1920
Adams R., Volwiler E.H.; US Patent No. 1,676,470; July 10, 1928

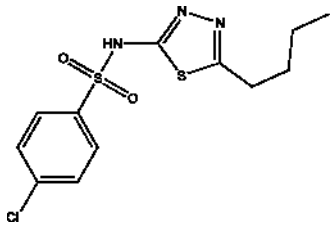
BUTADIAZAMIDE

Therapeutic Function: Oral hypoglycemic

Chemical Name: N-(5-Butyl-1,3,4-thiadiazol-2-yl)-4-chlorobenzenesulfonamide

Common Name: Butadiazamide

Structural Formula:



Chemical Abstracts Registry No.: 7007-88-7

Trade Name	Manufacturer	Country	Year Introduced
Butadiazamide	Onbio Inc.	-	-

Raw Materials

5-Amino-2-n-butyl-1:3:4-thiadiazole
p-Chlorobenzene sulfonyl chloride
Hydrochloric acid

Manufacturing Process

15.7 g of 5-amino-2-n-butyl-1:3:4-thiadiazole (0.1 mol) was dissolved in 150 ml dry pyridine and treated with 21.1 g of ρ-chlorobenzene sulfonyl chloride (0.1 mol). The mixture was heated on a steam bath for 4 h and the pyridine removed by distillation under reduced pressure. The residue was treated with 50 ml 2 N hydrochloric acid, and after filtration the 2-n-butyl-5-ρ-chlorobenzenesulfonamido-1:3:4-thiadiazole as colourless prisms, melting point 129-130°C (recrystallised from benzene) was obtained.

References

Macrae F.J., Drain D.J.; GB Patent No. 824,978; December 9, 1959; Assigned: T.J. Smith and Nephew Limited, a British Company, of Neptune Street, Kingston-upon-Hull, Yorkshire

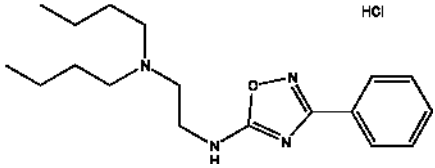
BUTALAMINE HYDROCHLORIDE

Therapeutic Function: Vasodilator

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

Common Name: -

Structural Formula:



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

Trade Name	Manufacturer	Country	Year Introduced
Surheme	Aron	France	1969
Surheme	Spemsa	Italy	1974
Adrevil	Zyma-Blaes	W. Germany	1975
Oxadilene	Leurquin	France	-
Surem	Cepa	Spain	-

Raw Materials

Benzaldehyde
Dibutylaminoethyl chloride
Cyanamide
Chlorine
Hydroxylamine
Sodium amide

Manufacturing Process

Benzaldehyde and hydroxylamine may be reacted, the product chlorinated and then reacted with cyanamide 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 and Engel p.126
I.N. p.166
Aron-Samuel, J.M.D. and Sterne, J.J.; US. Patent 3,338,899; August 29, 1967

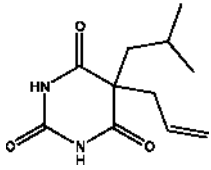
BUTALBITAL

Therapeutic Function: Hypnotic, Sedative

Chemical Name: 2,4,6(1H,3H,5H)-Pyrimidinetrione, 5-(2-methylpropyl)-5-(2-propenyl)-

Common Name: Alisobumalum; Allylbarbital; Butalbital; Itobarbital; Tetrallobarbital

Structural Formula:



Chemical Abstracts Registry No.: 77-26-9

Trade Name	Manufacturer	Country	Year Introduced
Axocet	Savage Labs	-	-
Esgic-Esgic Plus	Forest	-	-
Zyban	Glaxo-Wellcome	-	-
Fiorinal	Sandoz	-	-
Floricet	Sandoz	-	-
Sandoptal	Sandoz	-	-
Medigesic	US Pharmaceutical Corporation	-	-
Pacaps	Lunsco	-	-
Phrenilin	Canrick Labs	-	-
Repan	Everett Lab	-	-
Sedacap	Merz Pharmaceuticals	-	-
Tenake	Seatrace Pharmaceuticals	-	-
Tencon	Intarnational Ethical Labs	-	-

Raw Materials

Sodium
Ethyl malonic acid ester
Urea
Allyl bromide
Alcohol
2-Isobutyl bromide
Potassium hydroxide

Manufacturing Process

1 mole of sodium is dissolved in 10 to 12 times its weight of absolute alcohol

under a reflux condenser. To this are added 1 mole of ethyl malonic acid ester, and then gradually about 1.1 moles of 2-isobutyl bromide. The mixture is gently refluxed for some hours, or until it no longer shows alkaline reaction to moist litmus paper. Most of the alcohol is removed by vacuum distillation, leaving an oily residue. Water is added to this residue to dissolve the sodium bromide; and the oily layer, which is ethyl isopropyl-carbinyl malonic acid ester, is separated and dried. It is purified by fractional distillation in vacuum. When thus purified, ethyl isopropyl-carbinyl malonic acid ester is a colorless or pale yellow liquid, having a boiling point of 103°-105°C at about 4 mm pressure, and a refractive index at 25°C.

3 moles of sodium are dissolved in 10 to 12 times its weight of absolute alcohol under a reflux condenser. To this are added 1.6 moles of urea and 1 mole of ethyl isopropyl-carbinyl malonic acid ester. The mixture is gently refluxed for 2-4 h, after which most of the alcohol is removed by vacuum distillation. The residue is dissolved in water, and a sufficient amount of dilute acid is added to completely precipitate the isopropyl-carbinyl barbituric acid. The precipitate is filtered off, dried, and recrystallized from dilute alcohol.

1 mole of isopropyl-carbinyl barbituric acid is dissolved in a suitable vessel in a 10%-35% aqueous solution of 1 mole of potassium hydroxide. To this are added somewhat in excess of 1 mole of allyl bromide, and alcohol equal to about 10% of the total volume of the solution. The vessel is agitated for 50-75 h. At the end of this time, the solution, which may still exhibit two layers, is concentrated to about one-half its volume, to remove the excess allyl bromide and the alcohol. On cooling, an oily layer, which is isopropyl-carbinyl allyl barbituric acid, separates out as a sticky viscous mass. It is dried, washed with petroleum ether, and dissolved in the minimum amount of benzene. Any unreacted isopropyl-carbinyl barbituric acid, which does not dissolve, is filtered off. The addition of petroleum ether to the clear filtrate causes the isopropyl-carbinyl allyl barbituric acid to precipitate as an oily mass. This is separated, washed with petroleum ether, and dried in vacuum.

References

Shonle H.A.; US Patent No. 1,954,429; April 10, 1934; Assigned: Eli Lilly and Company, Indianapolis, Ind., a Corporation of Indiana

BUTAMIRATE CITRATE

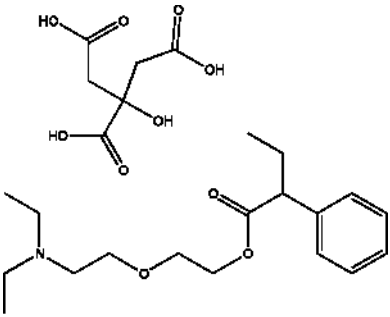
Therapeutic Function: Antitussive

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

Common Name: Butamyrate

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

Structural Formula:



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.	-
Intussin	Spofa	Czechoslovakia	-
Sincoden	Hommel	Switz.	-
Sincodix	Beta	Argentina	-
Sinecod	Abello	Spain	-
Pertix-Hommel	Hommel	W. Germany	-

Raw Materials

α-Phenylbutyric 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 and Engel p.127
OCDS Vol.2 p.76 (1980)
DOT 9 (7) 280 (1973)
I.N. p. 166
Heusser, J.; US Patent 3,349,114; October 24, 1967; Assigned to Hommel AG, Switzerland

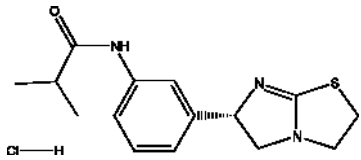
BUTAMISOLE HYDROCHLORIDE

Therapeutic Function: Anthelmintic

Chemical Name: (S)-2-Methyl-N-[3-(2,3,5,6-tetrahydroimidazo[2,1-b]thiazol-6-yl)phenyl]propanamide monohydrochloride

Common Name: Butamisole hydrochloride; Styquin

Structural Formula:



Chemical Abstracts Registry No.: 54400-62-3

Trade Name	Manufacturer	Country	Year Introduced
Butamisole hydrochloride	American Cyanamid (AHP)	-	-

Raw Materials

3'-Acetylacetanilide
2-Amino-2-thiazoline
Isobutyric anhydride
Sodium hydroxide
Ammonium hydroxide
Bromine
Sodium borohydride
Sulfuric acid
Hydrochloric acid

Manufacturing Process

To a stirred solution of 110.0 g (0.62 mole) of 3'-acetylacetanilide in 2400 ml of chloroform is added dropwise a solution of 33.0 ml (102.9 g; 0.644 mole)

of bromine in 240 ml of chloroform. The solution is stirred 1 h and the resultant precipitate is then filtered, washed with ether and dried. The solid is stirred in a large volume of water to give an oily precipitate which crystallizes on further stirring. The solid is filtered, washed with water and then 2-propanol, dried to give 148.34 g of the 3'-bromacetylacetanilide, melting point 108.5-110°C (recrystallized from 2-propanol).

A solution of 5.12 g (0.020 mole) of 3'-bromoacetylacetanilide in 70 ml of acetone is added to a stirred solution of 2.04 g (0.020 mole) of 2-amino-2-thiazoline in 30 ml of acetone. The mixture is stirred 1.5 h and the precipitate then filtered, washed with acetone and dried to give 6.00 g of 3'-[(2-imino-3-thiazolidinyl)acetyl]acetanilide hydrobromide, meltng point 275-277°C (recrystallization from water).

To a stirred slurry of 63.47 g (0.177 mole) of 3'-[(2-imino-3-thiazolidinyl) acetyl]acetanilide hydrobromide in 1 L of 95% ethanol, maintained at 5°C, is added 5.70 g (0.15 mole) of sodium borohyride. After stirring 40 min an additional 4.10 g of sodium borohydride is added and the mixture is acidified with hydrochloric acid and evaporated under reduced pressure. The residue is partitioned between chloroform and dilute aqueous ammonium hydroxide. Two further chloroform extracts are combined with the original, washed with brine, dried (sodium sulfate) and evaporated to give an oil. Treatment with acetone gives 6.77 g (48%) of 3'-[l-hydroxy-2-(2-imino-3-thiazolidinyl)ethyl]acetanilide hydrochloride as white crystalline, melting point 235-237°C.

Addition of 5.00 g (0.0158 mole) of 3'-[1-hydroxy-2-(2-imino-3-thiazolidinyl)ethyl]acetanilide hydrochloride to 15 ml of concentrated sulfuric icid is carried out in small increments over 0.5 h. The orange solution is stirred an additional 1 h, poured onto ice and made basic with concentrated ammonium hydroxide. The aqueous base is extracted twice with chloroform and the combined organic layers washed with water, brine, dried (sodium sulfate) and evaporated at reduced pressure to give 3.32 g (80% crude yield) of the 3'-(2,3,5,6-tetrahydroimidazo[2,1-b]thiazol-6-yl)acetanilide, melting point 164-166°C (recrystallization from 2-propanol).

A solution of 1.00 g (0.0038 mole) of 3'-(2,3,5,6-tetrahydroimidazo[2,1-b]thiazol-6-yl)acetanilide in 17 ml of 6 N hydrochloric acid is heated at reflux for 2.5 h and then allowed to stand overnight at room temperature. The solution is concentrated at reduced pressure, made basic with concentrated aqueous sodium hydroxide while cooling and then extracted with 3 portions of chloroform. The combined organic layers are washed with brine, dried (sodium sulfate) and evaporated to give 0.84 g of an oil, i.e., 6-(m-aminophenyl)-2,3,5,6-tetrahydroimidazo[2,1-b]thiazole free base. The oil is dissolved in hot methanol and strongly acidified with hydrogen chloride in 2-propanol. Evaporation of the solution give the 6-(m-aminophenyl)-2,3,5,6-tetrahydroimidazo[2,1-b]thiazole dihydrochloride, melting point 198-201°C (crystallization from 2-propanol).

2.2 g (0.010 mole) of 6-(m-aminophenyl)-2,3,5,6-tetrahydroimidazo[2,1-b]thiazole dihydrochloride is disolved in a mixture of 15 ml methanol and 15 ml water and the pH is adjusted to about 6 with an aqueous hydrochloric acid solution. This solution is then added to 3.2 g (0.020 mole) of isobutyric anhydride. The mixture is allowed to stand at room temperature for 12 h. The

reaction mixture is then added to a mixture of 100 ml methylene chloride and 50 ml water and then made basic (pH 10) with an aqueous sodium hydroxide. The methylene chloride layer is removed and the water layer is washed twice with 75 ml of fresh methylene chloride. The methylene chloride extract are then combined, dried over magnesium sulfate, and the methylene chloride evaporated leaving a tacky solid. The free base of the product is recrystallized from a chloroformethyl ether mixture. The yield of the 3'-(2,3,5,6-tetrahydroimidazo[2,1-b]thiazol-6-yl)isobutyranilide is 1.6 g (55%).

References

Spicer L.D., Hand J.J.; US Patent No. 3,899,583; August,1975; Assigned: American Cyanamid Company, Stamford, Conn.

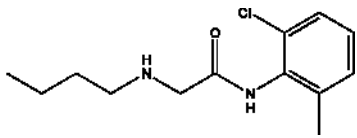
BUTANILICAINE

Therapeutic Function: Local anesthetic

Chemical Name: 2-(Butylamino)-6'-chloro-o-acetoluidide

Common Name: Butacetoluide; Butanilicaine

Structural Formula:



Chemical Abstracts Registry No.: 3785-21-5

Trade Name	Manufacturer	Country	Year Introduced
Butanilicaine	Enreco, INC	-	-

Raw Materials

4-Bromo-2-methylaniline
n-Butylamine
Chloroacetyl chloride
Hydrochloric acid

Manufacturing Process

To a solution of 4-bromo-2-methylaniline is added 13 g of chloroacetyl chloride. After the reaction is finished to the mixture id added a solution of 33 g sodium acetate in 138 ml of water. Chloroacetic acid 4-bromo-2-methylanilide is filtered; yield 24 g, M.P. 135°C (crystallization from ethanol).

20 g of chloroacetic acid 4-bromo-2-methylanilide is dissolved in 200 ml of

butylamine. After about 15 hours to the solution is added 2 N hydrochloric acid. Butylaminoacetic acid 4-bromo-2-methylanilide hydrochloride is removed by suction and washed with water; yield 90%, M.P. 252-253°C (from methanol).

References

Merck Index, Monograph number: 1542, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Walter A. et al., DE Patent No. 1,009,633; 1957.06.06; Assigned to Hoechst AG

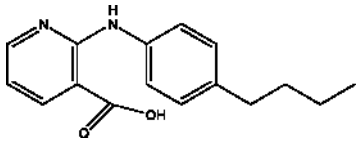
BUTANIXIN

Therapeutic Function: Analgesic, Antiinflammatory

Chemical Name: 2-(p-Butanilino)nicotinic acid

Common Name: Butanixin

Structural Formula:



Chemical Abstracts Registry No.: 55285-35-3

Trade Name	Manufacturer	Country	Year Introduced
Butanixin	ZYF Pharm Chemical	-	-

Raw Materials

2-Chloronicotinic acid
p-n-Butyl aniline

Manufacturing Process

5 g 2-chloronicotinic acid and 9.4 g p-n-butyl aniline were heated for 1 hour at 160°C by vigorous stirring under a nitrogen atmosphere. Then the mixture was dissolved in 2 N sodium hydroxide and extracted with benzene. The water layer was acidified and a precipitate obtained was filtered off, washed with water and dried. 5 g 2-[(4-butylphenyl)amino]-3-pyridinecarboxylic acid yielded. MP: 171°-173°C (deg.).

References

Stampa A.; D.E. Patent No. 2,409,260; January 30, 1975; Laboratorios Hermes S.A. Barcelona (Spain)

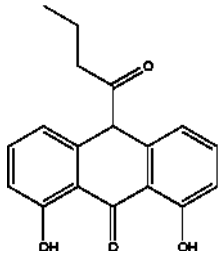
BUTANTRONE

Therapeutic Function: Antipsoriatic

Chemical Name: 1,8-Dihydroxy-10-(1-oxobutyl)-9(10H)-anthracenone

Common Name: Butantrone

Structural Formula:



Chemical Abstracts Registry No.: 75464-11-8

Trade Name	Manufacturer	Country	Year Introduced
Butantrone	Onbio Inc.	-	-

Raw Materials

Anthralin
Pyridine
Butyryl chloride

Manufacturing Process

To a solution of 56.6 g (0.25 mol) of anthralin in 1750 ml of absolute toluene and 27.3 ml of pyridine, 31.5 ml (0.3 mol) of butyryl chloride was added with stirring over 30 min at room temperature. The reaction mixture was then heated to 85°C for 1 hour. After this mixture had recooled to room temperature, 27.3 ml of pyridine and 31.5 ml of butyryl chloride were again added. The suspension obtained was then heated to 85-90°C for 1 hour. The precipitated pyridinium hydrochloride was eliminated by filtration then washed with toluene. The toluene filtrates were concentrated to around 500 ml under reduced pressure, washed several times with water then dried over magnesium sulfate. The product was then fractionated by chromatography on

silica gel, using toluene and then a mixture of toluene and ethyl acetate as the mobile phase. The different fractions containing the 1,8-dihydroxy-10-(1-oxobutyl)-9(10H)-anthracenone were then concentrated and recrystallized from a toluene-hexane mixture. In this way 25 g of yellow crystals of 1,8-dihydroxy-10-(1-oxobutyl)-9(10H)-anthracenone having a melting point of 138°C was obtained.

References

Shroot Braham, Lang Gerard, Maignan Jean; US Patent No. 4,696,941; September 29, 1987; Assigned to Groupement d'Interet Economique dit: Centre International 'de Recherches (Valbonne, FR)

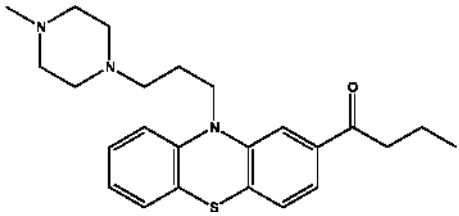
BUTAPERAZINE

Therapeutic Function: Neuroleptic, Antiemetic

Chemical Name: 1-Butanone, 1-(10-(3-(4-methyl-1-piperazinyl)propyl)-10H-phenothiazin-2-yl)-

Common Name: Butaperazine; Butyrylperazine

Structural Formula:



Chemical Abstracts Registry No.: 653-03-2

Trade Name	Manufacturer	Country	Year Introduced
Bayer 1362	Bayer	-	-
Repoise	Robins	-	-
Butyrylperazine	Robins	-	-
Randolectil	Bayer	-	-
AHR 712	Robins	-	-

Raw Materials

Sodium amide
2-Buterylphenothiazine
Sodium hydroxide

Manufacturing Process

To a suspension of sodamide in liquid ammonia is added of 2-buterylphenothiazine. After stirring for one hour, there is added 1-bromo-3-chloropropane. The ammonia is allowed to evaporate and the residue is diluted with the water. The mixture is extracted with ether and the ether solution is dried over anhydrous sodium sulfate, filtered and concentrated. The residue consists of crude 10-(3-chloropropyl)-2-buterylphenothiazine as viscous oil and is used in the next step without further purification.

A mixture of 1-methylpiperazine and crude 10-(3-chloropropyl)-2-buterylphenothiazine is heated on a steam bath for 18 hours. The mixture is diluted with the water and extracted with ether. The ether solution is extracted with dilute hydrochloric acid. The aqueous acid solution is made alkaline with sodium hydroxide and the product is extracted with ether. The ether extracts are dried and concentrated to a residue consisting of the free base 2-butyryl-10-(3-(4-methyl-1-piperazinyl)propyl)phenothiazine.

References

Merck Index, Monograph number: 1543, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Sheriock M.H. et al.; US Patent No. 2,985,654; May 23, 1961; Assigned to Schering Corporation, Bloomfield, N.Y., a corporation of New Jersey

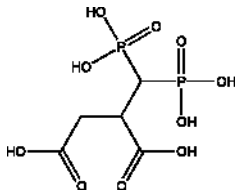
BUTEDRONIC ACID

Therapeutic Function: Diagnostic aid

Chemical Name: (Diphosphonomethyl)butanedioic acid

Common Name: Butedronic acid

Structural Formula:



Chemical Abstracts Registry No.: 51395-42-7

Trade Name	Manufacturer	Country	Year Introduced
Butedronic acid	Bayer A.G.	-	-

Raw Materials

Methylene diphosphonic acid tetraethyl ester
Maleic acid diethyl ester
Sodium ethylate
Acetic acid
Hydrochloric acid

Manufacturing Process

0.5 mole of methylene diphosphonic acid tetraethyl ester is heated for 6 h to 110°C with 0.5 mole of maleic acid diethyl ester in the presence of 25 ml of a saturated sodium ethylate solution. The sodium ethylate is then neutralized with acetic acid and the reaction mixture is quickly distilled invacuo in order to avoid decomposition. The crude distillate is redistillated, the main fraction accumulating in the range from 190-213°C at a pressure of 0.05 Torr, yield 50%.

The ester is hydrolyzed by boiling with concentrated hydrochloric acid. 1,1-Diphosphonopropane-2,3-dicarboxylic acid crystallizes out after purification with active carbon and concentration of the hydrolysis product, yield 100%.

References

Heins A. et al.; US Patent No. 3,923,876; December 2, 1975; Assigned: Bayer Aktiengesellschaft, Leverkusen, Germany

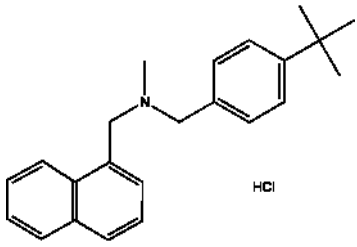
BUTENAFINE HYDROCHLORIDE

Therapeutic Function: Antifungal

Chemical Name: 1-Naphthalenemethanamine, N-((4-(1,1-dimethylethyl) phenyl)methyl)-N-methyl-, hydrochloride

Common Name: Butenafine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 101827-46-7

Trade Name	Manufacturer	Country	Year Introduced
Butenafine Hydrochloride	Shenzhen Fangye Industries Co., Ltd.	China	-
KP-363	Shenzhen Fangye Industries Co., Ltd.	China	-
Lotrimin Ultra	Schering-Plough HealthCare Products, Inc.	-	-
Mentax-TC	Bertek	-	-

Raw Materials

N-Methyl-1-naphtylmethylamine hydrochloride
p-tret-Butylbenzyl bromide

Manufacturing Process

N-Methyl-1-naphtylmethylamine hydrochloride (2.1 g, 0.01 mole) was dissolved in 50 ml of dry dimethylformamide, and 3.71 g (0.035 mole) of anhydrous sodium carbonate was added, then 2.49 g (0.011 mole) of p-t-butylbenzyl bromide was added by stirring and the mixture was reacted at 30° to 40°C for 5 hours. Ice water was added, and the mixture was extracted with toluene. The organic layer was washed with water, and toluene was evaporated. The residue was chromatographed on silica gel column, and eluated with 5% ethyl acetate/n-hexane. The eluate was concentrated to give 2.98 g (yield 94%) of an oily substance. Hydrochloric acid/ethanol was added to 1 g of this oily product, and the mixture was concentrated. The residue was recrystallized from methanol/acetic acid to give 0.95 g of desired 1-naphthalenemethanamine, N-((4-(1,1-dimethylethyl)phenyl)methyl)-N-methyl-, hydrochloride having melting point 200° to 202°C.

References

Arita et al.; US Patent No. 4,822,822; Apr. 18, 1989; Assigned Mitsui Toatsu Chemicals, Inc., Tokyo, Japan

BUTERIZINE

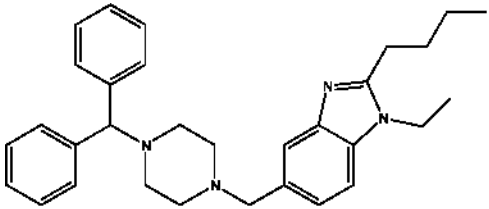
Therapeutic Function: Vasodilator

Chemical Name: 2-Butyl-5-[[4-(diphenylmethyl)-1-piperazinyl]methyl]-1-ethyl-1H-benzimidazole

Common Name: Buterizine

Chemical Abstracts Registry No.: 68741-18-4

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Buterizine	Shanghai Chemfrom Chemical Co., Ltd.	-	-

Raw Materials

1-Chloro-4-(chloromethyl)-2-nitrobenzene
Nickel Raney
Sodium hydroxide
Pentyl ethanimidate hydrochloride
1-(Diphenylmethyl)piperazine
Ethanamine
Hydrogen
Acetic acid

Manufacturing Process

A mixture of 10.3 parts of 1-chloro-4-(chloromethyl)-2-nitrobenzene, 25.2 parts of 1-(diphenylmethyl)piperazine and 120 parts of ethanol is stirred and refluxed for 4 h. The reaction mixture is cooled and evaporated. The residue is taken up in about 100 parts of water and the product is extracted with methylbenzene. The extract is washed with water, dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using trichloromethane as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from a mixture of 2,2'-oxybispropane and hexane (1:2 by volume). The product is filtered off, washed with hexane and dried, yielding 19.6 parts of 1-(4-chloro-3-nitrophenylmethyl)-4-(diphenylmethyl)piperazine; melting point 101.6°C.

During 20 h, gaseous ethanamine is bubbled through a stirred and hot (60-70°C) mixture of 1-(4-chloro-3-nitrophenylmethyl)-4-(diphenylmethyl)piperazine and dimethylsulfoxide. The reaction mixture is cooled and poured onto ice-water. The precipitated product is filtered off, washed with water and taken up in methylbenzene. The latter is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol as eluent. The pure fractions are collected and the eluent is evaporated, yielding 4-[4-(diphenylmethyl)-1-piperazinylmethyl]-N-ethyl-2-nitrobenzenamine; melting point 128.2°C (crystallized from 2,2'-oxybispropane).

A solution of 4-[4-(diphenylmethyl)-1-piperazinylmethyl]-N-ethyl-2-nitrobenzenamine in methanol is hydrogenated at normal pressure and at room temperature with Raney-nickel catalyst. After the calculated amount of hydrogen is taken up, the catalyst is filtered off and the filtrate is evaporated,

yielding 4-[4-(diphenylmethyl)-1-piperazinylmethyl]-N1-ethyl-1,2-benzenediamine.

A mixture of 4-[4-(diphenylmethyl)-1-piperazinylmethyl]-N1-ethyl-1,2-benzenediamine and acetic acid is stirred at room temperature till all solid enters solution. Then there are added pentyl ethanimidate hydrochloride and stirring is continued first for 1 h at room temperature and further for 1 h at reflux. The reaction mixture is evaporated and the residue is stirred in water. The whole is alkalized with a sodium hydroxide solution and the product is extracted with dichloromethane. The extract is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol as eluent. The pure fractions are collected and the eluent is evaporated. The product is filtered off and dried, yielding 5-[4-(diphenylmethyl)-1-piperazinylmethyl]-1-ethyl-2-butyl-1H-benzimidazole; melting point 124.8°C (crystallized from 4-methyl-2-pentanone).

References

Raeymaekers A.H.M. et al.; US Patent No. 4,179,505; December 18, 1979; Assigned: Janssen Pharmaceutica N.V. Beers, Belgium

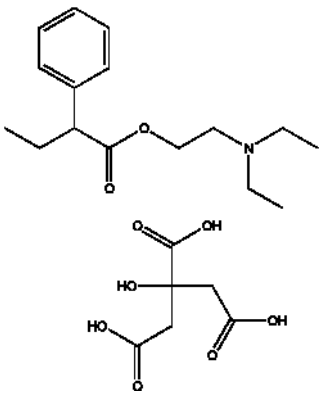
BUTETAMATE CITRATE

Therapeutic Function: Anticholinergic, Spasmolytic, Antitussive

Chemical Name: 2-(Diethylamino)ethyl-2-phenylbutyrate, citrate salt

Common Name: Butetamate citrate; Phenethylamincitrat; Butethamate citrate

Structural Formula:



Chemical Abstracts Registry No.: 14007-64-8

Trade Name	Manufacturer	Country	Year Introduced
Butetamat-dihydrogencitrat	Chemische Werke Hommel GmbH and Co.KG	-	-
Convenil	Hommel	-	-
Convenal	Hommel	-	-
Hicoseen	Klimitschek	-	-
Phenetin	Alpinapharm	-	-
Aspectonetten	Krewel Meuselbach	-	-
CAM	Rybar-Ireland	-	-

Raw Materials

alpha-Phenylbutiric acid
beta-Diethylaminoethylchloride hydrochloride
Potassium carbonate

Manufacturing Process

16.4 parts of alpha-phenylbutiric acid, 17.5 parts of beta-diethylaminoethylchloride hydrochloride and 35 parts of dry potassium carbonate in 60 parts diisopropyl ether was stirred for 18 hours under reflux. To the reaction mixture at 40°C was added 120 parts of the water. Organic layer was washed with the water. The solvent was removed and the 2-(diethylamino)ethyl-2-phenylbutyrate was distilled at 167-168°C/10 mm; melting point of hydrochloride 167-169°C.

In practice it is usually used as citrate.

References

Schweizerische Patent No. 291,375; Sept. 16, 1953; Assigned to Aktiengesellschaft Hommels Haematogen, Zurich

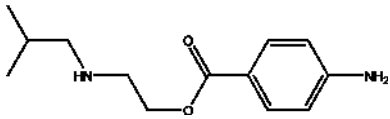
BUTETHAMINE

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 salt)

Trade Name	Manufacturer	Country	Year Introduced
Monoceine	Novocol	US	1941
Dentocaine	Amer. Chem.	US	-

Raw Materials

Isobutylaminoethanol
Tin
4-Nitrobenzoyl chloride
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 and Engel p.128
DOT 15 (7) 368 (1979)
I.N. p.168
Goldberg, S.D.; US Patent 2,139,818; December 13, 1938; assigned to Novocol Chemical Mfg. Co., Inc.

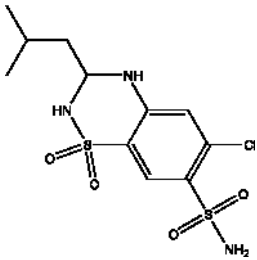
BUTHIAZIDE

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
Ammonia
Chlorosulfonic acid
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 and 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

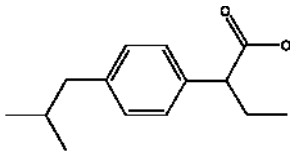
BUTIBUFEN

Therapeutic Function: Antiinflammatory, Analgesic

Chemical Name: 2-(p-Isobutylphenyl)butyric acid

Common Name: Butilopan

Structural Formula:



Chemical Abstracts Registry No.: 55837-18-8

Raw Materials

Trade Name	Manufacturer	Country	Year Introduced
Butibufen	Onbio Inc.	-	-
Butilopan	Juste	-	-
Butilopan	Merck	-	-

Paraformaldehyde
Hydrogen chloride
Sodium amide
Sodium hydroxide
Hydrochloric acid
Zinc chloride
Sodium cyanide
Ethyl iodide
Sodium

Manufacturing Process

1st method:

4-Isobutylphenylbenzyl chloride was prepared by passing a stream of hydrogen chloride into a suspension of p-bromoaldehyde and anhydrous zinc chloride in isobutylbenzene. A mixture of 137 g (0.75 mol) of 4-isobutylbenzyl chloride thus prepared, 44.1 g (0.90 mol) of sodium cyanide, 216 g of 99% ethanol, and 81.3 g of water was heated refluxed for 6 hours. The mixture became reddish-black in color. From this mixture, 215 ml of ethanol and water

was then distilled and the residue was filtered. The solids that were separated by filtration were washed with 100 ml of diethyl ether and the ether washings were combined with the original filtrate, to which 800 ml of water was then added. The organic phase was then separated from the aqueous phase, washed with five 400 ml portions of water and dried over anhydrous sodium sulfate. The ether was evaporated from the dried organic phase by vacuum distillation and the residue which distilled between 130°C and 132°C at a pressure of 7 mm of mercury was collected. The yields of 4-isobutylbenzene cyanide 100-113 g.

To a solution of 6.7 g of sodium amide in 100 ml of anhydrous diethyl ether was added dropwise 26 g of 4-isobutylbenzene cyanide while the mixture was stirred and heated under gentle reflux. After all of the 4-isobutylbenzene cyanide had been added, the mixture was heated under gentle reflux for 15 min, after which 23.4 g of ethyl iodide was slowly added dropwise thereto from the dropping funnel. After completion of the addition of the ethyl iodide, the mixture was heated under gentle reflux for an initial period of 15 min, after which it was diluted with an equal volume of water and shaken. The two layers that formed were separated and the aqueous layer was then extracted with two 50 ml portions of diethyl ether. The ether extracts were combined and then washed with two 80 ml portions of water and dried over anhydrous magnesium sulfate. The dried ether extract was then distilled at a subatmospheric pressure. In this manner, 25 g of a clear transparent uncolored liquid having a boiling point of 118-122°C at a pressure of 1mm of mercury, which consisted of 2-(4-isobutylphenyl)butyronitrile, was collected. This yield was equivalent to 83% of the theoretical.

A mixture of 40 g (0.2 mol) of 2-(4-isobutylphenyl)butyronitrile and 78 ml of a freshly prepared solution of sodium hydroxide that was prepared by dissolving 28 g of sodium hydroxide in 25 ml of distilled water and the volume of which was brought to 100 ml by addition thereto of methanol, was heated under gentle reflux in a flask provided with a stirrer and reflux condenser while the mixture was stirred during a period of 9 hours. From the mixture the methanol and a portion of the water were distilled and the mixture was then cooled, the crystals began to separate. The mixture was then diluted with 150 ml of water and extracted with two 25 ml portions of diethyl ether. The remaining aqueous solution containing the sodium salt of 2-(4-isobutylphenyl)butyric acid was then saturated with sodium chloride until the salt started to precipitate. The solution was then cooled to 5°C and the precipitated salt was separated by filtration, recrystallized from isopropanol, and dried in a vacuum desiccator at a pressure of 1 mm of mercury until it had attained a constant weight. In this manner, 32 g of sodium 2-(4-isobutylphenyl)butyrate having a melting point of 188-191°C, which is equivalent to a yield of 67% of the theoretical, was obtained.

Dilute hydrochloric acid (19% by weight of hydrogen chloride) was slowly added to a cold solution of 25 g of the sodium 2-(4-isobutylphenyl)butyrate thus prepared in 100 ml of water until the solution corresponded to pH of 1.0. The oil which precipitated was then allowed to solidify to a white solid by standing in a refrigerator. The white solid was then separated by filtration, dried, and recrystallized from petroleum ether. It had a melting point of 50-52°C, and its elementary analysis corresponded to the 2-(4-isobutylphenyl)butyric acid.

2nd method:

5.0 g of small pellets of sodium metal were added slowly with stirring to 150 ml of absolute ethanol, while a current of nitrogen gas was passed there through so as to blanket the solution from the atmosphere. After all of the sodium metal had been dissolved and while the solution was maintained at a temperature of 50°C, a solution of 52 g of ethyl 2-(4-isobutylphenyl)cyanoacetate in 50 ml of absolute ethanol was added dropwise while the mixture was stirred. Subsequently, 81 g of ethyl iodide was gradually added to the mixture with stirring, after which the introduction of nitrogen gas into the mixture was discontinued and the mixture was heated for a period of 2.5 hours under gentle reflux. Thereafter, the ethanol and excess ethyl iodide were distilled from the mixture and the residue was then diluted with three times its volume of water and shaken therewith. The 2-(4-isobutylphenyl)-2-(ethoxycarbonyl)butyronitrile was then extracted from the mixture with three 50 ml portions of diethyl ether, the extracts were combined, washed with a 20% aqueous solution of sodium bisulfate and dried over anhydrous magnesium sulfate. The ether was then expelled from the extract by distillation and the residue was distilled at a subatmospheric pressure, yielding 45 g of a fraction containing 2-(4-isobutylphenyl)-2-(ethoxycarbonyl)butyronitrile having a boiling point of 150-155°C/3 mm of mercury (78% of the theoretical yield).

In a 2-liter flask provided with a stirrer and reflux condenser a solution of 129 g of 2-(4-isobutylphenyl)-2-(ethyoxycarbonyl)butyronitrile in 980 ml of a 20% solution of potassium hydroxide in methanol was heated with stirring at 40°C for a period of 1 hour. The mixture was then heated under gentle reflux with stirring for an additional period of 3 hours, during which a white solid precipitated. This mixture was then poured into 1.5 liters of water and acidified with an aqueous solution of hydrochloric acid (concentrated hydrochloric acid diluted with an equal volume of water) to a hydrogen ion concentration corresponding to a pH of 2.5, while carbon dioxide was evolved therefrom. The aqueous mixture was then extracted with diethyl ether. The extracts were washed successively with a saturated solution of sodium bicarbonate and water, dried over anhydrous magnesium sulfate, and distilled at a subatmospheric pressure, to yield 86.5 g of a fraction consisting of 2-(4-isobutylphenyl)butyronitrile having a boiling point of 124-128°C at a pressure of 1.5 mm of mercury, which is equivalent to approximately 0.43 mol and a yield of 91% of the theoretical based on the original 2-(4-isobutylphenyl)-2-(ethoxycarbonyl)butyronitrile.

The 2-(4-isobutylphenyl)butyronitrile was converted to sodium 2-(4-isobutylphenyl)butyrate and subsequently to 2-(4-isobutylphenyl)butyric acid in the same manner as described in Method 1 hereinbefore.

References

Aparicio Luis, Gayo Nenesio, Carretero Jose, Martin Jose Luis, Ron Armando; US Patent No. 4,031,243; June 21, 1977; Assigned to Juste, S.A. Quimico-Farmaceutica (Madrid, ES)

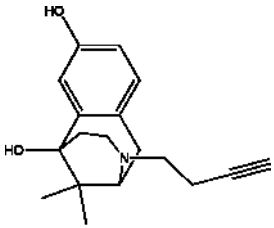
BUTINAZOCINE

Therapeutic Function: Analgesic

Chemical Name: (-)-3-(3-Butynyl)-1,2,3,4,5,6-hexahydro-11,11-dimethyl-2,6-methano-3-benzazocine-6,8-diol

Common Name: Butinazocine

Structural Formula:



Chemical Abstracts Registry No.: 93821-75-1

Trade Name	Manufacturer	Country	Year Introduced
Butinazocine	ZYF Pharm Chemical	-	-

Raw Materials

2-(4-Methoxybenzyl)-1,3,3-trimethyl-4-piperidone hydrochloride
Sodium hydroxide
Ammonia
Lithium aluminum hydride
Toluene-4-sulfonic acid but-3-ynyl ester
Methyliodide
Nitrobenzene
Aluminum trichloride
Hydrochloric acid
Cyanogen bromide
Sodium hydride
Calcium carbonate
Ethanethiol

Manufacturing Process

A mixture of 59.5 g (0.2 mol) 2-(4-methoxybenzyl)-1,3,3-trimethyl-4-piperidone hydrochloride and 53.8 g (0.4 mol) of aluminum trichloride and 54.0 g of nitrobenzene in 1500 ml of dry benzene are boiled under reflux for 1 h. After cooling the reaction mixture is extracted with 750 ml 4 N sodium hydroxide solution, the temperature being maintained below 35°C. The organic phase is separated and extracted with 750 ml 1 N hydrochloric acid. The acid aequeous phase is rendered alkali by the addition of 100 ml 25% ammonia and extracted three times with 250 ml chloroform. The collected chloroformic phases are dried with sodium sulfate and evaporated under reduced pressure. The residue, 46.7 g, is converted into the hydrochloride by reaction with iso-propanol/HCl and crystallized from a mixture of methanol and ethylacetate. 44.6 g of the 5-hydroxy-2'-methoxy-2,9,9-trimethyl-6,7-benzomorphan hydrochloride are obtained, melting point 233-236° C (dec.).

21.8 g (0.5 mol) of a 55% dispersion of sodium hydride in oil are added to 52.2 g (0.2 mol) of 5-hydroxy-2'-methoxy-2,9,9-trimethyl-6,7-benzomorphan in 500 ml of dry peroxide-free tetrahydrofuran, followed by the drop-wise addition over 45 min of 142.0 g (1.0 mol) of methyliodide, and the mixture is stirred for 4 h at room temperature, 9 ml of water are added carefully to the obtained reaction mixture and the tetrahydrofuran is evaporated off under reduced pressure. After addition of 250 ml of water the residue is extracted 3 times with 250 ml of chloroform. The combined chloroformic phases are dried over sodium sulfate and concentrated under reduced pressure. The residue is converted into the hydrochloride, washed with toluene to remove paraffin oil and crystallized form methanol/ethylacetate. There are obtained 53.5 g of the 2',5-dimethoxy-2,9,9-trimethoxy-6,7-benzomorphan hydrochloride, melting point 212-214°C (dec.).

A solution of 4.68 g (44 mmol) cyanogenbromide in 28 ml chloroform are added drop-wise within 5 min to a solution of 8.25 g (30 mmol) 2',5-dimethoxy-2,9,9-trimethyl-6,7-benzomorphan in 20 ml dry ethanol free chloroform. After boiling for 4 h under reflux the solution is concentrated under reduced pressure, the residue dissolved in 150 ml toluene, washed twice with 50 ml 2 N hydrochloric acid and once with water, dried over sodium sulfate and evaporated to dryness under reduced pressure to yield 7.82 g 2-cyano-2',5-dimethoxy-2,9,9-trimethyl-6,7-benzomorphan. The obtained residue is dissolved in 40 ml of dry peroxide-free tetrahydrofuran and the solution added drop-wise under a nitrogen atmosphere over a period of 20 min to a suspension of 2.10 g (61.7 mmol) of lithium aluminum hydride in 85 ml tetrahydrofuran. After boiling for 3 h under reflux and cooling, 2.1 ml water, 1.6 ml 4 N sodium hydroxide solution, 7.3 ml water and 85 ml chloroform are added sequentially. After stirring for 30 min the obtained hydroxide is filtered off over hyflo. The precipitate is stirred 3 times with 50 ml chloroform/butanol (9:1). The filtrate washed with water, dried over sodium sulfate and concentrated under reduced pressure. The residue is converted into the hydrochloride and crystallized from methanol/ethylacetate to yield 4.9 g of the 2',5-dimethoxy-9,9-dimethyl-6,7-benzomorphan hydrochloride, melting point 220-222°C (dec.).

A solution of ethanethiol in dimethylformamide (DMF) are added dropwise to a suspension of sodium hydride (55% suspension in oil) in dry DMF. The obtained suspension is stirred for a further 45 min and a solution of 2',5-dimethoxy-9,9-dimethyl-6,7-benzomorphan in 190 ml of dry DMF are added dropwise over 20 min. The initially formed volatile components are distilled off and the reaction mixture heated until the DMF boils. After boiling for 6 h under reflux the reaction mixture is concentrated under reduced pressure and the residue taken up in toluene and 2 N hydrochloric acid. The acid aqueous phase is made alkaline with 25% ammonia and extracted 3 times with chloroform/butanol (8:2). After evaporation of the organic phase, the residue is converted into the 9,9-dimethyl-2',5-dihydroxy-6,7-benzomorphan hydrochloride, (crystallized from isopropanol).

A mixture of 9,9-dimethyl-2',5-dihydroxy-6,7-benzomorphan hydrochloride, calcium carbonate and toluene-4-sulfonic acid but-3-ynyl ester in dimethylformamide is heated and subsequently concentrated under reduced pressure. The residue is taken up in a mixture of water and chloroform (1:1) and the aequeous phase extracted twice with chloroform/butanol (9:1). The combined organic phases are concentrated under reduced pressure to give the

2-butynyl-9,9-dimethyl-2',5-dihydroxy-6,7-benzomorphan (crystallized from methanol/ethylacetate).

References

Akkerman A.M. et al.; US Patent No. 4,425,353; January 10, 1984; Assigned: ACF Chemiefarma NV, Maarssen, Netherlands

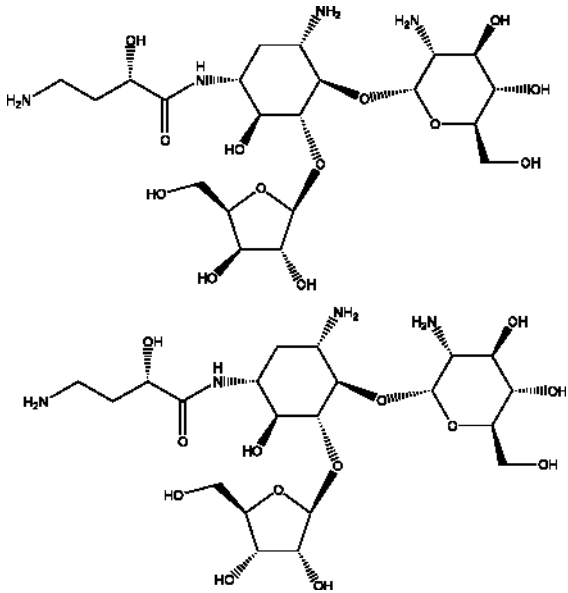
BUTIROSIN

Therapeutic Function:

Chemical Name: N^1-(4-Amino-2-hydroxybutyryl)-4-O-2,6-diamino-2,6-didexy-D-glucopyranosyl)-5-O-D-xelofuranosyl-2-deoxystreptamine (mixture of A- and B-form)

Common Name: Ambutyrosin; Butirosin

Structural Formula:



Chemical Abstracts Registry No.: 12772-35-9

Trade Name	Manufacturer	Country	Year Introduced
Butirosin	SigmaAldrich	-	-

Raw Materials

Amberlite	5-β-D-Xylofuranosylneamine
Carbobenzoxy chloride	L-(-)-γ-Amino-α-hydroxybutyric acid
N-Hydroxysuccinimide	Dicyclohexylcarbodiimide
Palladium on charcoal	

Manufacturing Process

Ambutyrosin is the another name of butirosin. Ambutyrosin obtained from fermentation broths of Bacillus circulans contains a major proportion of N^1-(4-amino-2-hydroxybutyryl)-4-O-2,6-diamino-2,6-didexy-D-glucopyranosyl)-5-O-D-xelofuranosyl-2-deoxystreptamine (ambutyrosin A) and a minor proportion (up to 10-15%) of N^1-(4-amino-2-hydroxybutyryl)-4-O-2,6-diamino-2,6-didexy-D-glucopyranosyl)-5-O-D-ribofuranosyl-2-deoxystreptamine (ambutyrosine B). A process for preparation of ambutyrosin by semisynthetic procedure of acylating of 5-β-D-xylofuranosylneamine or 5-β-ribofuranosylneamine is described below.

Preparation of 5-β-D-pentofuranosyIneamine: ambutyrosin A (1.0 g) in 30 ml of 0.5 N sodium hydroxide solution was refluxed for one hour, then neutralized with 6 N hydrochloric acid and applied on a column of Amberlite CG-50 (NH_4^+ form, 30 ml). The column was washed with water (ca. 100 ml) until the ninhydrin test became negative, and then eluted with 0.2 N ammonium hydroxide. Biologically active fractions were collected, concentrated in vacuum to 5 ml and treated with 5 ml of methanol to induce precipitation. It was further purified by re-precipitation from aqueous methanol to yield 607 mg (65%) of deacylated ambutyrosin A hereafter referred to as DA_1.

The wash water of the above CG-50 column was adjusted to pH 7.0 and applied on a column of Amberlite IR-120 (H^+ form, 30 ml). The column was washed with water and then eluted with 1 N ammonium hydroxide. Ninhydrin-positive fractions were combined, treated with active carbon and neutralized with IRC-50 resin (H^+ form). The solution was concentrated to a small volume, treated with ethanol, and kept in the cold overnight to yield 160 mg (75%) of γ-amino-α-hydroxybutyric acid as colorless needles which melted at 217°C-218°C. $[\alpha]_D^{23}$= -30.3° (c=1.0%, H_2O).

The above experiments were also carried out on 1.0 g of ambutyrosin B yielding 579 mg (62%) of deacylated ambutyrosin B, hereafter called DA_2.

L-(-)-γ-benzyloxycarbonylamino-α-ydroxybutyric acid: L-(-)-γ-amino-α-hydroxybutyric acid (7.4 g, 0.062 mole) was added to 50 ml of aqueous sodium 3 hydroxide solution (5.2 g, 0.13 mole). To the solution was added dropwise 11.7 g (0.068 mole) of carbobenzoxy chloride with stirring at 0°C to 5°C for one hour. The reaction mixture was washed with 50 ml of ether, adjusted to pH 2 with dilute hydrochloric acid, and extracted with four 80-ml portions of ether. The extracts were combined, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and filtered. The filtrate was evaporated in vacuum, and the residue was crystallized from benzene to give 11.6 g (74%) of 4 colorless plates. M.P: 78.5°-79.5°C.

N-Hydroxysuccinimide ester of L-(-)-γ-benzyloxycarbonylamino-α-

hydroxybutyric acid: a solution of L-(-)-γ-benzyloxycarbonylamino-α-hydroxybutyric acid (10.6 s g, 0.042 mole) and N-hydroxysuccinimide (4.8 g, 0.042 mole) in 200 ml of ethyl acetate was cooled to 0°C and added to 8.6 g (0.042 mole) of dicyclohexylearbodiimide. The mixture was stirred overnight at 5°C. The dicyclohexylurea which separated was removed by filtration, and the filtrate was concentrated in vacuum. The product was obtained as colorless plates. Yield: 13.4 g (92%). M.P: 117°-118°C $[\alpha]_D^{23}$= +1.5° (c= 2.0%, $CHCl_3$).

N-(Benzyloxycarbonyloxy)succinimide: N-hydroxysuccinimide (23 g, 0.2 mole) was dissolved in 200 ml of aqueous NaOH solution (9 g, 0.22 mole). To the stirred solution was added dropwise 34 g (0.2 mole) of carbobenzoxy chloride with water-cooling. The mixture was stirred overnight at room temperature, and the precipitate which separated was collected by filtration, washed with water, and air dried. Yield: 41.1 g (82%). Recrystallization from benzene-n-hexane (10:1) gave colorless prisms melting at 78°-79°C.

6'-Carbobenzoxy-DA_1 and 1,6'-dicarbobenzoxy-DA_1:

To a solution of 9.1 g (20 mmoles) of above prepared DA_1 in 150 ml of water and 60 ml of tetrahydrofuran (THF) was slowly added, under vigorous stirring and cooling (5°C), a solution of 5.17 g (20.8 mmoles) of N-(benzyloxycarbonyloxy)succinimide in 60 ml of THF. The mixture was stirred for 24 hours at 5°C and for an additional 16 hours at room temperature and then concentrated in vacuum to dryness. The crude product thus obtained was roughly separated into two fractions by a preparative counter-current distributor (52 tubes, 100 ml/tube) using a solvent system of n-BuOH-$CHCl_3$·H_2O (4:1:5). Tube No. 1-15 were combined and evaporated in vacuum to give 9.75 g of solid. The solid was dissolved in 20 ml of water and applied on a column of amberlite CG-50 (NH_4^+ form, 120 ml). The column was washed with water and then eluted with aqueous 0.1 N ammonium hydroxide collecting each 20-ml fraction. Fractions No 62-93 were combined and concentrated in vacuum to give 5.75 g (49%) of 6'-carbobenzoxy-DA_1 as a white solid. NMR in D_2O and elememtal analysis confirmed its structure.

Tubes No. 36-49 from the above current distribution were combined and evaporated in vacuum to give 2.91 g of solid. The solid was further purified by silica gel column chromatography developed with methanol-ethyl acetate (4:1) to yield 1.11 g (7.5%) of 1,6'-dicarbobenzoxy-DA_1. TLC [silica gel plate, MeOAc-n-PrOH-28% NH_4OH (45:105:60)]. R_f=0.44.

1-[L-(-)-γ-Amino-α-hydroxybutyryl]-DA_1: a solution of 6'-carbobenzoxy-DA_1 (588 mg, 1 mmole) in 10 ml of water and 5 ml of THF was added dropwise to a solution of N-hydroxysuccinimide ester of L-(-)-γ-benzyloxycarbonylamino-α-hydroxybutyric acid (350 mg, 1 mmole) in 5 ml of THF with stirring and cooling (5°C). The mixture was stirred overnight at room temperature and then concentrated in vacuum to dryness. The residue was shaken with a mixture of n-butanol-ethyl acetate-water (4:1:5). The upper layer of the solvent mixture was separated and evaporated in vacuum to dryness. The solid thus obtained was dissolved in 30% aqueous ethanol and hydrogenated over 250 mg of 10% palladium-on-charcoal at room temperature. The reaction mixture was filtered to remove the palladium catalyst, and the filtrate

was concentrated in vacuum to dryness. The residual solid was dissolved in 10 ml of water and chromatographed on a column of CG-50 (NH_4^+ form, 40 ml). The column was washed by water and then eluted fractionally with aqueous 0.5 N NH_4OH. Biologically active fractions which showed R_f=0.20 by TLC were collected, concentrated in vacuum and lyophilized to give 94 mg (14%) of product as a white solid, which was identified with ambutyrosin A in every respect. It melts with decomposition over a wide range beginning at about 149°C. $[\alpha]_D^{25}$= +26°C (1.4%, water). Ambutyrosin B was prepared in a similar manner. It melts with decomposition at about 146°C $[\alpha]_D^{25}$=+33° (1.5%, water).

References

Kawaguchi H. et al.; US Pataent No. 3,792,037; February 12, 1974; Assigned to Bristol-Myers Company, New York, N.Y.

Woo P.W.K. et al.; US Patent No. 3,541,078; November 17, 1970; Assigned to Parke, Davis and Company, Detroit, Mich., a corporation of Michigan

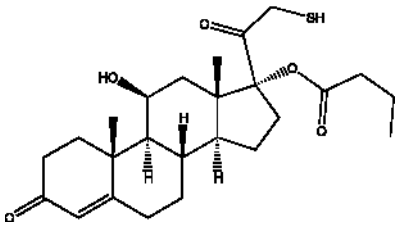
BUTIXOCORT

Therapeutic Function: Glucocorticoid

Chemical Name: 11β,17-Dihydroxy-21-mercaptopregn-4-ene-3,20-dione 17-butyrate

Common Name: Butixocort; Tixocortol butyrate

Structural Formula:



Chemical Abstracts Registry No.: 120815-74-9

Trade Name	Manufacturer	Country	Year Introduced
Butixocort	Jouveinal	-	-
Butixocort	Onbio Inc.	-	-

Raw Materials

S-Thioacetic acid
Hexametapol
Sodium methylate methanolic solution
Cortisol-21-mesylate-17-butyrate

Manufacturing Process

3,20-Dione-11β-hydroxypregn-4-ene-21-thioacetate-17-butyrate (or hydrocortisone): 10.0 g (0.129 mole) of S-thioacetic acid and 220 ml of hexametapol are introduced into a reactor 27.7 ml of a 4.65 N sodium methylate methanolic solution (0.129 mole) are introduced, accompanied by stirring, at a temperature close to 20°C and then the beige solution is stirred for 1 hour at ambient temperature. Within 10 minutes, a solution of 44.0 g (0.086 mole) of cortisol-21-mesylate-17-butyrate is introduced into 440 ml of hexametapol. The solution is stirred for 2.5 hours at ambient temperature. The orange solution is precipitated in 8 liters of ice water. The insoluble substances formed are filtered and then taken up in methyl ether. The ethereal solution is extracted twice with 250 ml of 1 N sodium hydroxide solution and then three times with 500 ml of saturated sodium chloride solution. After drying the ethereal phase, the solvent is eliminated by distillation. The residue (39 g) is purified by column chromatography with the aid of 1 kg of "Florisil''. Elution by a mixture of dichloromethane and acetone 95:5 (v/v) makes it possible to collect 21 g of purified product. This product is finally recrystallized in 170 ml of a mixture of methanol and water 8:2 (v/v). Weight=19 g. Yield=44.3%. Melting point: 130°C; the structure of prepared compound is confirmed by NMR spectrum.

References

Aubard et al; US Patent No. 4,933,331; June 12, 1990; Assigned to Jouveinal, S.A., Paris, France

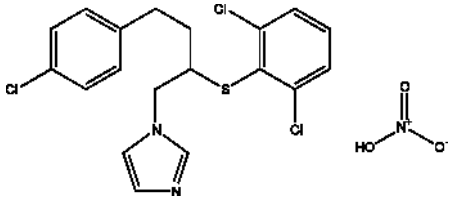
BUTOCONAZOLE NITRATE

Therapeutic Function: Antifungal

Chemical Name: 1H-Imidazole, 1-(4-(4-chlorophenyl)-2-((2,6-dichlorophenyl)thio)butyl)-, mononitrate

Common Name: Butoconazole nitrate

Structural Formula:



Chemical Abstracts Registry No.: 64872-77-1

Trade Name	Manufacturer	Country	Year Introduced
Butoconazole nitrate	Cipla Limited	India	-

Trade Name	Manufacturer	Country	Year Introduced
Femstat	Hoffmann - LaRoche Inc.	-	-
Femstat 3	Procter and Gamble	-	-
Femstat 3	Roche	-	-
Gynazole-1	KV Pharmaceutical Co.	USA	-
Gynomyk	Will-Pharma B.V.	Netherlands	-

Raw Materials

Imidazole	4-Chloromagnesium chloride
Glycidyl tosylate, (+/-)-	Sodium hydride
Triethylamine	Dilithium tetrachlorocuprate(II)
Methanesulfonyl chloride	2,6-Dichlorobenzenethiol

Manufacturing Process

1H-Imidazole, 1-(4-(4-chlorophenyl)-2-((2,6-dichlorophenyl)thio)butyl)-, (+/-)-, mononitrate may be prepared by the same way as described below for enantiomers.

To a solution of Li_2CuCl_4 (0.10 M, 8.8 ml, 0.88 mmol) in dry THF (75 ml) was added dropwise a solution of 4-chloromagnesium chloride (17.5 mmol) in ether (15 ml) at -35°C. After stirring for 45 min, a pre-cooled (-35°C) solution of (S)-(+)-glycydil tosylate (2.0 g, 8.8 mmol) in THF (5 ml) was added via syringe. After 2 h at -35°C, the mixture was quenched with saturated NH_4Cl and extracted with ether. The organic layer was dried (Na_2SO_4), evaporated to dryness and purificated by flash chromatography affording (2S)-1-(p-toluenesulphonyloxy)-4-(4-chlorophenyl)butan-2-ol, as a white solid (1.9 g, 77%), m.p. 72.7-74°C.

(2S)-1-[2-Hydroxy-4-(4-chlorophenyl)butyl]-1H-imidazole was prepared as follows: to a solution of imidasole (0.52 g, 7.61 mmol) in dry DMF (5 ml) at 0°C under N_2 was added NaH (60% dispersion in oil, 0.3 g, 7.61 mmol). The reaction mixture was warmed to room temperature and stirred for 30 min. A solution of (2S)-1-(p-toluenesulphonyloxy)-4-(4chlorophenyl)butan-2-ol in DMF (15 ml) was then added dropwise over 15 min. The reaction mixture was heated at 75°C for 24 h, cooled poured into water and extracted with ethyl acetate. The organic phase was dried and evaporated and was the residue purified by flash chromatography. Gradient elution (1-5% MeOH/CH_2Cl_2) afforded (2S)-1-[2-hydroxy-4-(4-chlorophenyl)butyl]-1H-imidazole which was recrystallized from EtOAc/Et_2O (236 mg, 67%), m.p. 128°-131°C; $[\alpha]_D^{25}$-23.23 (c 0.4, $CHCl_3$).

(2S)-1-[2-Hydroxy-4-(4-chlorophenyl)butyl]-1H-imidazole nitrate was prepared as follows. To a solution of (2S)-1-(p-toluenesulphonyloxy)-4-(4-chlorophenyl)butan-2-ol (250 mg, 1 mmol) in THF (5 ml) at 0°C was added triethylamine (0.28 ml, 2.0 mmol), followed by methanesulfonyl chloride (0,15 ml, 2.0 mmol). The reaction mixture was was warmed to room temperature and stirred for 1 h. The mixture was poured into aq. $NaHCO_3$, extracted with EtOAC, and the organic phase dried and evaporated to dryness. The resulting mesylate was dissolved in acetone (50 ml), then 2,6-dichlorobenzenethiol

(464 mg, 2.6 mmol) and K_2CO_3 (568 mg, 4.1 mmol) were added. The mixture was heated at reflux under N_2, cooled to room temperature, evaporated to dryness and partionated between water and EtOAc. The organic phase was dried (Na_2SO_4), evaporated, and residue purified by flash chromatography (1-2% MeOH/CH_2Cl_2 gradient elution) to give an oil which was converted to nitrate salt. Recrystallization from EtOAc/Et_2O gave 260 mg (55%) (2S)-1-[2-hydroxy-4-(4-chlorophenyl)butyl]-1H-imidazole nitrate, m.p. 120°-124°C; $[\alpha]_D^{25}$+22.68 (c 0.4, EtOH).

The R enantiomer was prepared the same way from (-)-glycidyl tosylate.

References

Walker K.A.M. et al.; US Patent No. 4,036,970; July 19, 1977; Assigned: Syntex (U.S.A.) Inc. (Palo Alto, CA)
Tetrahedron, v.4, No 7, pp. 1521-1526, 1993, D.M. Rotstein, K.A.M. Walker

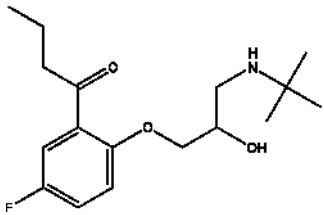
BUTOFILOLOL

Therapeutic Function: Beta-adrenergic 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
Propyl Magnesium Bromide
Hydrogen chloride
1-Chloro-2-hydroxy-3-t-butylaminopropane
Sodium hydride

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-11l-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 1N 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 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) and 19 (2)112 (1983)
I.N. p.169
Demame, H.; US Patent 4,252,825; February 24, 1981; assigned to C.M. Industries.

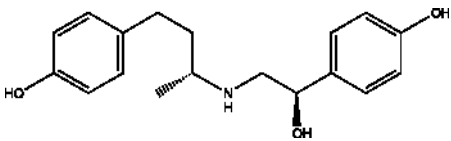
BUTOPAMINE

Therapeutic Function: Cardiotonic

Chemical Name: 4-Hydroxy-α-[[[3-(4-hydroxyphenyl)-1-methylpropyl] amino]methyl]benzenemethanol

Common Name: Butopamine

Structural Formula:



Chemical Abstracts Registry No.: 66734-12-1

Trade Name	Manufacturer	Country	Year Introduced
Butopamine	ZYF Pharm Chemical	-	-
Butopamine	Lilly	-	-

Raw Materials

Ammonia
Hydrochloric acid
Palladium on carbon
Sodium hydroxide
Methyl 2-(4-benzyloxyphenyl)ethyl ketone
Hydrogen
1-(4-Hydroxyphenyl)-2-aminoethanol

Manufacturing Process

A solution of 32.8 g (0.2 m) of methyl 2-(4-hydroxyphenyl)ethyl ketone and 42.6 g (0.2 m) of 1-(4-hydroxyphenyl)-2-aminoethanol in 380 ml of ethanol

containing 3.8 g of 5% palladium on carbon was stirred for 16 h at 60°C under hydrogen at 55 psi. The reaction mixture was then filtered, and the filtrate was diluted by addition of 350 ml of water. The aqueous mixture was concentrated to a volume of about 400 ml, and then washed with dichloromethane.

The aqueous mixture was acidified by addition of 50 ml of conc. hydrochloric acid. After standing at room temperature for 2 h, the aqueous acid mixture was filtered and the filter cake was washed with 40 ml of ice water and dried at 50°C in vacuum to provide 47.0 g of 1-(4-hydroxyphenyl-2-propylamino]ethanol hydrochloride, melting point 124-129°C.

The 1-(4-hydroxyphenyl)-2-[1-methyl-3-(4-hydroxyphenyl)propylamino] ethanol was obtained by treatment of 1-(4-hydroxyphenyl-2-propylamino]ethanol hydrochloride with sodium hydroxide.

References

Anderson D.B. et al.; US Patent No. 4,690,951; September 1, 1987; Assigned: Eli Lilly and Company, Indianapolis, Ind.

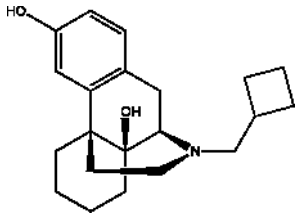
BUTORPHANOL

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	US	1978
Stadol	Bristol-Myers	UK	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-9-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) and 3 (5) 330 (1978)
Kleeman and 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.; US Patent 3,775,414; November 27, 1973; Monkovic, I., Wong, H. and Lim, G.; US Patent 3,980,641; September 14, 1976; Pachter, I.J., Belleau, B.R. and Monkovic, I.; US Patent 3,819,635; June 25, 1974; and Lim, G. and Hooper,

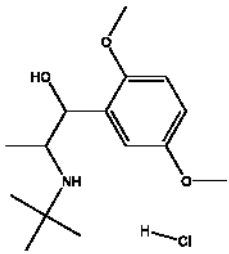
BUTOXAMINE HYDROCHLORIDE

Therapeutic Function: Oral hypoglycemic, Antihyperlipidemic

Chemical Name: Benzenemethanol, α-(1-((1,1-dimethylethyl)amino)ethyl)-2,5-dimethoxy-, (R*,S*)-(+-)-, hydrochloride

Common Name: Butaxamine hydrochloride; Butoxamine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 5696-15-1

Trade Name	Manufacturer	Country	Year Introduced
Butoxamine hydrochloride	SigmaAldrich	-	-

Raw Materials

Butylamine
Platinum
Hydrochloric acid
2,5-Dimethoxy-α-bromopropiophenone
Hydrogen
Sodium hydroxide

Manufacturing Process

548.0 g (2 mol) of 2,5-dimethoxy-α-bromopropiophenone was dissolved in 500 ml of acetanitrile and 365.0 g (5 mol) of t-butylamine was added. The solution was allowed to stand at room temperature for 64 h and was then diluted with 2 L of anhydrous ether. The precipitated t-butylamine hydrobromide was filtered off and washed with ether. The filtrate and washings were concentrated in vacuo using a water-bath kept at 40°C. When most of the solvent had been removed, the residual material was dissolve in cold methanol and acidified with hydrochloric acid. The solution was then taken down to dryness in vacuo on the steam bath and the 1-(2,5-dimethoxyphenyl)-2-(t-butylamino)propiophenone was obtained, melting point 175-176°C (recrystallised from an ethanol ether mixture).

The bulk of the 1-(2,5-dimethoxyphenyl)-2-(t-butylamino)propiophenone was dissolved in methanol and hydrogenated over platinum (Adams' catalyst). After removal of the catalyst, the solvent was removed in vacuo and the residual solid was dissolved in water and the solution was washed with ether.

The aqueous layer was basified (dilute sodium hydroxide solution) and the base was taken into ether. After drying over anhydrous potassium carbonate, the ether was evaporated and the base was distille at 0.3 mm pressure. So the DL-erythro 1-(2,5-dimethoxyphenyl)-2-(t-butylamino)propanol, boiling point 127-128°C was obtained.

References

GB Patent No. 1,104,292; February 21, 1968; Assigned: The Wellcome Foundation Limited, of 183-193 Euston Road, London

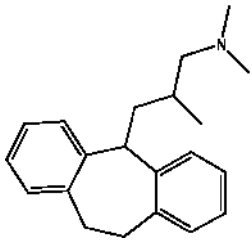
BUTRIPTYLINE

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 salt)

Trade Name	Manufacturer	Country	Year Introduced
Evadyne	Ayerst	UK	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 distiiled to yield the product.

References

Merck Index 1506
Kleeman and Engel p.131
OCDS Vol.1 p.151 (1977)
DOT 9 (6) 219 (1973) and 10 (7) 235 (1974)
I.N. p.170
Villani, F.J.; US Patent 3,409,640; November 5, 1968; assigned to Schering Corporation

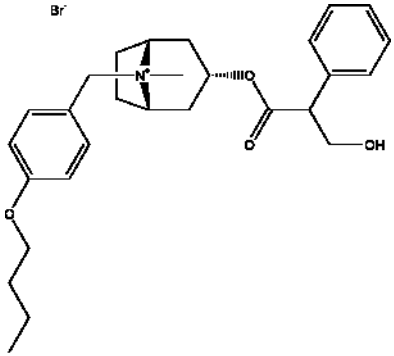
BUTROPIUM BROMIDE

Therapeutic Function: Spasmolytic

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

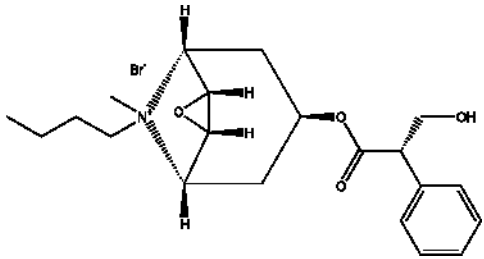
BUTYLSCOPOLAMINE BROMIDE

Therapeutic Function: Anticholinergic, Spasmolytic

Chemical Name: 1-alpha-H,5-alpha-H-Tropanium, 8-butyl-6-beta,7-beta-epoxy-3-alpha-hydroxy-, bromide, (-)-tropate

Common Name: Butylscopolamin(e) bromide; Butylscopolamini bromidum; Butylscopolammonium bromide; Hyoscine butyl bromide; Scopolamine butyl bromide; Scopolaminium butylbromatum

Structural Formula:



Chemical Abstracts Registry No.: 149-64-4; 7182-53-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Butylscopolamine bromide	China Pharm Chemical Co., Ltd.	-	-
Scopolamine N-butyl bromide	Andard-Mount Company Limited	-	-
Butylscopolamine bromide	Shchem Corporation	-	-
Scopolamine Butylbromide BP98	Shanghai Lancheng Corporation	-	-
Buscopan	Boehringer Ingelheim Vetmedica, Inc.	-	-
Antispasmin	Green Cross	-	-
BS-ratiopharm	Ratiopharm	-	-

Trade Name	Manufacturer	Country	Year Introduced
Buscol	Pliva	-	-
Buscolysin	Pharmachim-Holding AD	-	-
Buscolysin	Sopharma	-	-
Buscolysin	Pharmachim S.A	-	-
Buscopan	Boehringer Ingelheim Pharma	-	-
Buscovital	Vitalia K SA	-	-
Buscovital	Omega Pharma	-	-
Buspin	Intas	-	-
Buspon	Toyo Pharmar	-	-
Butilescopolamina Duncan	Duncan	-	-
Butipolan	Tobishi	-	-
Butopan	Biofarma Ilac San. ve Tic. A.S.	-	-
Butylpan	Hokuriku Seiyaku Co. Ltd.	-	-
Butysco	Kobayashi Kako Co. Ltd.	-	-
Cifespasmo	Northia	-	-
Colobolina	Fabra	-	-
Cryopina	Highnoon Laboratories Limited	-	-
Dhacopan	Haw Par Healthcare Ltd.	-	-
Dividol Remedica	Remedica Ltd.	-	-
Espa-butyl	Innopharm	-	-
Hioscina	Veinfar	-	-
Hioscina, butilbromuro	Fabra	-	-
Hioscina	Zimaia	-	-
Hioscina Fada	Fada Pharma	-	-
Hioscina N-butyl bromuro	Bussie S.A.	-	-
N-Butylbromuro de hioscina	Laboratorios Synthesis	-	-
Hioscina N-Butil	Richmond	-	-
Hybropan	Binex	-	-
Hyospan	Howards/LCPW	-	-
Hyospasmol	Pharmacare Limited	-	-
Hyospasmol	Lennon	-	-
Hyospasmol	Aspen Pharmacare	-	-
Hyscopan	M/s. Indus, Karachi.	-	-

Trade Name	Manufacturer	Country	Year Introduced
Hyscopan	Armoxindo Farma	-	-
Hysopan	Rephco Laboratories Ltd.	-	-
Hysopan	Lahore Chemical and Pharmaceutical Works (LCPW) (PVT.) Ltd.	-	-
Luar G	Klonal	-	-
Pasmodina	Drawer	-	-
Rupe N	Bioquim	-	-
Scobut	Laboratoarele Magistra	-	-
Scobutil	Sicomed S.A.	-	-
Scopex	Propan	-	-
Scopinal	Julphar	-	-
Scopolan	Herbapol Wroclaw	-	-
Selpiran-S	Laboratorios Diba, S. A.	-	-
Sparicon	Masung and Co., Ltd.	-	-
Spasman scop.	Merckle	-	-
Spasmopan	APM	-	-
Spasmopan	LEX LECIVA a.s	-	-
Spasmowern	Pharma Wernigerode	-	-

Raw Materials

Scopolamine
n-Butyl bromide

Manufacturing Process

1300 g of scopolamine base and 350 g of n-butylbromide in 600 ml acetonitrile is heated at 65°C for 160 hours. The oil obtained is dissolved in methanol. The solution is cooled and crystalline scopolamine N-n-butylbromide is filtered. After recrystallization from methanol was obtained scopolamine N-n-butylbromide with melting point 142-144°C and $[\alpha]_d^{20}$ = -20.5° (3% solution in water); yield 65%.

References

Merck Index, Monograph number: 1624, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Adickes F., DE Patent No. 856,890; 1952.11.24; Assigned to Boenhringer Sohn Ingelheim