B

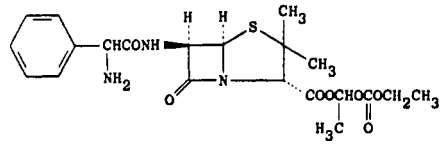
BACAMPICILLIN

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)

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	U.K.	1981
Spectrobid	Pfizer	U.S.	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

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-aminophenylacetamido)penicillinate (94 g), MP 171°–176°C.

References

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

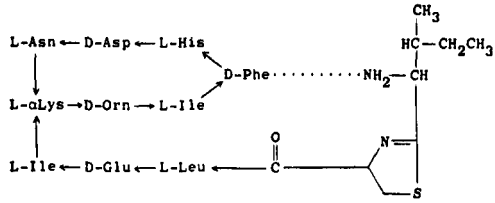
BACITRACIN

Therapeutic Function: Antibacterial

Chemical Name: Complex polypeptide mixture containing predominantly bacitracin A

Common Name: —

Structural Formula:



bacitracin A

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

Trade Name	Manufacturer	Country	Year Introduced
Baciguent	Upjohn	U.S.	1948
Topitracin	Comm. Solv.	U.S.	1948
Bacitracine	Novopharm	Switz.	—
Bacitracine	Diamant	France	1953
Bacitracin	Kayaku	Japan	—
Bacitracin	Upjohn	U.S.	—
Batrax	Gewo	W. Germany	—
Cicatrin	Calmic	U.K.	—
Cicatrex	Wellcome	W. Germany	—
Enterostop	Schiapparelli	Italy	—
Fortracin	A.L. Labs	U.S.	—
Hydroderm	Merck Sharpe & Dohme	U.K.	—
Medicrucin	Medice	W. Germany	—

Trade Name	Manufacturer	Country	Year Introduced
Nebacetin	Byk-Gulden	W. Germany	–
Neobacrin	Glaxo	U.K.	–
Neo-Caf	Francia	Italy	–
Neo-Polycin	Dow	U.S.	–
Neosporin	Burroughs-Wellcome	U.S.	–
Orobicin	Fulton	Italy	–
Polybactrin	Calmic	U.K.	–
Polybactrin	Wellcome	W. Germany	–
Polycin	Dow	U.S.	–
Polyfax	Wellcome	U.K.	–
Polysporin	Burroughs-Wellcome	U.S.	–
Rikospray	Riker	U.K.	–
Topitracin	Reed & Carnrick	U.S.	–

Raw Materials

Bacillus subtilis
Nutrient Medium (Soy Bean Oil Meal)

Manufacturing Process

The early patent, U.S. 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-sulfonic acid.

A subsequent patent, U.S. 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, U.S. 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, U.S. Patent 2,915,432 describes a process of recovering and concentrating bacitracin from aqueous filtered fermentation broth containing on the order of 3% proteinaceous 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 U.S. Patents 3,795,663 and 4,101,539.

Raw Materials

Merck Index 937

Kleeman & Engel p. 70
PDR p. 888
I.N. p. 113
REM p. 1201
Chaiet, L. and Cochrane, T.J., Jr.; U.S. Patent 2,915,432; December 1, 1959; assigned to Merck & Co., Inc.
Johnson, R.A. and Meleney, F.L.; U.S. Patent 2,498,165; February 21, 1950; assigned to U.S. Secretary of War
Freaney, T.E. and Allen, L.P.; U.S. Patent 2,828,246; March 25, 1958; assigned to Commercial Solvents Corporation
Zinn, E. and Chornock, F.W.; U.S. Patent 2,834,711; May 13, 1958; assigned to Commercial Solvents Corporation
Miescher, G.M.; U.S. Patent 3,795,663; March 5, 1974; assigned to Commercial Solvents Corp.
Kindraka, J.A. and Gallagher, J.B.; U.S. Patent 4,101,539; July 18, 1978; assigned to IMC Chemical Group, Inc.

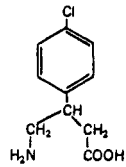
BACLOFEN

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.	–
Lioresal	Ciba-Geigy	W. Germany	1971
Lioresal	Ciba-Geigy	U.K.	1972
Lioresal	Ciba-Geigy	France	1974
Lioresal	Ciba-Geigy	Italy	1974
Lioresal	Ciba-Geigy	U.S.	1977
Lioresal	Ciba-Geigy	Japan	1979
Gabalon	Daiichi	Japan	1979
Bacion	*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 & 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.; U.S. Patent 3,471,548; October 7, 1969; assigned to Ciba Corporation
Keberle, H., Faigle, J.W. and Wilhelm, M.; U.S. Patent 3,634,428; January 11, 1972; assigned to Ciba Corporation

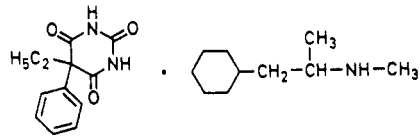
BARBEXACLONE

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 & Engel p. 73
I.N. p. 115
Suranyi, L.; U.S. Patent 3,210,247; October 5, 1965; assigned to Knoll A.G.

BATROXOBIN

Therapeutic Function: Hemostatic

Chemical Name: See under structural formula; no defined name

Common Name: –

Structural Formula:

It is a complex enzyme of molecular weight 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.; U.S. Patent 3,849,252; November 19, 1974; assigned to Pentapharm A.G.

BECLAMIDE

Therapeutic Function: Anticonvulsant

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

Common Name: Benzchloropropamide, Chloroethylphenamide, Benzylchloropropionamide

Structural Formula: $ClCH_2CH_2CONHCH_2C_6H_5$

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	U.K.	—
Nydrane	Aron (Rona)	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. Yeild, 109 pounds. Melting point 92° to 93°C.

References

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

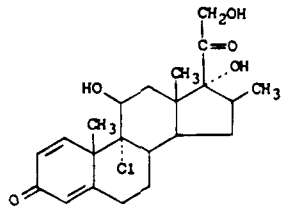
BECLOMETHASONE DIPROPIONATE

Therapeutic Function: Topical anti-inflammatory; glucocorticoid

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

Common Name: —

Structural Formula:



(base)

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

Trade Name	Manufacturer	Country	Year Introduced
Propaderm	Kyowa Hakko	Japan	1972
Becotide	Allen & Hanburys	U.K.	1972
Cleniderm	Chiesi	Italy	1974
Sanasthmyl	Glaxo	W. Germany	1975
Becotide	Glaxo	France	1976
Beconase	Glaxo	W. Germany	1976
Vanceril	Schering	U.S.	1976
Beclotide Nasal	Glaxo	Italy	1977
Becotide	Glaxo	Japan	1978
Aldesin	Shionogi	Japan	1978
Beclovent	Glaxo	U.S.	1979
Becotide	Glaxo	Switz.	1981
Becloforte	Allen & Hanburys	U.K.	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	U.S.	—
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	U.K.	—
Rino-Clenil	Chiesi	Italy	—
Turbinal	Valeas	Italy	—
Vaderm	Schering	—	—
Vancenase	—	U.S.	—
Viarex	Essex	Italy	—

Trade Name	Manufacturer	Country	Year Introduced
Viarex	Schering	U.S.	–
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
Methane Sulfonyl Chloride
Sodium Methoxide
N-Chlorosuccinimide
Perchloric Acid

Manufacturing Process

6 grams of 16β-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 16β-methyl-1,4,9(11)-pregnatriene-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)-pregnatriene-17α, 21-diol-3,20-dione. To a suspension of 3 grams of 16β-methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione-21-acetate in 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°C 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 by filtration. A solution of 250 mg of the chlorohydrin in 5 ml of 0.25 N 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 & Engel p. 74
PDR pp. 906, 1659
DOT 9 (8) 335 (1973)
I.N. p. 118
REM p. 962
Merck & Co., Inc. British Patent 912,378; December 5, 1962
Taub, D., Wendler, N.L. and Slates, H.L.; U.S. Patent 3,345,387; October 3, 1967; assigned to Merck & Co., Inc.

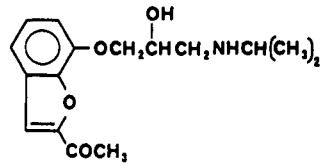
BEFUNOLOL

Therapeutic Function: Beta-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 Kakko	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)benzofuran having 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.; U.S. Patent 3,853,923; December 10, 1974; assigned to Kakenyaku Kakko Co., Ltd.

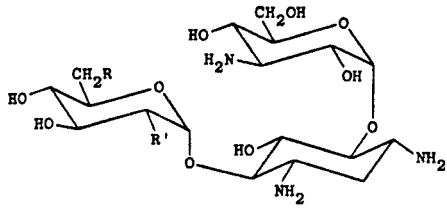
BEKANAMYCIN SULFATE

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:



(base)

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

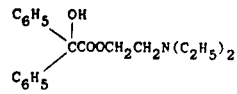
BENACTYZINE HYDROCHLORIDE

Therapeutic Function: Tranquilizer; anticholinergic

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

Common Name: β-Diethylaminoethylbenzilate hydrochloride

Structural Formula:



(base)

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

Trade Name	Manufacturer	Country	Year Introduced
Suavitil	Merck Sharp & Dohme	U.S.	1957
Phebex	Hoechst	U.S.	1958
Cedad	Recordati	Italy	–
Cevanol	I.C.I.	U.K.	–
Deprol	Wallace	U.S.	–
Lucidil	Smith & Nephew	U.K.	–
Morcain	Tatsumi	Japan	–
Nutinal	Boots	U.K.	–
Parasan	Medix	Spain	–
Parpon	Santen	Japan	–
Phobex	Lloyd	–	–
Phobex	Dabney & Westerfield	–	–

Raw Materials

Ethyl Benzilate
Sodium
β-Diethylaminoethanol
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 & 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.; U.S. Patent 2,394,770; February 12, 1946; assigned to American Cyanamid

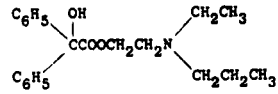
BENAPRYZINE HYDROCHLORIDE

Therapeutic Function: Anticholinergic, antiparkinsonism

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

Common Name: 2-Ethylpropylaminoethyl diphenylglycollate hydrochloride

Structural Formula:



(base)

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

Trade Name	Manufacturer	Country	Year Introduced
Brizin	Beecham	U.K.	1973

Raw Materials

Sodium Methoxide
2-Ethylpropylaminomethanol
Methyl α,α-diphenyl Glycollate
Hydrogen Chloride

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 1 N 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 & Engel p. 77
OCDS Vol. 2 p. 74 (1980)
DOT 9 (6) 241 (1973)
I.N. p. 121
Mehta, M.D. and Graham, J.; U.S. Patent 3,746,743; July 17, 1973; assigned to Beecham Group Limited

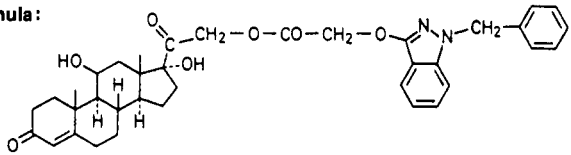
BENDACORT

Therapeutic Function: Glucocorticoid

Chemical Name: 21-ester of [(1-benzyl-1H-indazol-3-yl-oxy]-acetic acid with 11β,17α, trihydroxy-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.; U.S. Patent 4,001,219; January 4, 1977

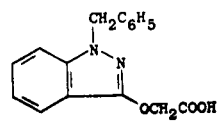
BENDAZAC

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 & Engel p. 79
OCDS Vol. 2 p. 351 (1980)
I.N. p. 121
Palazzo, G.; U.S. Patent 3,470,194; September 30, 1969; assigned to Aziende Chimiche Riunite Angelini, Francesco ACRAF SpA, Italy

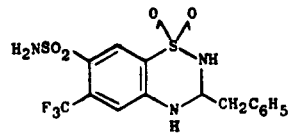
BENDROFLUMETHIAZIDE

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: Bendrofluazide, Benzydroflumethiazide, Benzylhydroflumethiazide

Structural Formula:



Chemical Abstracts Registry No.: 73-48-3

Trade Name	Manufacturer	Country	Year Introduced
Naturetin	Squibb	U.S.	1959
Sinesalin	I.C.I.	W. Germany	–
Naturine Leo	Leo	France	1961
Benuron	Bristol	U.S.	1965
Aprinox	Boots	U.K.	–
Benzide	Protea	Australia	–
Berkozide	Berk	U.K.	–
Bristuric	Bristol	U.S.	–
Bristuron	Bristol	–	–
Centyl	Leo	Denmark	–
Centyl	Leo-Sankyo	Japan	–
Corzide	Squibb	U.S.	–
Neo-Naclex	Glaxo	U.K.	–
Neo-Rontyl	Leo	Denmark	–
Notens	Farge	Italy	–
Pluryl	Leo	Denmark	–
Polidiuril	Bios	Italy	–
Poliuron	Lepetit	Italy	–
Rauzide	Squibb	U.S.	–
Salural	ICB	Italy	–
Salures	Ferrosan	Denmark	–
Seda-Repicin	Boehringer-Ing.	W. Germany	–
Sinesalin	Arcana	Austria	–
Sodiuretic	Squibb	Italy	–
Tensionorm	Leo	France	–
Urizid	Rekah	Israel	–

Raw Materials

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

Manufacturing Process

The process is described in U.S. 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, whereafter 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°C, 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-disulfamyl-aniline, 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-Sulfamyl-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-disulfamylaniline 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 U.S. Patent 3,265,573.

References

Merck Index 1036
Kleeman & 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.; U.S. Patent 3,265,573; August 9, 1966; assigned to E.R. Squibb & Sons, Inc.
Lund, F., Lyngby, K. and Godtfredsen, W.O.; U.S. Patent 3,392,168; July 9, 1968; assigned to Lovens Kemiske Fabrik ved A. Kongsted, Denmark

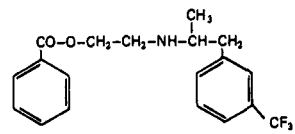
BENFLUOREX HYDROCHLORIDE

Therapeutic Function: Hypolipemic agent, cardiovascular drug

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

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

Trade Name	Manufacturer	Country	Year Introduced
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 4.7 N 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 & Engel p. 80
DOT 13 (1) 12 (1977)
I.N. p. 122
Beregi, L. Hugon, P. and Le Douarec, J.C.; U.S. Patent 3,607,909; September 21, 1971; assigned to Science Union et Cie Societe Francaise de Recherche Medicale

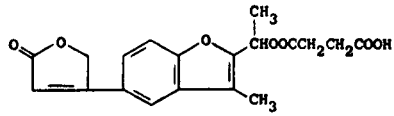
BENFURODIL HEMISUCCINATE

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

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

Raw Materials

4-(4-Methoxyphenyl)-2-oxo-2,5-dihydrofuran
Aluminum Chloride
Sodium Borohydride
Succinic Anhydride
Chloroacetone
Acetyl Chloride
Hydrogen Chloride

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_c = 155°-157°C.

(C) Preparation of 2-Acetyl-3-Methyl-5-(2-Oxo-2,5-Dihydro-4-Furyl)Benzo[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. Thereafter 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 reaciton 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 & Engel p. 81
OCDS Vol. 2 p. 355 (1980)
DOT 6 (6) 203 (1970)
I.N. p. 123
Schmitt, J.; U.S. Patent 3,355,463; November 28, 1967; assigned to Etablissements Clin-Byla, France

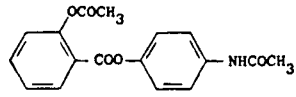
BENORYLATE

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	U.K.	1972
Benortan	Winthrop	W. Germany	1975
Benortan	Winthrop	France	1976
Benorile	Rubio	Spain	–
Benortan	Pharmacal	Finland	–
Bentum	Inpharzam	Belgium	–
Salipran	Bottu	France	–
Sinalgin	Robin	Italy	–
Triadol	Sterling Heath	U.K.	–
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 ½ 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 & Engel p. 82
DOT 8 (6) 208 (1972)
I.N. p. 123
Robertson, A.; U.S. Patent 3,431,293; March 4, 1969; assigned to Sterling Drug, Inc.

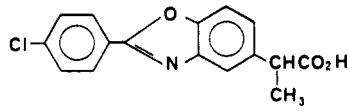
BENOXAPROFEN

Therapeutic Function: Antiinflammatory, analgesic

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

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 51234-28-7

Trade Name	Manufacturer	Country	Year Introduced
Opren	Dista Lilly	U.K.	1980
Coxigon	Lilly	W. Germany	1981
Inflamid	Lilly	France	1981
Coxigon	Lilly	Switz.	1982
Coxigon	Schweiz. Serum I	Switz.	1982
Oraflex	Lilly	U.S.	1982
Bexopron	Lilly	–	–

Raw Materials

Ethyl-2-(3-hydroxy-4-aminophenyl)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-p-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 & 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, T.A.; U.S. Patent 3,912,748; October 14, 1975; assigned to Lilly Industries Ltd.
Evans, D., Dunwell, D.W. and Hicks, T.A.; U.S. Patent 3,962,441; June 8, 1976; assigned to Lilly Industries, Ltd.
Evans, D., Dunwell, D.W. and Hicks, T.A.; U.S. Patent 3,962,452; June 8, 1976; assigned to Lilly Industries, Ltd.

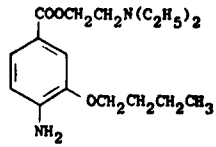
BENOXINATE HYDROCHLORIDE

Therapeutic Function: Topical anesthetic

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

Common Name: Oxybuprocaine

Structural Formula:



(base)

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

Trade Name	Manufacturer	Country	Year Introduced
Dorsacaine HCl	Dorsey	U.S.	1953
Novesine	Merck-Chibret	France	1960
Anemixin	Zeria	Japan	—
Benoxil	Santen	Japan	—

Trade Name	Manufacturer	Country	Year Introduced
Benoxinate	Barnes-Hind	U.S.	–
Cebesine	Chausin-Blache	France	–
Colirio Anestesico	Collado	Spain	–
Collu-Blache	Chauvin-Blache	France	–
Conjuncain	Mann	W. Germany	–
Lacrimin	Santen	Japan	–
Minims Benoxinate	Smith & Nephew	U.K.	–
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
Diethylamino Ethanol
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 diethyl-amino-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 2mm 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 & Engel p. 671
I.N. p. 716
REM p. 1057
Dr. A. Wander, AG, Switzerland; British Patent 654,484; June 20, 1951

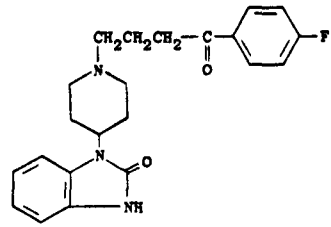
BENPERIDOL

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-Compar-Byla	France	1965
Gliahimon	Tropon	W. Germany	1966
Anquil	Janssen	U.K.	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 & 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.; U.S. Patent 3,161,645; December 15, 1964; assigned to Research Laboratorium Dr. C. Janssen N.V.

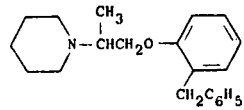
BENPROPERINE

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	–

(The above trade names are for phosphate and pamoate derivatives)

Raw Materials

o-Benzylphenoxy-β-chloropropane
Piperidine

Manufacturing Process

A mixture of 26.1 g of o-benzylphenoxy-β-chloropropane and 17 g of pipiridine 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 & Engel p. 83
OCDS Vol. 2 p. 100 (1980)
DOT 13 (6) 223 (1977)
I.N. p. 124
Rubinstein, K.; U.S. Patent 3,117,059; January 7, 1964; assigned to A.B. Pharmacia

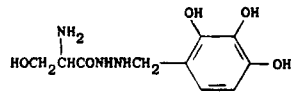
BENSERAZIDE

Therapeutic Function: Antiparkinsonism

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	U.K.	1975
Modopar	Roche	France	1975
Madopar	Roche	W. Germany	1975
Neodopasol	Daiichi	Japan	1980
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
Kleeman & Engel p. 84
DOT 10 (9) 322 (1974)
I.N. p. 124
Hegedus, B. and Zeller, P.; U.S. Patent 3,178,476; April 13, 1965; assigned to Hoffmann-La Roche Inc.

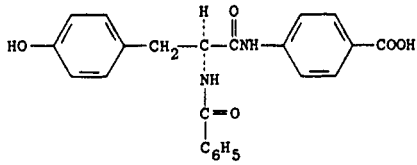
BENTIROMIDE

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	U.S.	–

Raw Materials

L-Tyrosine
Benzoyl Chloride
N-Methylmorpholine
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 13.2 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 1 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.; U.S. Patent 3,745,212; July 10, 1973; assigned to Rohm & Haas Co.

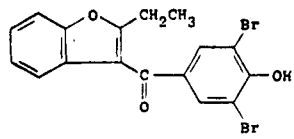
BENZBROMARONE

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	U.S.	—
Hipuric	Labaz	—	—
Max-Uric	Labinca	Argentina	—
Minuric	Labaz	—	—
Narcaricin	Heumann	W. Germany	—
Normurat	Grunenthal	W. Germany	—
Obaron	Mepha	Switz.	—

Raw Materials

Chloroacetone
Hydrazine Hydrate
Bromine
Salicyclic Aldehyde
Anisoyl Chloride

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 purified 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-anisoyl coumarone 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-3-p-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 slight 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 & Engel p. 87
OCDS Vol. 2 p. 354 (1980)
I.N. p. 127
Hoi, N.P.B. and Beaudet, C.; U.S. Patent 3,012,042; December 5, 1961; assigned to Societe Belge de l'Azote et des Produits Chimiques du Marly, Belgium

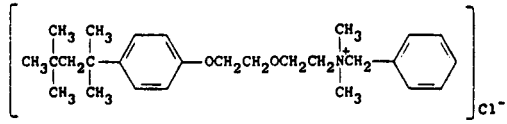
BENZETHONIUM CHLORIDE

Therapeutic Function: Topical Antiinfective

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

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 121-54-0

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

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.; U.S. Patents 2,115,250; April 26, 1938; 2,170,111; August 22, 1939; and 2,229,024; January 21, 1941; all assigned to Rohm & Haas Co.

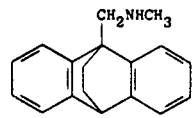
BENZOCTAMINE HCl

Therapeutic Function: Sedative, muscle relaxant

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

Common Name: –

Structural Formula:



(base)

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

Trade Name	Manufacturer	Country	Year Introduced
Tacitin	Ciba Geigy	Switz.	–
Tacitine	Ciba Geigy	France	1970

Trade Name	Manufacturer	Country	Year Introduced
Tacitin	Ciba Geigy	U.K.	1971
Tacitin	Ciba Geigy	Italy	1971
Tacitin	Ciba Geigy	W. Germany	1972

Raw Materials

Anthracene
Acrolein
Monomethylamine
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 100 cc 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 & Engel p. 88
DOT 6 (4) 123 (1970)
I.N. p. 129
Schmidt, P., Wilhelm, M. and Eichenberger, K.; U.S. Patent 3,399,201; August 27, 1968; assigned to Ciba Corp.

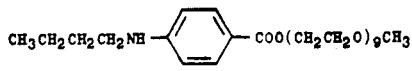
BENZONATATE

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)	U.S.	1958
Ventusasin	Warren Teed	U.S.	1964
Tessalon	Ciba Geigy	Switz.	—

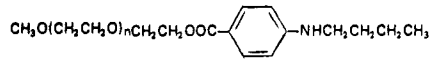
Raw Materials

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 & Engel p. 89
PDR p. 862
I.N. p. 130
REM p. 870
Matter, M.; U.S. Patent 2,714,608; August 2, 1955; assigned to Ciba Pharmaceutical Products, Inc.

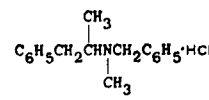
BENZPHETAMINE HYDROCHLORIDE

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	U.S.	1960
Inapetyl	Upjohn	France	1969
Didrex	Upjohn	U.K.	–

Raw Materials

d-Desoxyephedrine Hydrochloride
Benzyl Chloride
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 & 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.; U.S. Patent 2,789,138; April 16, 1957; assigned to The Upjohn Company

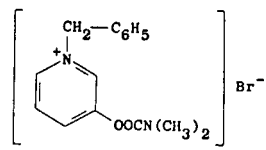
BENZPYRINIUM BROMIDE

Therapeutic Function: Cholinergic

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

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 587-46-2

Trade Name	Manufacturer	Country	Year Introduced
Stigmonene	Warner Lambert	U.S.	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.; U.S. Patent 2,489,247; November 22, 1949; assigned to William R. Warner & Co., Inc.

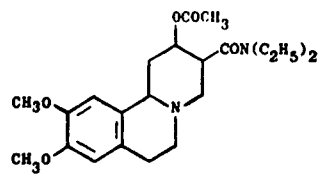
BENZQUINAMIDE

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)

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

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 U.S. Patent 3,055,894, a solution consisting of 3.4 grams (0.01 mol) 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 U.S. 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-diethylcarboxamido)-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-11b-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 & 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.; U.S. Patent 3,053,845; September 11, 1962; assigned to Chas. Pfizer & Co., Inc.
Lombardino, J.G. and McLamore, W.M.; U.S. Patent 3,055,894; September 25, 1962; assigned to Chas. Pfizer & Co., Inc.

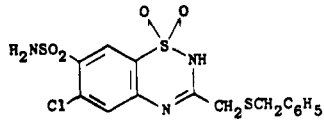
BENZTHIAZIDE

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	U.S.	1960
Dytide	SK&F	U.K.	1960
Diteriam	Roussel	France	1962
Aquatag	Tutag	U.S.	1965
Edemex	Savage	U.S.	1970
Lemazide	Lemmon	U.S.	1970
Aquapres	Coastal	U.S.	—
Aquastat	Lemmon	U.S.	—
Aquatag	Reid-Provident	U.S.	—
Decaserpyl	Roussel	France	—
Dihydrex	Astra	Sweden	—
Exosalt	Bayer	W. Germany	—
Fovane	Taito Pfizer	Japan	—
Hydrex	Trimen Labs	U.S.	—
Hy-Drine	Zemmer	U.S.	—
Proaqua	Reid Provident	U.S.	—
Regulon	Yamanouchi	Japan	—
Tensimic	Roussel	France	—
Urese	Pfizer	U.S.	—

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

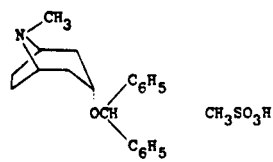
BENZTROPINE MESYLATE

Therapeutic Function: Antiparkinsonism

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

Common Name: Tropine benzohydryl ether methanesulfonate, Benztropine methanesulfonate (See also Benzatropine Mesylate)

Structural Formula:



Chemical Abstracts Registry No.: 132-17-2

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

Raw Materials

Diphenyldiazomethane
Tropine
Hydrogen Bromide
Sodium Hydroxide
Methane Sulfonic Acid

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

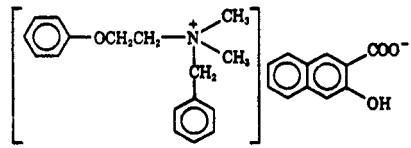
BEPHENIUM HYDROXYNAPHTHOATE

Therapeutic Function: Anthelmintic

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

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 7181-73-9

Trade Name	Manufacturer	Country	Year Introduced
Alcopar	Wellcome	U.K.	1960
Alcopar	Wellcome	France	1965
Alcopara	Burroughs-Wellcome	U.S.	1967
Alcopar	Wellcome-Tanabe	Japan	—

Raw Materials

Chloro-2-phenoxyethane
Benzyl Chloride
Dimethyl Amine
2-Hydroxy-3-naphthoic acid

Manufacturing Process

First, dimethylamino-2-phenoxyethane was 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 (0.5 N; 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 & Engel p. 93
DOT 4 (3) 114 (1968)
I.N. p. 134
Copp, F.C.; U.S. Patent 2,918,401; December 22, 1959; assigned to Burroughs Wellcome & Co., Inc.

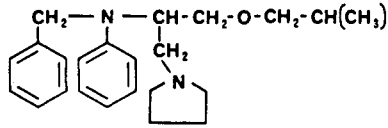
BEPRIDIL

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

1-(3-Isobutoxy-2-hydroxy)propyl Pyrrolidine
N-Benzylaniline
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°C. 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 & 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.; U.S. Patent 3,962,238; June 8, 1976; assigned to Centre Europeen de Recherches Mauvernay "CERM"