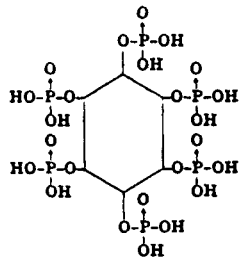
PHYTATE SODIUM

Therapeutic Function: Hypocalcemic

Chemical Name: Myo-Inositol hexakis(dihydrogen phosphate)sodium salt

Common Name: –

Structural Formula:



(acid)

Chemical Abstracts Registry No.: 83-86-3 (Acid)

Trade Name	Manufacturer	Country	Year Introduced
Rencal	Squibb	U.S.	1962
Iliso	Made	Spain	–

Raw Materials

Corn steep water
Lime
Cation exchange resin

Manufacturing Process

Cereal grains are particularly rich in phytates; corn steep water produced in the wet milling of corn, is one of the best sources of such material. To recover the phytate from corn steep water it is customary to neutralize the same with an alkaline material, suitably lime, causing the phytate to precipitate as a crude salt which can be removed readily by filtration. This material contains substantial amounts of magnesium, even though lime may have been employed as precipitant, and traces of other metallic ions, as well as some proteinaceous materials and other contaminants from the steep water. It may be partially purified by dissolving in acid and reprecipitating but, nevertheless, such commercial phytates do not represent pure salts. They always contain some magnesium, appreciable amounts of iron and nitrogenous materials, and traces of heavy metals, such as copper.

Heretofore, no economical method for preparing pure phytic acid was known. The classical method was to dissolve calcium phytate in an acid such as hydrochloric acid, and then add a solution of a copper salt, such as copper sulfate to precipitate copper phytate. The latter was suspended in water and treated with hydrogen sulfide, which formed insoluble copper sulfide and released phytic acid to the solution. After removing the copper sulfide by filtration, the filtrate was concentrated to yield phytic acid as a syrup.

The phytic acid in the form of a calcium phytate press cake may however be contacted with a cation exchange resin to replace the calcium with sodium to yield phytate sodium.

References

Merck Index 7269
I.N. p. 25

Baldwin, A.R., Blatter, L.K. and Gallagher, D.M.; U.S. Patent 2,815,360; December 3, 1957; assigned to Corn Products Refining Co.

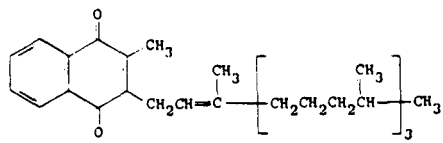
PHYTONADIONE

Therapeutic Function: Prothrombogenic vitamin

Chemical Name: 2-Methyl-3-(3,7,11,15-tetramethyl-2-hexadecenyl)-1,4-naphthalenedione

Common Name: Vitamin K, phytomeanadion, phylloquinone

Structural Formula:



Chemical Abstracts Registry No.: 84-80-0

Trade Name	Manufacturer	Country	Year Introduced
Mephyton	MSD	U.S.	1941
Konakion	Roche	U.S.	1959
Aquamephyton	MSD	U.S.	1960
Mono-Kay	Abbott	U.S.	1961
Eleven-K	Nippon Shinyaku	Japan	–
Hymeron	Yamanouchi	Japan	–
Kanavit	Spofa	Czechoslovakia	–
Kativ-N	Takeda	Japan	–
Kayeine	Kanto	Japan	–
Kaywan	Eisai	Japan	–
K-Eine	Hokuriku	Japan	–
Keipole	Kyowa	Japan	–
Kennegin	Kowa	Japan	–
Kephton	Toyo Jozo	Japan	–
Kinadione	Chugai	Japan	–
Kisikonon	Kyorin	Japan	–
K-Top Wan	Sawai	Japan	–
Monodion	Maruko	Japan	–
Nichivita-K	Nichiiko	Japan	–
One-Kay	Mohan	Japan	–
Synthex P	Tanabe	Japan	–
Vita-K	Kobayashi	Japan	–
Vitamine K1	Delagrange	France	–

Raw Materials

2-Methyl-1,4-naphthohydroquinone
Phytol
Hydrogen

Manufacturing Process

11 parts by weight of 2-methyl-1,4-naphthohydroquinone, 30 parts by volume of water-free

dioxane and 1.5 parts by volume of boron trifluoride etherate are heated to 50°C. While agitating and introducing nitrogen, 10 parts by weight of phytol dissolved in 10 parts by volume of dioxane are added in the course of 15 minutes. Thereupon, the dark colored reaction mixture is stirred for 20 additional minutes at 50°C, cooled down and 60 parts by volume of ether are added. The reaction mixture is washed first with water, then with a mixture of 3 parts of N-sodium hydroxide and 2 parts of a 2.5% solution of sodium hydrosulfite and again with water. The aqueous extracts are washed with ether. The ether solutions are collected, dried over sodium sulfate and concentrated, toward the end under reduced pressure.

The waxlike condensation product so obtained is mixed with 60 parts by volume of petroleum ether (boiling limits 30°C to 40°C) and agitated with hydrogen in the presence of a little active palladium lead catalyst (Pd-$CaCO_3$ catalyst, the activity of which is reduced by the addition of lead and quinoline). During the operation, the condensation product separates in the form of a voluminous white precipitate. The latter is separated by filtration in the absence of air while adding an inert coarse-grained adsorption agent (for example, aluminum silicate salt for filter purposes), and washed with cooled petroleum ether. Thereupon, the 2-methyl-3-phytyl-1,4-naphthohydroquinone is extracted from the filter cake by means of ether, the ethereal solution is concentrated to 100 parts by volume and the reaction product is oxidized by stirring the solution with 6.6 parts by weight of silver oxide during 30 minutes. The solution is filtered through sodium sulfate, the latter is rinsed with ether and the solvent is evaporated. There are obtained 5.7 parts by weight of 2-methyl-3-phytyl-1,4-naphthoquinone (vitamin K_1) in the form of a golden yellow oil.

References

Merck Index 9834
Kleeman & Engel p. 724
PDR pp. 1140, 1488
I.N. p. 770
REM p. 1011
Isler, O. and Doebel, K.; U.S. Patent 2,683,176; July 6, 1954; assigned to Hoffmann-La Roche, Inc.

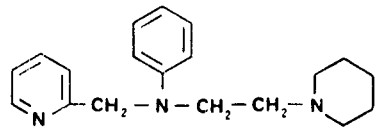
PICOPERINE

Therapeutic Function: Antitussive

Chemical Name: N-(2-Piperidinoethyl)-N-(2-pyridylmethyl)aniline

Common Name: Picoperamidine

Structural Formula:



Chemical Abstracts Registry No.: 21755-66-8

Trade Name	Manufacturer	Country	Year Introduced
Coben	Takeda	Japan	1971

Raw Materials

N-(2-Pyridylmethyl)aniline
Sodium amide
2-Piperidinoethyl chloride

Manufacturing Process

To a simultaneously stirred and refluxed suspension of 5.6 parts by weight of sodamide in 60 parts by volume of anhydrous toluene, there is added dropwise a solution of 18.4 parts by weight of N-(2-pyridylmethyl)aniline in 20 parts by volume of anhydrous toluene. After the addition is complete, the mixture is refluxed for two hours under constant stirring.

To the resulting mixture there is added dropwise a solution of 14.9 parts by weight of 2-piperidinoethyl chloride in 20 parts by volume of anhydrous toluene and the whole mixture is stirred and refluxed for another two hours. After cooling, water is added carefully to decompose the unreacted sodamide, the separated toluene layer is dried over anhydrous sodium sulfate and the solvent removed under reduced pressure.

The residual oil is subjected to distillation under reduced pressure, the fraction boiling in the range of 185°C to 198°C/4 mm Hg being collected. Purification of the fraction by redistillation under reduced pressure gives 22.5 parts by weight of N-(2-piperidinoethyl)-N-(2-pyridylmethyl)-aniline which boils at 195°C to 196°C/4 mm Hg. Yield 76.3%.

References

Merck Index 7285
DOT 8 (5) 185 (1972)
I.N. p. 771
Mitano, S. and Kase, Y.; U.S. Patent 3,471,501; October 7, 1969; assigned to Takeda Chemical Industries, Ltd.

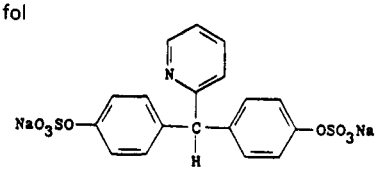
PICOSULFATE SODIUM

Therapeutic Function: Laxative

Chemical Name: 4,4'-(2-pyridinylmethylene)bisphenol bis(hydrogen sulfate) (ester) disodium salt

Common Name: Picosulfol

Structural Formula:



Chemical Abstracts Registry No.: 10040-45-6

Trade Name	Manufacturer	Country	Year Introduced
Guttalax	De Angelini	Italy	1967
Laxoberal	Thomae	W. Germany	1972
Laxoberal	W.B. Pharm.	U.K.	1975
Laxoberon	Teijin	Japan	1980

Trade Name	Manufacturer	Country	Year Introduced
Contumax	Casen	Spain	–
Evacuol	Almirall	Spain	–
Gocce Euchessina	Antonetto	Italy	–
Gocce Lassative Aicardi	Aicardi	Italy	–
Laxante Azoxico	Bescansa	Spain	–
Laxidogol	Dolorgiet	W. Germany	–
Picolax	Falqui	Italy	–
Skilax	Prodes	Spain	–
Trali	Sintyal	Argentina	–

Raw Materials

2-Pyridinaldehyde
2-Chlorophenol
Sodium hydroxide
Chlorosulfonic acid

Manufacturing Process

Preparation of 3,3'-Dichloro-4,4'-Dioxy-Diphenyl-(2-Pyridyl)-Methane: 75 g (0.7 mol) of 2-pyridinaldehyde are dropped during about 1 hour to a homogeneous mixture [obtained between 0° and 10°C from 107 ml of concentrated sulfuric acid and 292.9 g (2.28 mols) of 2-chlorophenol], maintaining the temperature between 0° and 5°C. The mixture is stirred for ½ hour at this temperature, which is then allowed to rise spontaneously, taking care not to exceed 30°C. After stirring for 1½ hours, the mixture is maintained overnight at room temperature, then it is dissolved, with external cooling, with a 10% sodium hydroxide solution, filtered with charcoal and neutralized with 5% hydrochloric acid. The precipitate obtained, consisting of crude product, filtered, washed with water, dried, triturated with ether and dried again, weighs 211 g.

The isomer 2,4'-dioxy-3,3'-dichloro-diphenyl-(2-pyridyl)-methane is removed by thoroughly washing with 430 ml of 95°C boiling alcohol, obtaining 167 g of isomer-free product (yield 69%). The 3,3'-dichloro-4,4'-dioxy-diphenyl-(2-pyridyl)-methane is a white solid, crystallizing from 95% alcohol; MP 212° to 215°C.

Preparation of 4,4'-Dioxy-Diphenyl-(2-Pyridyl)-Methane: 100 g of 3,3'-dichloro-4,4'-dioxy-diphenyl-(2-pyridyl)-methane, obtained as above described, are dissolved in 660 ml of 10% sodium hydroxide and 49 g of Raney-nickel alloy are added to the solution with vigorous stirring, at room temperature and during 4 hours. The mixture is stirred overnight at room temperature, then it is filtered and brought to pH 5 with 10% acetic acid. The precipitate obtained, filtered, washed and dried is then dissolved in 1,500 ml of 95°C boiling alcohol to eliminate the insoluble salts. The residue obtained after the evaporation of the alcoholic solution weighs 74 g (yield 92%). The yield in respect to 2-pyridinaldehyde is 63.5%. The compound is a white solid, crystallizing from 95% alcohol; MP 248° to 250.5°C, according to U.S. Patent 3,558,643.

Preparation of Disodium 4,4'-Disulfoxy-Diphenyl-(2-Pyridyl)-Methane: In ½ hour, 102 g chlorosulfonic acid are added to a solution of 100 g 4,4'-dihydroxydiphenyl-(2-pyridyl)-methane in 750 ml of anhydrous pyridine, the temperature being maintained at between 0° and 5°C. Towards the end of the addition of acid, a precipitate is formed which is slowly redissolved during subsequent agitation.

Upon completion of the addition, the mixture is agitated for 7 hours at ambient temperature. The solution is then poured into 3 liters of water/ice obtaining a clear solution of dark yellow color which is rendered alkaline upon phenolphthalein with 30% NaOH and extracted with ethyl ether to eliminate the majority of the pyridine. The mixture is filtered with active charcoal, the pH adjusted to 8 with hydrochloric acid 1:1 and extracted with chloroform to remove the 4,4'-dihydroxydiphenyl-(2-pyridyl)-methane which has not reacted.

The aqueous solution is then concentrated to dryness at an outside temperature of 40° to 45°C and at low pressure. The residue, obtained by drying in a vacuum at 40° to 45°C is triturated in a mortar with ethyl ether and, after filtration, is extracted with 3,400 ml boiling absolute ethanol. The ethanol extract is separated from the undissolved part by filtration, cooled and the product which crystallizes by cooling is filtered and dried at 40°C in a vacuum. In that manner the disodium (4,4'-disulfoxy-diphenyl)-(2-pyridyl)-methane bi-hydrate is obtained, which takes the form of a white solid, according to U.S. Patent 3,528,986.

References

Merck Index 7286
Kleeman & Engel p. 725
DOT 8 (8) 302 (1972)
I.N. p. 771
Pala, G.; U.S. Patent 3,528,986; September 15, 1970; assigned to Istituto de Angeli S.p.A., Italy
Pala, G.; U.S. Patent 3,558,643; January 26, 1971; assigned to Istituto de Angeli S.p.A., Italy

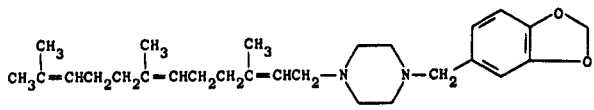
PIFARNINE

Therapeutic Function: Antiulcer

Chemical Name: 1-(1,3-Benzodioxol-5-ylmethyl)-4-(3,7,11-trimethyl-2,6,10-dodecatrienyl)-piperazine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 56208-01-6

Trade Name	Manufacturer	Country	Year Introduced
Pifazin	Pierrel	Italy	1983

Raw Materials

1-Bromo-3,7,11-trimethyl-2,6,10-dodecatriene
Piperonylpiperazine
Triethylamine

Manufacturing Process

A solution of 45 mmols of 1-bromo-3,7,11-trimethyl-2,6,10-dodecatriene (obtained from synthetic farnesol, commercially available and containing four isomers) in 10 ml of benzene was added dropwise at 0°C to a stirred solution of 45 mmols of piperonylpiperazine in 60 ml of benzene containing 5 g of triethylamine. The mixture was stirred for 2 hours and then the precipitated triethylammonium bromide was filtered off. The benzene solution was washed first with water and then with K_2CO_3 solution and finally dried (K_2CO_3). Removal of ben-

zene under reduced pressure gave a crude oily residue which was dissolved in acetone and treated at 5°C to 8°C with a slight excess of 37% HCl solution. The precipitated hydrochloride was filtered, washed with acetone and with absolute ethanol. The corresponding base was purified on a silica gel column and the purity of all fractions was checked by thin layer chromatography and gas liquid chromatography. Thin layer chromatography on silica gel gave three spots in the solvent system ethylacetate-petrol ether 1:1. Gas liquid chromatography showed three peaks indicating the presence of four possible isomers. The pure product was a colorless oil.

References

Merck Index 7299
DFU 2 (12) 829 (1977)
Kleeman & Engel p. 725
I.N. p. 772
Zumin, S.T., Riva, M. and Iafolla, G.; U.S. Patent 3,875,163; April 1, 1975; assigned to Pierrel S.p.A. (Italy)

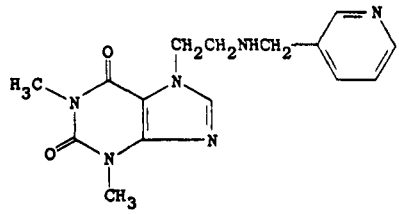
PIMEFYLLINE NICOTINATE

Therapeutic Function: Coronary vasodilator

Chemical Name: 3,7-dihydro-1,3-dimethyl-7-[2-[(3-pyridinylmethyl)amino] ethyl]-1H-purine-2,6-dione nicotinate

Common Name: 7-(β-3'-picolylaminoethyl)theophylline nicotinate

Structural Formula:



(base)

Chemical Abstracts Registry No.: 10058-07-8; 10001-43-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Teonicon	Bracco	Italy	1975
Teonicon	Neopharmed	Japan	—

Raw Materials

7-(β-Bromoethyl)theophylline
3-Picolylamine
Nicotinic acid

Manufacturing Process

77 g 7-(β-bromoethyl)-theophylline (*C.A.* 50, 12071f) and 57.8 g 3-picolylamine in 750 ml toluene were refluxed 16 hours with vigorous agitation. The 3-picolylamine hydrobromide formed was filtered off, and the filtrate was evaporated in a vacuum to about one-third of its original volume. About 300 to 400 ml diisopropyl ether were added, and the solution was seeded with a few pure crystals of the desired product.

7-(β-3'-picolylaminoethyl)-theophylline crystallized over a period of a few hours. It was filtered off with suction, washed with a little diisopropyl ether, and dried. The yield of crude product was 69.3 g (82%), its MP 103° to 106°C. The MP was 111° to 112°C after recrystallization from isopropyl acetate. The compound was identified by microanalysis.

39.3 g 7-(β-3'-picolylaminoethyl)-theophylline were dissolved in 300 ml boiling isopropanol, and 15.4 g nicotinic acid were added to the solution in which the acid promptly dissolved. The nicotinate formed crystallized after a short time. It was filtered with suction and dried. The yield was 52.3 g (95.5%). The MP of 159° to 160°C was not significantly changed by recrystallization from ethanol.

References

Merck Index 7306
Kleeman & Engel p. 727
Suter, H. and Zutter, H.; U.S. Patent 3,350,400; October 31, 1967; assigned to Eprova Limited, Switzerland

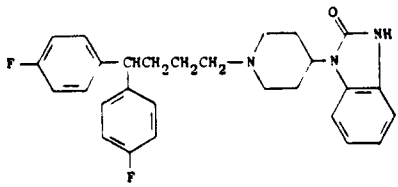
PIMOZIDE

Therapeutic Function: Antipsychotic

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

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 2062-78-4

Trade Name	Manufacturer	Country	Year Introduced
Orap	Janssen	W. Germany	1971
Opiran	Cassenne	France	1971
Orap	Janssen	U.K.	1971
Orap	Fujisawa	Japan	1974
Orap	Janssen	Italy	1977
Norofren	Dif-Dogu	Turkey	–
Oralep	Abic	Israel	–
Pimotid	Medica	Finland	–

Raw Materials

Cyclopropyl-di-(4-fluorophenyl)-carbinol
Thionyl chloride
Hydrogen
4-(2-Oxo-1-benzimidazolinyl)-piperidine

Manufacturing Process

To a solution of 130 parts cyclopropyl-di-(4-fluorophenyl)-carbinol in 240 parts benzene are added dropwise 43 parts thionyl-chloride. The whole is refluxed until no more gas is evolved. The reaction mixture is then evaporated. The residue is distilled in vacuo, yielding 4-chloro-1,1-di-(4-fluorophenyl)-1-butene, boiling point 165°C to 167°C at 6 mm pressure; n_D^{20}: 1.5698; d_{20}^{20}: 1.2151.

A solution of 61 parts 4-chloro-1,1,-di-(4-fluorophenyl)-1-butene in 400 parts 2-propanol is hydrogenated at normal pressure and at room temperature in the presence of 5.5 parts palladium-on-charcoal catalyst 10% (exothermic reaction: temperature rises to about 30°C). After the calculated amount of hydrogen is taken up, hydrogenation is stopped. The catalyst is filtered off and the filtrate is evaporated. The oily residue is distilled in vacuo, yielding 1-chloro-4,4-di-(4-fluorophenyl)-butane, boiling point 166°C to 168°C at 6 mm pressure; n_D^{20}: 1.5425; d_{20}^{20}: 1.2039.

To a mixture of 4.4 parts of 4-(2-oxo-1-benzimidazolinyl)-piperidine, 3.3 parts sodium carbonate, a few crystals of potassium iodide in 200 parts 4-methyl-2-pentanone are added portionwise 6.2 parts 1-chloro-4,4-di-(4-fluorophenyl)-butane. After the addition is complete, the whole is stirred and refluxed for 65 hours. After cooling the reaction mixture, there are added 70 parts water. The organic layer is separated, dried over potassium carbonate, filtered and evaporated. The solid residue is triturated in diisopropyl-ether, filtered off again and recrystallized from a mixture of 120 parts acetone and 80 parts 4-methyl-2-pentanone, yielding the crude product. After recrystallization of this crop from 80 parts acetone, 1-[4,4-di-(4-fluorophenyl)-butyl]-4-(2-oxo-1-benzimidazolinyl)-piperidine is obtained, melting point 217°C to 219°C.

References

Merck Index 7310
Kleeman & Engel p. 727
PDR p. 1091
OCDS Vol. 2 p. 390 (1980)
DOT 5 (1) 36 (1969); 7 (5) 176 (1971); and 9 (6) 235 (1973)
I.N. p. 774
REM p. 1092
Janssen, P.A.J.; U.S. Patent 3,196,157; July 20, 1965; assigned to Research Laboratorium Dr. C. Janssen N.V. (Belgium)

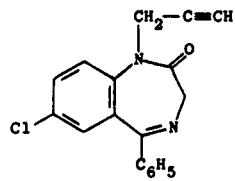
PINAZEPAM

Therapeutic Function: Antidepressant

Chemical Name: 7-Chloro-1,3-dihydro-5-phenyl-1-(2-propynyl)-2H-1,4-benzodiazepin-2-one

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 52463-83-9

Trade Name	Manufacturer	Country	Year Introduced
Domar	Zambeletti	Italy	1975
Duna	Zambeletti	Italy	–

Raw Materials

2-Amino-5-chlorobenzophenone
Phthalimido acetyl chloride
Propargyl bromide
Hydrazine hydrate

Manufacturing Process

46.3 g (0.2 mol) of 2-amino-5-chlorobenzophenone were dissolved in 100 ml (1.28 mols) of propargyl bromide and the mixture refluxed for 4 hours. Thereafter, the whole was evaporated to dryness and the residue recrystallized from methanol to give 32.4 g (60.2%) of the desired 2-propargylamino-5-chlorobenzophenone; melting point 92°C to 93°C.

2.7 g (0.01 mol) of the 2-propargylamino-5-chlorobenzophenone obtained as above and 2.23 g (0.01 mol) of phthalimido-acetyl-chloride were added to 30 ml of chloroform and the whole was refluxed overnight. Thereafter, the reaction mixture was evaporated to dryness and the residue recrystallized from methanol to give 2.66 g (58.3%) of the desired 2-(N-propargyl)-phthalimidoacetamide-5-chlorobenzophenone. Melting point: 176°C.

A suspension of 22.8 g (0.05 mol) of 2-(N-propargyl)-phthalimidoacetamido-5-chlorobenzophenone in 250 ml ethanol containing 7.5 g hydrazine hydrate (0.15 mol) was heated under reflux for 2 hours, at the end of which time the reaction mixture was set aside overnight at ambient (25°C) temperature. Thereafter, the crystalline phthalyl hydrazide which had precipitated out was removed by filtration and washed with 3 X 50 ml aliquots of chloroform. The filtrate and washings were diluted with water and exhaustively extracted with chloroform. The chloroform extract was then evaporated and the residue washed with 100 ml hexane to promote crystallization. The crude 7-chloro-1-propargyl-3H-1,4-benzodiazepine-2(1H)-one was recrystallized from a methanol-water mixture to give 10.5 g (71.4%) of the pure product. Melting point: 140°C to 142°C.

References

Merck Index 7316
Kleeman & Engel p. 728
DOT 12 (4) 147 (1976)
I.N. p. 774
Podesva, C. and Vagi, K.; U.S. Patent 3,842,094; October 15, 1974; assigned to Delmar Chemicals Ltd. (Canada)

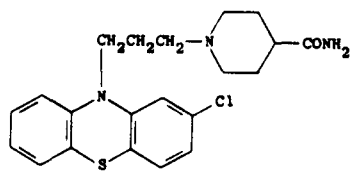
PIPAMAZINE

Therapeutic Function: Antiemetic

Chemical Name: 1-[3-(2-Chloro-10H-phenothiazin-10-yl)propyl] 4-pyridinecarboxamide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 84-04-8

Trade Name	Manufacturer	Country	Year Introduced
Mornidine	Searle	U.S.	1959
Nausidol	Gremy-Longuet	France	—

Raw Materials

4-Piperidinecarboxamide
2-Chloro-10-(γ-chloropropyl)phenothiazine

Manufacturing Process

To a stirred and refluxing suspension of 4.95 parts of 4-piperidinecarboxamide, 1 part of sodium iodide and 8.4 parts of potassium carbonate in 40 parts of butanone there are added in the course of 30 minutes 9.3 parts of 2-chloro-10-(γ-chloropropyl)phenothiazine in 40 parts of butanone. Stirring and refluxing are continued for 12 hours after which the mixture is cooled and filtered. The filtrate is concentrated under vacuum to give a residue which is recrystallized from a mixture of 2-propanol and petroleum ether. The 1-[γ-(2'-chloro-10'-phenothiazine)propyl] piperidine-4-carboxamide thus obtained melts at approximately 139°C.

This base is dissolved in a small amount of 2-propanol and treated with a 25% solution of hydrogen chloride in 2-propanol. Upon treatment of this solution with anhydrous ether a hydrochloride precipitates as a white solid melting at about 196°C to 197°C with formation of bubbles.

References

Merck Index 7326
Kleeman & Engel p. 729
OCDS Vol. 1 p. 385 (1977)
I.N. p. 775
Cusic, J.W. and Sause, H.W.; U.S. Patent 2,957,870; October 25, 1960; assigned to G.D. Searle & Co.

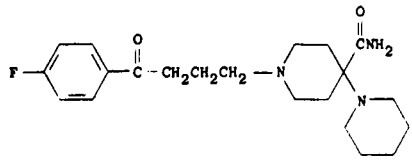
PIPAMPERONE

Therapeutic Function: Antipsychotic

Chemical Name: 1'-[4-(4-Fluorophenyl)-4-oxobutyl] -[1,4'-bipiperidine] -4'-carboxamide

Common Name: Floropipamide

Structural Formula:



Chemical Abstracts Registry No.: 1893-33-0

Trade Name	Manufacturer	Country	Year Introduced
Dipiperon	Janssen	W. Germany	1961

Trade Name	Manufacturer	Country	Year Introduced
Dipiperon	Janssen-Le Brun	France	1968
Piperonil	Lusofarmaco	Italy	1970
Propitan	Eisai	Japan	—

Raw Materials

Piperidine hydrochloride
1-Benzyl-4-piperidone
γ-Chloro-4-fluorobutyrophenone
Potassium cyanide
Sulfuric acid
Hydrogen

Manufacturing Process

To a stirred solution of 130.4 parts of potassium cyanide and 243.2 parts of piperidine hydrochloride in a mixture of 800 parts of water and 320 parts of ethanol is added portionwise 378 parts of 1-benzyl-4-piperidone. After about one hour a solid starts to precipitate. Stirring is continued for 24 hours. The reaction mixture is filtered and the solid is recrystallized from 1,200 parts of diisopropyl ether. On cooling to room temperature a first crop of 1-benzyl-4-cyano-4-piperidinopiperidine melting at about 104°C to 106°C is obtained. By concentrating and further cooling of the mother liquor a second crop of the above compound is obtained.

A mixture of 14.1 parts of 1-benzyl-4-cyano-4-piperidinopiperidine and 40 parts of 90% sulfuric acid is heated on a steam bath for 10 minutes. Without further heating, the mixture is stirred until a temperature of about 20°C is obtained. The mixture is then poured into 150 parts of ice-water and the resultant solution is alkalized with excess ammonium hydroxide solution. The aqueous solution is decanted from the precipitated oil. On treating this oil with 80 parts of acetone, crystallization sets in. After one hour the solid is filtered off and dried to yield 1-benzyl-4-piperidinopiperidine-4-carboxamide melting at about 137.5°C to 140°C.

A mixture of 215 parts of 1-benzyl-4-piperidinopiperidine-4-carboxamide, 1,200 parts of isopropyl alcohol, 1,000 parts of distilled water and 157 parts of hydrogen chloride is debenzylated under atmospheric pressure and at a temperature of about 40°C in the presence of 40 parts of a 10% palladium-on-charcoal catalyst. After the calculated amount of hydrogen is taken up, hydrogenation is stopped. The mixture is filtered and the filtrate is evaporated. The semisolid residue is treated with a mixture of 80 parts of acetone and 80 parts of benzene and evaporated again. The residue is triturated in 200 parts of methanol and filtered, yielding the dihydrochloride of 4-piperidinopiperidine-4-carboxamide melting at about 299°C to 300.8°C with decomposition. A sample of 20 parts of the dihydrochloride is dissolved in 30 parts of water. The aqueous solution is alkalized with 15 parts of 44% sodium hydroxide and stirred for a short time. The solid obtained is filtered off yielding crude product. To separate the free base from organic and inorganic salts, it is extracted overnight in a Soxhlet apparatus with toluene. The toluene extract is evaporated and the solid residue is filtered off, yielding 4-piperidinopiperidine-4-carboxamide melting at about 118.5°C to 119.5°C.

To a mixture of 4.1 parts of 4-piperidinopiperidine-4-carboxamide, 6.4 parts of sodium carbonate, and a few crystals of potassium iodide in 100 parts of anhydrous toluene is added dropwise a solution of 5.6 parts of γ-chloro-4-fluorobutyrophenone and 40 parts of anhydrous toluene at a temperature of 30°C to 40°C. The mixture is stirred and refluxed for 48 hours. The reaction mixture is cooled and divided between 50 parts of water and 60 parts of chloroform. The combined organic layers—toluene and chloroform—are dried over potassium carbonate, filtered, and evaporated. The oily residue solidifies on treatment with 80 parts of ether. After cooling for 30 minutes at 0°C, there is obtained 1-[γ-(4-fluorobenzoyl)propyl]-4-piperidinopiperidine-4-carboxamide melting at about 124.5°C to 126°C.

References

Merck Index 7327
Kleeman & Engel p. 729
OCDS Vol. 2 p. 388 (1980)

I.N. p. 775
Janssen, P.A.J.; U.S. Patent 3,041,344; June 26, 1962; assigned to Research Laboratorium Dr. C. Janssen N.V. (Belgium)

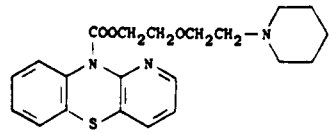
PIPAZETHATE

Therapeutic Function: Antitussive

Chemical Name: 10H-Pyrido[3,2-b][1,4]benzothiadiazine-10-carboxylic acid 2-(2-piperidinoethoxy)ethyl ester

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 2167-85-3; 6056-11-7 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Theratuss	Squibb	U.S.	1962
Dipect	Draco	Sweden	–
Lenopect	Draco	Sweden	–
Selvigon	Homburg	W. Germany	–

Raw Materials

1-Azaphenothiazine carboxylic acid chloride
Piperidinoethoxy ethanol

Manufacturing Process

8.5 parts of 1-azaphenothiazine carboxylic acid chloride and 14 parts of piperidino-ethoxy-ethanol were introduced into 100 parts of chlorobenzene and the mixture boiled under reflux for 5 minutes. After cooling off the precipitated hydrochloride salt of piperidino-ethoxy-ethanol was filtered off on a suction filter. Water was added to the filtrate and the pH thereof adjusted to 5 to 6 with dilute HCl. The aqueous phase was then removed, a caustic soda solution added thereto and then extracted with ether. The ethyl extract was washed with water, then dried with potash and the ether distilled off. 9.4 parts of the piperidino-ethoxy-ethyl ester of 1-azaphenothiazine carboxylic acid were obtained. This product was dissolved in 20 parts of isopropanol and the solution neutralized with isopropanolic HCl. The monohydrochloride which precipitated out after recrystallization from isopropanol had a melting point of 160°C to 161°C.

References

Merck Index 7328
Kleeman & Engel p. 730
OCDS Vol. 1 p. 390 (1977)
I.N. p. 775
Schuler, W.A.; U.S. Patent 2,989,529; June 20, 1961; assigned to Degussa (Germany)

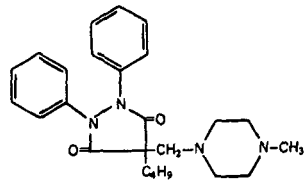
PIPEBUZONE

Therapeutic Function: Antiinflammatory

Chemical Name: 1,2-Diphenyl-3,5-dioxo-4-n-butyl-4-(N'-methylpiperazinomethyl)pyrazolidine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 27315-91-9

Trade Name	Manufacturer	Country	Year Introduced
Elarzone	Dausse	France	1973

Raw Materials

Phenylbutazone
Formaldehyde
N-Methylpiperazine

Manufacturing Process

77 g (0.25 mol) of phenylbutazone, 30 ml of a 30% strength solution of formaldehyde and 50 ml of ethyl alcohol are introduced into a 500 ml flask, 25 g (0.25 mol) of N-methylpiperazine are slowly added to this mixture which is stirred mechanically. The mixture is then heated for one hour on a water bath, left to cool, and crystallization started by scratching.

After being left in the refrigerator overnight the mixture, which has set solid, is triturated with 50 ml of isopropyl alcohol and the solid product filtered off and dried in vacuo over phosphorus pentoxide. 63 g (60% yield) of 1,2-diphenyl-3,5-dioxo-4-n-butyl-4-(N'-methylpiperazinomethyl)pyrazolidine are obtained, melting at 129°C after recrystallization from 150 ml of isopropyl alcohol.

References

Merck Index 7329
Kleeman & Engel p. 730
DOT 9 (11) 476 (1973)
I.N. p. 775
Dausse, S.A.; British Patent 1,249,047; October 6, 1971

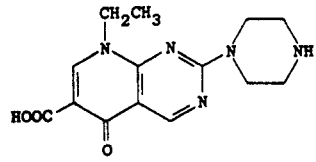
PIPEMIDIC ACID

Therapeutic Function: Antibacterial (urinary)

Chemical Name: 8-ethyl-5,8-dihydro-5-oxo-2-(1-piperazinyl)pyrido[2,3-d] pyrimidine-6-carboxylic acid

Common Name: Piperamic acid

Structural Formula:



Chemical Abstracts Registry No.: 51940-44-4

Trade Name	Manufacturer	Country	Year Introduced
Pipram	Bellon	France	1975
Deblaston	Madaus	W. Germany	1975
Pipram	RBS Pharma	Italy	1978
Dolcol	Dainippon	Japan	1979
Pipram	Bellon	Italy	1979
Pipedac	Mediolanum	Italy	1980
Deblaston	Madaus	Switz.	1981
Filtrax	Biomedica Foscama	Italy	—
Gastrurol	Gibipharma	Italy	—
Memento	Volpino	Argentina	—
Nuril	Prodes	Spain	—
Pipedase	Scalari	Italy	—
Pipemid	Gentili	Italy	—
Pipurin	Brocchieri	Italy	—
Priper	Synero	Argentina	—
Septidron	Ethimed	S. Africa	—
Tractur	Baldacci	Italy	—
Uropimid	C.T.	Italy	—
Urotractin	Zambeletti	Italy	—
Uroval	Firma	Italy	—

Raw Materials

6-Amino-2-methylthiopyrimidine
Ethoxymethylene malonic acid diethyl ester
Piperazine hydrate
Sodium hydroxide
Diethyl sulfate

Manufacturing Process

A mixture containing 1.33 g of 5,8-dihydro-8-ethyl-2-methylthio-5-oxopyridol[2,3-d]-pyrimidine-6-carboxylic acid, 1.94 g of piperazine hexahydrate and 20 ml of dimethyl sulfoxide was heated at 110°C for 1 hour with stirring. The separated solid was collected by filtration, washed with ethanol, and then dried at such a temperature that did not rise above 50°C to give 1.57 g of the trihydrate of the product as nearly colorless needles, MP 253° to 255°C.

The starting material may be produced by reacting 6-amino-2-methylthiopyrimidine with ethoxymethylene malonic acid diethyl ester. The intermediate thus produced is converted by boiling in diphenyl ether to 6-ethoxycarbonyl-2-methylthio-5-oxo-5,8-dihydropyrido-[2,3-d]pyrimidine. That is hydrolyzed by sodium hydroxide to cleave the ethoxy group and then ethylated with diethyl sulfate to give the starting material.

References

Merck Index 7332
Kleeman & Engel p. 731

DOT 11 (10, 408 (1975) & 12 (3) 99 (1976)
I.N. p. 36
Minami, S., Matsumoto, J.-I., Kawaguchi, K., Mishio, S., Shimizu, M., Takase, Y. and Nakamura, S.; U.S. Patent 3,887,557; June 3, 1975; assigned to Dainippon Pharmaceutical Co. Ltd., Japan
Minami, S., Matsumoto, J.-I., Kawaguchi, K., Mishio, S., Shimizu, M., Takase, Y. and Nakamura, S.; U.S. Patent 3,962,443; June 8, 1976; assigned to Dainippon Pharmaceutical Co. Ltd., Japan

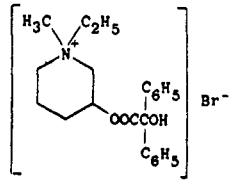
PIPENZOLATE BROMIDE

Therapeutic Function: Antispasmodic

Chemical Name: 1-ethyl-3-[(hydroxydiphenylacetyl)oxy]-1-methylpiperidinium bromide

Common Name: N-ethyl-3-piperidyl benzilate methobromide

Structural Formula:



Chemical Abstracts Registry No.: 125-51-9

Trade Name	Manufacturer	Country	Year Introduced
Piptal	Merrell National	U.S.	1955
Piptal	Roger Bellon	France	1960
Piper	Panthox & Burck	Italy	—

Raw Materials

N-Ethyl-3-chloropiperidine
Benzilic acid
Methyl bromide

Manufacturing Process

N-ethyl-3-chloropiperidine was prepared according to the method of Fuson and Zirkle described in Volume 70, *J. Am. Chem. Soc.*, p 2760. 12.0 g (0.081 mol) of N-ethyl-3-chloropiperidine was mixed with 18.6 g (0.081 mol) of benzilic acid and 80 cc of anhydrous isopropyl alcohol as a solvent. The mixture was refluxed for 72 hours. The solution was then filtered and concentrated at 30 mm of mercury. The concentrate was dissolved in water, acidified with hydrochloric acid and extracted with ether to remove the unreacted benzilic acid.

The aqueous layer was neutralized with sodium bicarbonate and the product was extracted with ether. The ethereal solution of the product was dried with potassium carbonate, the ether was removed by distillation and the residue was distilled at 0.12 to 0.18 mm of mercury, the BP being 194° to 198°C. A yield of 16.5 g (60% of theoretical) of N-ethyl-3-piperidyl-benzilate was obtained.

34 g (0.1 mol) of the basic ester is dissolved in 75 cc of isopropyl alcohol and treated with 9.5 g (0.1 mol) of methyl bromide. The mixture is allowed to stand at room temperature until precipitation is complete. The product is removed by filtration and washed with isopropyl alcohol, yield 33 g, MP 175° to 177°C. On recrystallization from isopropyl alcohol, the MP was raised to 179° to 180°C dec.

References

Merck Index 7333
Kleeman & Engel p. 732
I.N. p 776
Biel, J.H.; U.S. Patent 2,918,406; December 22, 1959; assigned to Lakeside Laboratories, Inc.

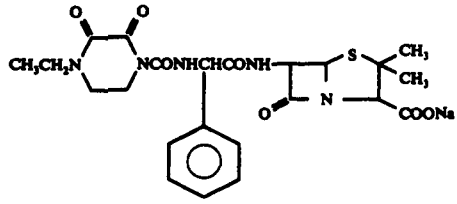
PIPERACILLIN SODIUM

Therapeutic Function: Antibiotic

Chemical Name: Sodium salt of 6-[D(−)-α-(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)-phenylacetamido] penicillanic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 59703-84-3; 61477-96-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Pentcillin	Toyama	Japan	1980
Pipril	Lederle	W. Germany	1980
Pipril	Lederle	Switz.	1980
Piperallin	Toyama	France	1981
Piprii	Lederle	U.K.	1982
Avocin	Cyanamid	Italy	1982
Pipracil	Lederle	U.S.	1982
Pentocillin	Sankyo	Japan	–

Raw Materials

N-Ethylethylenediamine
Diethyl oxalate
Phosgene
6-[D(−)-α-aminophenylacetamido] penicillanic acid
Trimethylsilyl chloride
Sodium 2-ethyl hexanoate

Manufacturing Process

To a suspension of 0.9 g of 6-[D(−)-α-aminophenylacetamido] penicillanic acid in 30 ml of anhydrous ethyl acetate were added at 5°C to 10°C 0.55 g of triethylamine and 0.6 g of trimethylsilyl chloride. The resulting mixture was reacted at 15°C to 20°C for 3 hours to form trimethylsilylated 6-[D(−)-α-aminophenylacetamido] penicillanic acid.

To this acid was then added 1 g of 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride (from the reaction of N-ethylethylenediamine and diethyl oxalate to give 2,3-dioxo-4-ethyl-piperazine which is then reacted with phosgene) and the resulting mixture was reacted at 15°C to 20°C for 2 hours. After the reaction, a deposited triethylamine hydrochloride was separated by filtration, and the filtrate was incorporated with 0.4 g of n-butanol to deposit crystals. The deposited crystals were collected by filtration to obtain 1.25 g of white crystals of 6-[D(−)-α-(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetamido] penicillanic acid. Into a solution of these crystals in 30 ml of tetrahydrofuran was dropped a solution of 0.38 g of a sodium salt of 2-ethyl-hexanoic acid in 10 ml of tetrahydrofuran, upon which white crystals were deposited. The deposited crystals were collected by filtration, sufficiently washed with tetrahydrofuran and then dried to obtain 1.25 g of sodium salt of 6-[D(−)-α-(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetamido] penicillanic acid, melting point 183°C to 185°C (decomposition), yield 90%.

References

Merck Index 7335
DFU 3 (11) 829 (1978)
Kleeman & Engel p. 732
PDR p. 1026
OCDS Vol. 3 p. 207 (1984)
DOT 17 (1) 29 (1981)
I.N. p. 776
REM p. 1199

Saikawa, I., Takano, S., Yoshida, C., Takashima, O., Momonoi, K., Kuroda, S., Komatsu, M., Yasuda, T. and Kodama, Y.; U.S. Patents 4,087,424; May 2, 1978; 4,110,327; Aug. 29, 1978; 4,112,090; September 5, 1978; all assigned to Toyama Chemical Co., Ltd.

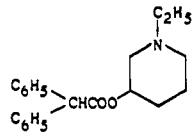
PIPERIDOLATE

Therapeutic Function: Antispasmodic

Chemical Name: α-phenylbenzeneacetic acid 1-ethyl-3-piperidinyl ester

Common Name: N-ethyl-3-piperidyl diphenylacetate

Structural Formula:



Chemical Abstracts Registry No.: 82-98-4; 129-77-1 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Dactil	Merrell National	U.S.	1954

Trade Name	Manufacturer	Country	Year Introduced
Dactil	Roger Bellon	France	1958
Cactiran	Kyorin	Japan	–
Crapinon	Sanzen	Japan	–
Dactylate	Sawai	Japan	–
Edelel	Mochida	Japan	–

Raw Materials

Furfural
Hydrogen
Acetic acid
Ethylamine
Hydrogen bromide
Diphenylacetyl chloride

Manufacturing Process

To obtain the free base, 34 g (0.256 mol) of N-ethyl-3-piperidinol and 20 g (0.22 mol) of diphenylacetyl chloride were mixed in 80 cc of isopropanol and the solution was refluxed for 2 hours. The isopropanol was evaporated in vacuo at 30 mm pressure, the residue was dissolved in 150 cc of water and the aqueous solution was extracted several times with ether. The aqueous solution was then neutralized with potassium carbonate and extracted with ether. The ethereal solution was dried over anhydrous potassium carbonate and the ether removed by distillation. The product was then distilled at its boiling point 180° to 181°C at 0.13 mm of mercury whereby 14 g of a clear yellow, viscous liquid was obtained. The nitrogen content for $C_{21}H_{25}NO_2$ was calculated as 4.33% and the nitrogen content found was 4.21%.

The starting material was produced by the reaction of furfural with ethylamine followed by hydrogenation to give N-ethyl-N-(2-tetrahydrofurfuryl)amine. Treatment of that material with hydrogen bromide in acetic acid gives N-ethyl-3-piperidinol.

References

Merck Index 7345
Kleeman & Engel p. 733
OCDS Vol. 1 p. 91 (1977)
I.N. p. 778
Biel, J.H.; U.S. Patent 2,918,407; December 22, 1959; assigned to Lakeside Laboratories, Inc.

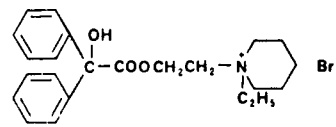
PIPETHANATE ETHOBROMIDE

Therapeutic Function: Anticholinergic, antiulcer

Chemical Name: Benzilic acid, 2-piperidinoethyl ester ethobromide

Common Name: Piperilate ethyl bromide

Structural Formula:



Chemical Abstracts Registry No.: 4546-39-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Panpurol	Nippon Shinyaku	Japan	–

Raw Materials

Pipethanate hydrochloride
Sodium hydroxide
Ethyl bromide

Manufacturing Process

Pipethanate hydrochloride is dissolved in water and the solution is made alkaline by adding 10% sodium hydroxide solution. The crystals that are separated are filtered off and recrystallized from dilute ethanol. The monohydrate thereby obtained is dehydrated at 100°C under reduced pressure for 20 minutes. The products that are now in the form of a syrup due to loss of water of crystallization are further dehydrated for 2 days in a desiccator over phosphorus pentoxide whereupon the anhydrous pipethanate is obtained.

3.8 g of the anhydrous pipethanate prepared by the method described is dissolved in 15 cc of acetone, 18 g of purified ethyl bromide is added, and the mixture heated for 8 hours in a sealed tube at 100°C to 110°C. After cooling the crystals are separated and isolated by filtration. They are then washed with acetone to give 5.2 g (95.6%) of pipethanate ethylbromide with a decomposition point of 218°C to 220°C. The crystals are almost pure.

References

Merck Index 7346
DOT 7 (1) 23 (1971)
I.N. p. 779
Nippon Shinyaku Co., Ltd.; British Patent 1,148,858; April 16, 1969

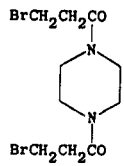
PIPOBROMAN

Therapeutic Function: Antineoplastic

Chemical Name: 1,4-Bis-(3-bromo-1-oxopropyl)piperazine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 54-91-1

Trade Name	Manufacturer	Country	Year Introduced
Vercyte	Abbott	U.S.	1966
Vercyte	Abbott	France	1970
Vercite	Abbott	Italy	1972
Amedel	Dainippon	U.K.	1973

Raw Materials

3-Bromopropionyl chloride
Piperazine

Manufacturing Process

To a solution of 17.2 g (0.10 mol) of 3-bromopropionyl chloride in 100 ml of anhydrous benzene was added dropwise with stirring a solution of 8.6 g (0.10 mol) of anhydrous piperazine in 20 ml of dry chloroform over a period of 30 minutes. The temperature rose spontaneously to 45°C during the addition. After the temperature ceased to rise, stirring was continued for another hour. The reaction mixture was then filtered to remove the piperazine hydrochloride by-product. The filtrate was evaporated to dryness and the residue recrystallized from ethanol to obtain the desired N,N'-bis-(3-bromopropionyl)piperazine as a white crystalline solid melting at 103°C to 104°C. The identity of the product was further established by elemental analysis.

References

Merck Index 7355
Kleeman & Engel p. 735
OCDS Vol. 2 p. 299 (1980)
I.N. p. 779
REM p. 1156
Abbott Laboratories; British Patent 921,559; March 20, 1963

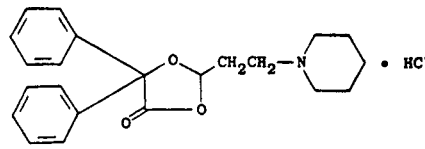
PIPOXOLAN HYDROCHLORIDE

Therapeutic Function: Antispasmodic

Chemical Name: 5,5-diphenyl-2-[2-(1-piperidinyl)ethyl]-1,3-dioxolan-4-one hydrochloride

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 18174-58-8; 23744-24-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Rowapraxin	Rowa/Wagner	W. Germany	1969

Raw Materials

β-Chloropropionaldehyde diethylacetal
Benzilic acid
Piperidine
Hydrogen chloride

Manufacturing Process

33 g (0.14 mol) of benzilic acid and 22 g (0.13 mol) of β-chloropropionaldehyde diethyl acetal were dissolved in 100 ml of glacial acetic acid by heating. After cooling to 40°C, a

slow stream of dry HCl gas was introduced while stirring for 2½ hours. After evaporating the glacial acetic acid in vacuo, the reforming oil was taken up in CH_2Cl_2 and treated with solid $KHCO_3$. After the evolution of CO_2 had ended, water was added and the organic phase was neutralized by means of $KHCO_3$ solution. After drying, the solvent was removed; the remaining oil distilled over under high vacuum at 0.001 mm and at 120° to 130°C to yield the compound 2-(β-chloroethyl)-4,4-diphenyl-1,3-dioxolan-5-one hydrochloride.

This compound was boiled with 12 g of dry piperidine in 120 ml of absolute benzene for 12 hours under reflux, a total of 6 g of piperidine hydrochloride being separated out. This was filtered off and the benzene solution was concentrated by evaporation. The residue was taken up in a little chloroform and the solution was applied to a dry aluminum oxide column (according to Brockmann); it was thereafter extracted with chloroform. After concentrating the solution by evaporation, an oil was obtained, which was taken up in absolute diethylether. Introduction of dry HCl gas into the cooled solution gave a precipitate which was dissolved and allowed to crystallize from isopropanol/ether. MP 193° to 199°C.

References

Merck Index 7358
Kleeman & Engel p. 736
DOT 6 (3) 95 (1970)
I.N. p. 780
Rowa-Wagner Kommanditgesellschaft Arzneimittelfabrik, Germany; British Patent 1,109,959; April 18, 1968

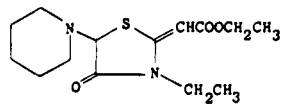
PIPROZOLIN

Therapeutic Function: Choleretic

Chemical Name: [3-Ethyl-4-oxo-5-(1-piperidinyl)-2-thiazolidinylidene] acetic acid ethyl ester

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 17243-64-0

Trade Name	Manufacturer	Country	Year Introduced
Probilin	Goedecke	W. Germany	1977
Probilin	Parke Davis	Italy	1979
Coleflux	Finadiet	Argentina	—
Epsyl	Exa	Argentina	—
Secrebil	Isnardi	Italy	—

Raw Materials

Ethyl thioglycolate
Sodium ethylate
Piperidine
Ethyl cyanoacetate
Diethyl sulfate

Manufacturing Process

Ethyl thioglycolate and ethyl cyanoacetate are first reacted in the presence of sodium ethylate to give 4-oxo-thiazolidin-2-ylideneacetic acid ethyl ester. That is reacted with diethyl sulfate and then with piperidine to give piprozolin.

References

Merck Index 7361
DFU 2 (10) 681 (1977)
Kleeman & Engel p. 737
OCDS Vol. 2 p. 270 (1980)
DOT 14 (1) 26 (1976)
I.N. p. 781
Satzinger, G., Herrmann, M. and Vollmer, K.O.; U.S. Patent 3,971,794; July 27, 1976; assigned to Warner-Lambert Co.

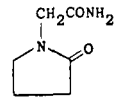
PIRACETAM

Therapeutic Function: Psychotropic

Chemical Name: 2-Oxo-1-pyrrolidineacetamide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 7491-74-9

Trade Name	Manufacturer	Country	Year Introduced
Nootropyl	UCB	France	1972
Nootropil	UCB-Smit	Italy	1974
Nootrop	UCB Chemie	W. Germany	1974
Normabrain	Cassella Riedel	W. Germany	1974
Gabacet	Carrion	France	1980
Ciclocetam	Callol	Spain	–
Ciclofalina	Almirall	Spain	–
Encefalux	Bama-Geve	Spain	–
Eumental	Wassermann	Spain	–
Genogris	Vita	Spain	–
Gericetam	Level	Spain	–
Huberdasen	Hubber	Spain	–
Ideaxan	Millot	France	–
Merapiran	Finadiet	Argentina	–
Nootron	Biosintetica	Brazil	–
Nootropicon	Sidus	Argentina	–
Norotrop	Drifen	Turkey	–
Norzetam	Albert Farma	Spain	–
Oikamid	Pliva	Yugoslavia	–
Pirroxil	S.I.T.	Italy	–
Pyramen	Pharmachim	Bulgaria	–
Stimubral	Lusofarmaco	Portugal	–
Stimucortex	Kalifarma	Spain	–

Raw Materials

2-Pyrrolidone
Ethyl chloroacetate
Sodium hydride
Ammonia

Manufacturing Process

2-Pyrrolidone is first reacted with sodium hydride, then with ethyl chloroacetate to give ethyl 2-oxo-1-pyrrolidine acetate.

A solution of 0.3 mol of ethyl 2-oxo-1-pyrrolidine acetate in 300 ml of methanol, saturated with ammonia at 20° to 30°C, is heated at 40° to 50°C for 5 hours, while continuously introducing ammonia. The reaction mixture is evaporated to dryness and the residue recrystallized from isopropanol. 2-Oxo-1-pyrrolidineacetamide is obtained in a yield of 86%. MP 151.5° to 152.5°C.

References

Merck Index 7363
Kleeman & Engel p. 737
DOT 9 (6) 215 (1973) & (8) 327 (1973)
I.N. p. 781
Morren, H.; U.S. Patent 3,459,738; August 5, 1969; assigned to UCB (Union Chimique-Chemische Bedrijven), Belgium

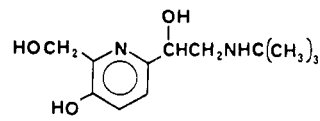
PIRBUTEROL

Therapeutic Function: Bronchodilator

Chemical Name: 2-Hydroxymethyl-3-hydroxy-(1-hydroxy-2-tert-butylaminoethyl)pyridine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 38677-81-5

Trade Name	Manufacturer	Country	Year Introduced
Exirel	Pfizer Taito	Japan	1982
Exirel	Pfizer	U.K.	1983
Exirel	Pfizer	Switz.	1983

Raw Materials

N-tert-butyl-2-(5-benzyloxy-6-hydroxymethyl-2-pyridyl)-2-hydroxyacetamide
Diborane
Hydrogen

Manufacturing Process

To 78 ml of a 1 M solution of diborane in tetrahydrofuran under nitrogen and cooled to 0°C is added dropwise over a period of 40 minutes 13.5 g of N-tert-butyl-2-(5-benzyloxy-6-hy-

droxymethyl-2-pyridyl)-2-hydroxyacetamide in 250 ml of the same solvent. The reaction mixture is allowed to stir at room temperature for 3.5 hours, and is then heated to reflux for 30 minutes and cooled to room temperature. Hydrogen chloride (70 ml, 1.34 N) in ethanol is added dropwise, followed by the addition of 300 ml of ether. The mixture is allowed to stir for 1 hour and is then filtered, yielding 11.0 g, melting point 202°C (dec.). The hydrochloride dissolved in water is treated with a sodium hydroxide solution to pH 11 and is extracted into chloroform (2 x 250 ml). The chloroform layer is dried over sodium sulfate, concentrated to dryness in vacuo, and the residue recrystallized from isopropyl ether, 3.78 g, melting point 81°C to 83.5°C.

A solution of 1.7 g of 2-hydroxymethyl-3-benzyloxy-(1-hydroxy-2-tert-butyl-aminoethyl)pyridine in 30 ml of methanol containing 1.2 ml of water is shaken with 700 mg of 5% palladium-on-charcoal in an atmosphere of hydrogen at atmospheric pressure. In 17 minutes the theoretical amount of hydrogen has been consumed and the catalyst is filtered. Concentration of the filtrate under reduced pressure provides 1.4 g of the crude product as an oil. Ethanol (5 ml) is added to the residual oil followed by 6 ml of 1.75 N ethanolic hydrogen chloride solution and, finally, by 5 ml of isopropyl ether. The precipitated product is filtered and washed with isopropyl ether containing 20% ethanol, 1.35 g, melting point 182°C (dec.).

References

Merck Index 7364
DFU 2 (1) 60 (1977)
OCDS Vol. 2 p. 280 (1980)
DOT 19 (2) 113 (1983) & (7) 384 (1983)
I.N. p. 782
Barth, W.E.; U.S. Patents 3,700,681; October 24, 1972; 3,763,173; October 2, 1973; 3,772,314; November 13, 1973; all assigned to Pfizer, Inc.

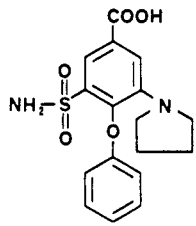
PIRETANIDE

Therapeutic Function: Diuretic

Chemical Name: 3-N-Pyrrolidino-4-phenoxy-5-sulfamylbenzoic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 55837-27-9

Trade Name	Manufacturer	Country	Year Introduced
Arelix	Hoechst	Italy	1980
Arelix	Cassella-Riedel	W. Germany	1982
Tauliz	Hoechst	W. Germany	–

Raw Materials

3-N-Succinimido-4-phenoxy-5-sulfamylbenzoic acid methyl ester
Sodium borohydride
Sodium hydroxide

Manufacturing Process

12.3 g (0.03 mol) of 3-N-succinimido-4-phenoxy-5-sulfamylbenzoic acid methyl ester are dissolved or suspended in 100 ml of absolute diglyme. 9 g of boron trifluoride etherate are added direct to this mixture and a solution of 2.4 g (~0.063 mol) of $NaBH_4$ in 80 ml of diglyme is then added dropwise at room temperature with stirring. As the reaction proceeds exothermically, it is necessary to cool with ice water. The reaction is normally complete after the dropwise addition and a short period of stirring thereafter.

The excess reducing agent is then decomposed by means of a little water (foaming), the solution is filtered and about 300 ml of water are added while stirring. The 3-N-pyrrolidino-4-phenoxy-5-sulfamylbenzoic acid methyl ester which has crystallized out is recrystallized from methanol in the form of colorless crystals, melting point 191°C to 192°C.

61 g of 3-N-pyrrolidino-4-phenoxy-5-sulfamylbenzoic acid methyl ester are suspended in 350 ml of 1 N NaOH and the suspension is heated for one hour on the waterbath. 3-N-pyrrolidino-4-phenoxy-5-sulfamylbenzoic acid is precipitated from the clear solution by means of 2 N HCl while stirring well. The almost pure crude product can be recrystallized from methanol/water in the form of light yellow platelets, melting point 225°C to 227°C, with decomposition.

References

Merck Index 7366
DFU 2 (6) 393 (1977)
OCDS Vol. 3 p. 58 (1984)
DOT 18 (6) 274 (1982) & (10) 555 (1982)
I.N. p. 782
Bormann, D., Merkel, W. and Muschaweck, R.; U.S. Patents 4,010,273; March 1, 1977; 4,093,735; June 6, 1978; 4,111,953; September 5, 1978; 4,118,397; October 3, 1978; and 4,161,531; July 17, 1979; all assigned to Hoechst AG

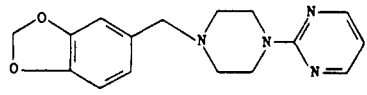
PIRIBEDIL

Therapeutic Function: Vasodilator (peripheral)

Chemical Name: 2-[4-(1,3-Benzodioxol-5-ylmethyl)-1-piperazinyl] pyrimidine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 3605-01-4

Trade Name	Manufacturer	Country	Year Introduced
Trivastal	Eutherapie	France	1969
Trivastan	Servier	Italy	1975
Trivastal	Pharmacodex	W. Germany	1975
Circularina	Searle	–	–

Raw Materials

2-Chloropyrimidine
1-(3':4'-Methylenedioxybenzyl)-piperazine

Manufacturing Process

To a solution of 21 g of 1-(3':4'-methylenedioxybenzyl)-piperazine in solution in 300 cc of anhydrous xylene there were added 28 g of anhydrous potassium carbonate and then 11.3 g of 2-chloropyrimidine. The suspension was then heated for 9 hours at boiling point (130°C). After this time, the mixture was cooled and extracted several times with 10% hydrochloric acid. The acid solution obtained was washed with ether and then rendered alkaline with potassium carbonate; the oily product which was separated was extracted with chloroform and this, after drying with potassium carbonate and evaporation, gave an oily residue weighing 20 g. By dissolution in boiling ethanol and crystallization, 15 g of crystals melting at 96°C were recovered.

References

Merck Index 7368
Kleeman & Engel p. 739
DOT (As ET-495) 6 (1) 29 (1970) & 10 (9) 324, 340 (1974)
I.N. p. 783
Regnier, G., Canevari, R. and Laubie, M.; U.S. Patent 3,299,067; January 17, 1967; assigned to Science Union Et Cie, Societe Francaise De Recherche Medicale (France)

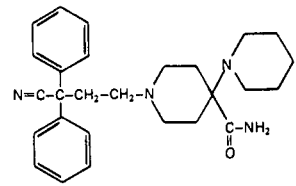
PIRITRAMIDE

Therapeutic Function: Analgesic

Chemical Name: 1-(3,3-Diphenyl-3-cyanopropyl)-4-piperidino-4-piperidinecarboxamide

Common Name: Pirinitramide

Structural Formula:



Chemical Abstracts Registry No.: 302-41-0

Trade Name	Manufacturer	Country	Year Introduced
Dipidolor	Janssen	W. Germany	1969
Dipidolor	Janssen	U.K.	1972
Piridolan	Leo	Sweden	—

Raw Materials

3,3-Diphenyl-3-cyanopropyl bromide
4-Piperidino-4-piperidinecarboxamide

Manufacturing Process

A mixture of 84 parts of 3,3-diphenyl-3-cyanopropyl bromide, 41 parts of 4-piperidino-4-piperidinecarboxamide, 64 parts of sodium carbonate, a small amount of potassium iodide and 1,200 parts of anhydrous toluene was stirred, and heated under reflux for 48 hours. At the end of this time the reaction mixture was allowed to cool to room temperature, and 500 parts of water were added. The resultant precipitate was removed by filtration, and triturated with diisopropyl ether. The crystalline material thus obtained was removed by filtration, and recrystallized from 320 parts of acetone, to give 1-(3,3-diphenyl-3-cyanopropyl)-4-piperidino-4-piperidinecarboxamide, melting at about 149°C to 150°C.

References

Merck Index 7373
Kleeman & Engel p. 739
OCDS Vol. 1 p. 308 (1977)
DOT 5 (3) 107 (1969)
I.N. p. 783
N.V. Research Laboratorium Dr. C. Janssen; British Patent 915,835; January 16, 1963
Janssen, P.A.J.; U.S. Patent 3,080,360; March 5, 1963; assigned to Research Laboratorium Dr. C. Janssen N.V.

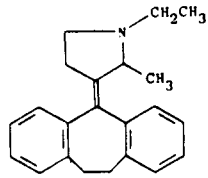
PIROHEPTINE

Therapeutic Function: Antiparkinsonian

Chemical Name: 3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-ethyl-2-methylpyrrolidine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 16378-21-5

Trade Name	Manufacturer	Country	Year Introduced
Trimol	Fujisawa	Japan	1974

Raw Materials

2-Methyl-3-(10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-ylidene)-1-pyrroline
Ethyl iodide
Sodium borohydride

Manufacturing Process

(1) To 3.8 g of 2-methyl-3-(10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-ylidene)-1-pyrroline, there were added 8 g of ethyl iodide. This mixture was placed into a closed vessel and heated at 80°C in a water-bath for one hour. After completing the reaction, the reaction mix-

ture was cooled and the unreacted ethyl iodide was distilled off to yield 5.5 g of 1-ethyl-2-methyl-3-(10,11-dihydro-5H-dibenzo[a,d] cycloheptene-5-ylidene)-1-pyrrolinium iodide in the form of yellow crystals. These crystals were recrystallized from a mixture of acetone and ether to yield yellow needles of the melting point 223°C.

(2) 1-Ethyl-2-methyl-3-(10,11)-dihydro-5H-dibenzo[a,d] cycloheptene-5-ylidene)-1-pyrrolinium iodide (4.7 g) was dissolved in 7 cc of methanol. To this solution there were added 1.4 g of sodium boron hydride within about 80 minutes with stirring and stirring of the solution was continued for two hours to complete the reaction. The reaction mixture was acidified with 10% aqueous hydrochloric acid solution and then the methanol was distilled off. The residual solution was alkalized with 20% aqueous sodium hydroxide solution and extracted with ether. The ether layer was dried over magnesium sulfate and the ether was distilled off. The resulting residue was further distilled under reduced pressure to yield 2.0 g of 1-ethyl-2-methyl-3-(10,11)-dihydro-5H-dibenzo[a,d]cycloheptene-5-ylidene)pyrrolidine (boiling point 167°C/4 mm Hg.).

References

Merck Index 7375
DOT 9 (6) 247 (1973) & 10 (9) 325 (1974)
I.N. p. 784
Deguchi, Y., Nojima, H. and Kato, N.; U.S. Patent 3,454,495; July 8, 1969; assigned to Fujisawa Pharmaceutical Co., Ltd. (Japan)

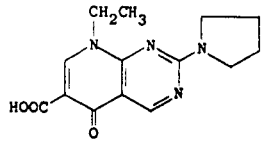
PIROMIDIC ACID

Therapeutic Function: Antibacterial (urinary)

Chemical Name: 8-Ethyl-5,8-dihydro-5-oxo-2-(1-pyrrolidinyl)pyrido[2,3-d] pyrimidine-6-carboxylic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 19562-30-2

Trade Name	Manufacturer	Country	Year Introduced
Panacid	Dainippon	Japan	1972
Pirodal	I.S.F.	Italy	1977
Bactramyl	Carrion	France	1978
Septural	Gruenenthal	W. Germany	1978
Adelir	Teikoku	Japan	–
Coltix	Gerardo Ramon	Argentina	–
Panerco	Erco	Denmark	–
Purim	Mayoly-Spindler	France	–
Reelon	Sanken	Japan	–
Uriclor	Almirall	Spain	–
Urisept	Srbolek	Yugoslavia	–
Zaomeal	Isei	Japan	–

Raw Materials

6-Amino-2-methylthiopyrimidine
Ethoxymethylenemalonic acid diethyl ester
Sodium hydroxide
Diethyl sulfate
Pyrrolidine

Manufacturing Process

150 mg of 6-carboxy-5,8-dihydro-8-ethyl-2-methylthio-5-oxopyrido[2,3-d] pyrimidine was added to 30 ml of absolute ethanol containing 1.1 g of dissolved pyrrolidine, and the mixture was reacted for 5 hours at 95°C in a sealed tube. The solvent was removed by distillation, and the residue was recrystallized from methanol-chloroform. There were obtained 111 mg of 6-carboxy-5,8-dihydro-8-ethyl-5-oxo-2-pyrrolidino-pyrido[2,3-d] pyrimidine having a MP of 314° to 316°C.

The starting material is produced by reacting 6-amino-2-methylthiopyrimidine with ethoxymethylenemalonic acid diethyl ester. That intermediate is thermally treated in diphenyl ether to give 6-ethoxycarbonyl-2-methylthio-5-oxo-5,8-dihydro-pyrido[2,3-d] pyrimidine. The ethoxy group is hydrolyzed off with sodium hydroxide and one nitrogen is ethylated with diethyl sulfate to give the starting material. These are the same initial steps as used in the pipemidic acid syntheses earlier in this volume.

References

Merck Index 7377
Kleeman & Engel p. 739
OCDS Vol. 2 p. 470 (1980)
DOT 7 (5) 188 (1971)
I.N. p. 36
Dainippon Pharmaceutical Co. Ltd., Japan; British Patent 1,129,358; October 2, 1968
Minami, S., Shono, T., Shmmizu, M. and Takase, Y.; U.S. Patent 3,673,184; June 27, 1972; assigned to Dainippon Pharmaceutical Co. Ltd.
Pesson, M.E. and Geiger, S.W.; U.S. Patent 4,125,720; November 14, 1978; assigned to Laboratoire Roger Bellon

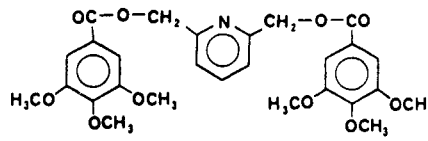
PIROZADIL

Therapeutic Function: Hypolipidemic; platelet aggregation inhibitor

Chemical Name: 2,6-Pyridinemethanol-bis(3,4,5-trimethoxybenzoate)

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 54110-25-7

Trade Name	Manufacturer	Country	Year Introduced
Pemix	Prodes	Spain	1982

Raw Materials

3,4,5-Trimethoxybenzoic acid
Thionyl chloride
Pyridine-2,6-dimethanol

Manufacturing Process

15 kg (70.7 mols) of 3,4,5-trimethoxybenzoic acid and 65 liters of benzene were introduced into a reactor, to which mixture was added 27.4 liters of thionyl chloride. The mass was heated to 56°C to 70°C during a period of 5 hours. The excess of benzene and thionyl chloride was distilled under vacuum. The residue was kept under vacuum at 120°C to 123°C for 1 hour, to obtain a hard crystalline solid.

A solution comprising 3.24 kg (23.3 mols) of pyridine-2,6-dimethanol in 35 liters of pure pyridine was added to the residue and the mass was heated to 80°C for 2½ hours. The reaction mass became brown in color. The chlorhydrate of pyridine so formed was cooled and crystallized. The resulting reaction mass was then poured into water. The precipitate obtained was filtered, repeatedly rinsed with water, and dissolved in 400 liters of methanol. The resulting solution was filtered with activated charcoal. From this filtration 50 liters of methanol were distilled at normal pressure and then crystallized. 8.35 kg (15.8 mols) of pyridine-2,6-dimethanol trimethoxybenzoate were obtained, which represented a yield of 68%.

The product was a white crystalline solid which melted at 119°C to 126°C. Recrystallization in methanolone gave a product which melted at 126°C to 127°C.

References

Merck Index 7379
DFU 6 (5) 290 (1981)
DOT 18, Suppl. 1
Instituto International Terapeutico; British Patent 1,401,608; July 30, 1975

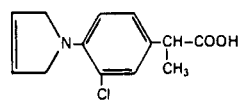
PIRPROFEN

Therapeutic Function: Antiinflammatory

Chemical Name: α-(3-Chloro-4-pyrrolinophenyl)-propionic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 31793-07-4

Trade Name	Manufacturer	Country	Year Introduced
Rengasil	Ciba-Geigy	France	1981
Rengasil	Ciba-Geigy	Switz.	1981

Raw Materials

Ethyl α-(3-chloro-4-aminophenyl)-propionate hydrochloride
1,4-Dibromo-2-butene

Manufacturing Process

To the mixture of 85.5 g ethyl α-(3-chloro-4-aminophenyl)-propionate hydrochloride, 142 g sodium carbonate and 600 ml dimethyl formamide, 107 g 1,4-dibromo-2-butene are added dropwise while stirring and the whole is refluxed for 5 hours and allowed to stand overnight at room temperature. The mixture is filtered, the filtrate evaporated in vacuo, the residue is triturated with hexane, the mixture filtered, the residue washed with petroleum ether and the filtrate evaporated. The residue is combined with 280 ml 25% aqueous sodium hydroxide and the mixture refluxed for 8 hours. After cooling, it is diluted with water, washed with diethyl ether, the pH adjusted to 5 to 5.2 with hydrochloric acid and extracted with diethyl ether. The extract is dried, filtered, evaporated and the residue crystallized from benzene-hexane, to yield the α-(3-chloro-4-pyrrolinophenyl)-propionic acid melting at 94°C to 96°C.

References

Merck Index 7380
DFU 1 (1) 23 (1976)
OCDS Vol. 2 p. 69 (1980)
DOT 11 (3) 103 (1975)
I.N. p. 784
Carney, R.W.J. and De Stevens, G.; U.S. Patent 3,641,040; February 8, 1972; assigned to Ciba Geigy Corp.

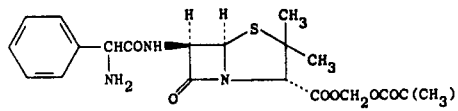
PIVAMPICILLIN

Therapeutic Function: Antibacterial

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

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 33817-20-8; 26309-95-5 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Maxifen	Sharp & Dohme	W. Germany	1972
Berocillin	Boehr. Ingel.	W. Germany	1972
Pondocillina	Sigma Tau	Italy	1972
Pivatil	MSD	Italy	1972
Pivatil	Chibret	France	1973
Pondocillin	Burgess	U.K.	1980
Acerum	Jeba	Spain	—
Bensamin	Turro	Spain	—
Brotacilina	Escaned	Spain	—
Co-Pivam	Sanchez Covisa	Spain	—
Crisbiotic	Crisol	Spain	—
Dancilin	Hemofarm	Yugoslavia	—
Devonian	Perga	Spain	—
Diancina	Septa	Spain	—

Trade Name	Manufacturer	Country	Year Introduced
Inacilin	Inibsa	Spain	–
Isvitrol	Therapia	Spain	–
Kesmicina	Kessler	Spain	–
Lancabiotic	Lanzas	Spain	–
Novopivam	Osiris	Argentina	–
Oxidina	Sanitas	Argentina	–
Penimenal	Alalan	Spain	–
Pibena	Jebena	Spain	–
Piva	Efesal	Spain	–
Pivabiot	Galepharma Iberica	Spain	–
Pivadilon	De La Cruz	Spain	–
Pivambol	B.O.I.	Spain	–
Pivamkey	Pereira	Spain	–
Pivapen	Juste	Spain	–
Pivastol	Graino	Spain	–
Piviotic	Miquel	Spain	–
Sanguicillin	Zdravlje	Yugoslavia	–
Tam-Cilin	Quimia	Spain	–
Tryco	Durban	Spain	–
Vampi-Framan	Oftalmiso	Spain	–

Raw Materials

Potassium D(−)-α-azidobenzylpenicillinate
Chloromethyl pivalate
Hydrogen

Manufacturing Process

(A) Pivaloyloxymethyl D(−)-α-azidobenzylpenicillinate: To a suspension of potassium D(−)-α-azidobenzylpenicillinate (4.14 g) and potassium dicarbonate (1.5 g) in acetone (100 ml) and 10% aqueous sodium iodide (2 ml), chloromethyl pivalate (2.7 ml) was added and the mixture refluxed for 2 hours. After cooling, the suspension was filtered and the filtrate evaporated to dryness in vacuo. The remaining residue was washed repeatedly by decantation with petroleum ether to remove unreacted chloromethyl pivalate. The oily residue was taken up in ethyl acetate (100 ml), and the resulting solution washed with aqueous sodium bicarbonate and water, dried and evaporated in vacuo to yield the desired compound as a yellowish gum, which crystallized from ether, melting point 114°C to 115°C.

(B) Pivaloyloxymethyl D(−)-α-aminobenzylpenicillinate, hydrochloride: To a solution of pivaloyloxymethyl D(−)-α-azidobenzylpenicillinate (prepared as described above) in ethyl acetate (75 ml) a 0.2 M phosphate buffer (pH 2.2) (75 ml) and 10% palladium on carbon catalyst (4 g) were added, and the mixture was shaken in a hydrogen atmosphere for 2 hours at room temperature. The catalyst was filtered off, washed with ethyl acetate (25 ml) and phosphate buffer (25 ml), and the phases of the filtrate were separated. The aqueous phase was washed with ether, neutralized (pH 6.5 to 7.0) with aqueous sodium bicarbonate, and extracted with ethyl acetate (2 X 75 ml). To the combined extracts, water (75 ml) was added, and the pH adjusted to 2.5 with 1 N hydrochloric acid. The aqueous layer was separated, the organic phase extracted with water (25 ml), and the combined extracts were washed with ether, and freeze-dried. The desired compound was obtained as a colorless, amorphous powder.

The purity of the compound was determined iodometrically to be 91%. A crystalline hydrochloride was obtained from isopropanol with a melting point of 155°C to 156°C (dec.).

References

Merck Index 7387
Kleeman & Engel p. 741

OCDS Vol. 1 p. 414 (1977)
DOT 8 (4) 148 (1972) & 19 (6) 331 (1983)
I.N. p. 785
REM p. 1201
Frederiksen, E.K. and Godtfredsen, W.O.; U.S. Patent 3,660,575; May 2, 1972; assigned to Lovens Kemiske Fabrik Produktionsaktieselskab (Denmark)
Binderup, E.T., Petersen, H.J. and Liisberg, S.; U.S. Patent 3,956,279; May 11, 1976; assigned to Leo Pharmaceutical Products Ltd. (Denmark)

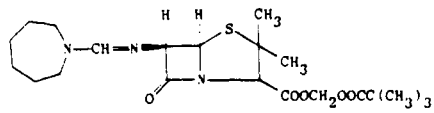
PIVMECILLINAM

Therapeutic Function: Antibacterial

Chemical Name: 6-[[(Hexahydro-1H-azepin-1-yl)methylene] amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylic acid (2,2-dimethyl-1-oxopropoxy)methyl ester

Common Name: Amdinocillin pivoxil

Structural Formula:



Chemical Abstracts Registry No.: 32886-97-8

Trade Name	Manufacturer	Country	Year Introduced
Selexid	Leo	U.K.	1977
Melysin	Takeda	Japan	1979
Selexid	Leo	Switz.	1980
Negaxid	Sigma Tau	Italy	1980

Raw Materials

N-Formylhexamethylene imine
Oxalyl chloride
Pivaloyloxymethyl 6-aminopenicillinate tosylate
Sodium bicarbonate

Manufacturing Process

The starting material N-formylhexamethyleneimine was prepared from hexamethyleneimine and chloral.

12.7 g of N-formylhexamethyleneimine were dissolved in 250 ml of dry ether. While stirring and cooling, 8.5 ml of oxalyl chloride in 50 ml of dry ether were added dropwise, whereafter the mixture was stirred overnight at room temperature. The precipitated amide chloride was filtered off and washed with dry ether, and was placed in an exsiccator.

27.5 g of pivaloyloxymethyl 6-aminopenicillinate tosylate was suspended in 1,500 ml of ethyl acetate with continuous stirring and cooling in an ice bath and 950 ml of ice-cold aqueous sodium bicarbonate (2%) were added. The ethyl acetate layer was separated and was shaken with 750 ml of ice-water containing 25 ml of aqueous sodium bicarbonate (2%), whereafter it was dried over magnesium sulfate at 0°C. After filtration, the solution was evaporated to dry-

ness *in vacuo*. The residue was dissolved in a solution of 15.5 ml of dry triethylamine in 75 ml of dry alcohol-free chloroform. To this solution, 10 g of the above prepared amide chloride dissolved in 75 ml of dry alcohol-free chloroform were added dropwise at a temperature of about -20°C. After standing for half an hour at -20°C, the temperature was raised to 0°C within 15 minutes and the solution was evaporated to dryness *in vacuo*. The residue was stirred with 750 ml of ether. Undissolved triethylamine hydrochloride was filtered off, and the filtrate was again evaporated to dryness *in vacuo*. The residue was reprecipitated from acetone (200 ml) – water (150 ml). After recrystallization from cyclohexane an analytically pure product was obtained with a melting point of 118.5°C to 119.5°C.

References

Merck Index 391
Kleeman & Engel p. 741
DOT 19 (6) 331 (1983)
I.N. p. 786
REM p. 1201
Lund, F.J.; U.S. Patent 3,957,764; May 18, 1976; assigned to Lovens Kemiske Fabrik Produktionsartieselskab (Denmark)

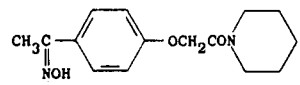
PIXIFENIDE

Therapeutic Function: Antiinflammatory

Chemical Name: 1-[[4-[1-(Hydroxyimino)ethyl] phenoxy] acetyl] piperidine

Common Name: N-(p-1-Nitrosoethyl)phenoxyacetylpiperidine, pifoxime

Structural Formula:



Chemical Abstracts Registry No.: 31224-92-7

Trade Name	Manufacturer	Country	Year Introduced
Flamanil	Salvoxyl/Wander	France	1975

Raw Materials

p-Hydroxyacetophenone
Methanol
Hydroxylamine
Chloroacetic acid
Piperidine

Manufacturing Process

(A) Preparation of p-Acetylphenoxyacetic Acid: p-Hydroxy-acetophenone is treated with chloroacetic acid in aqueous solution in the presence of sodium hydroxide. The desired acid is then isolated from its sodium salt in a total yield of 80 to 82%, excess of p-hydroxy-acetophenone having been extracted with methylene chloride.

(B) Preparation of Methyl p-Acetylphenoxy-Acetate: A mixture of 80 g of the acid obtained in (A) and 200 ml of methyl alcohol in 600 ml of dichloromethane is refluxed in the presence of sulfuric acid. The desired ester is isolated in accordance with a method known per se, and recrystallized. When the refluxing period is 12 hours, the ester is obtained with a yield of 70%. When the refluxing period is 18 hours, the yield for this ester is 85%.

(C) Preparation of N-(p-Acetylphenoxy-Acetyl)-Piperidine: The ester from (B) is refluxed for 8 hours with 2.5 mols of thoroughly dried piperidine. Then 1 volume of water is added and the product is left to crystallize in the cold. The desired amide is obtained in an 80% yield.

(D) Preparation of N-(p-[1-Isonitrosoethyl]-Phenoxy-Acetyl)-Piperidine: The amide from (C) is refluxed for 5 hours with technical (98%) hydroxylamine and alcohol denatured with methanol. The desired product is obtained in a 75% yield.

In semiindustrial synthesis, to achieve better yields, it is possible to omit (A), by directly preparing the ester (B) by reaction of p-hydroxy acetophenone on ethyl 2-bromoacetate in the presence of potassium carbonate in butanone. The yield of ester is 90%, and elimination of excess of p-hydroxyacetophenone is effected by washing with sodium hydroxide.

References

Merck Index 7300
Kleeman & Engel p. 725
DOT 12 (2) 50 (1976)
Mieville, A.; U.S. Patent 3,907,792; September 23, 1975

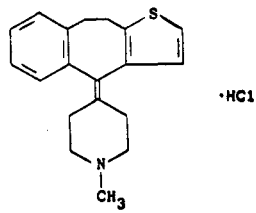
PIZOTYLINE HYDROCHLORIDE

Therapeutic Function: Migraine therapy

Chemical Name: 4-(9,10-Dihydro-4H-benzo[4,5]cyclohepta[1,2-b]thien-4-ylidene-1-methylpiperidine hydrochloride

Common Name: Pizotifen

Structural Formula:



Chemical Abstracts Registry No.: 15574-96-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Sandomigran	Sandoz	Italy	1972
Sandomigran	Sandoz	W. Germany	1974
Sanomigran	Wander	U.K.	1975
Mosegor	Wander	W. Germany	1976
Sanmigran	Salvoxy/Wander	France	1976
Polomigran	Polfa	Poland	–

Raw Materials

Thienyl-(2)-acetic acid
Phosphorus
1-Methyl-4-chloropiperidine
Hydrogen chloride
Phthalic anhydride
Phosphorus pentoxide
Magnesium

Manufacturing Process

(A) Preparation of Thenylidene-(2)-Phthalide: 24.2 g of thienyl-(2)-acetic acid, 52.0 g of phthalic acid anhydride, 4.0 g of anhydrous sodium acetate and 125 ml of 1-methylpyrrolidone-(2) are heated while stirring in an open flask for 3 hours to 205° to 208°C, while nitrogen is passed through. It is then cooled and the viscous reaction mixture poured into 1 liter of water. The precipitated substance is filtered off, washed with water and then dissolved in 200 ml of chloroform. After filtering off some undissolved substance, shaking is effected twice with 100 ml of 2 N sodium carbonate solution and then with water, drying is then carried out over sodium sulfate and the volume is reduced by evaporation. The crude phthalide is repeatedly recrystallized from ethanol, while treating with animal charcoal. It melts at 114° to 115°C.

(B) Preparation of o-[2-Thienyl-(2')-Ethyl] Benzoic Acid: 24.0 g of thenylidene-(2)-phthalide, 8.8 g of red pulverized phosphorus, 240 ml of hydrochloric acid (d = 1.7) and 240 ml of glacial acetic acid are heated to boiling under nitrogen and while stirring vigorously. 70 ml toluen are then added and 6.0 g of red phosphorus added in small portions over a period of 1 hour. It is then poured into 3 liters of ice water, stirred with 300 ml of chloroform and the phosphorus removed by filtration.

The chloroform phase is then removed, the aqueous phase extracted twice more with 200 ml of chloroform and the united extracts shaken out 4 times, each time with 200 ml of 2 N sodium hydroxide solution. The alkaline solution is then rendered acid to Congo red reagent, using hydrochloric acid and extracted 3 times with chloroform. After drying over sodium sulfate and evaporating the solvent, the residue is chromatographed on aluminum oxide (Activity Stage V). The substance eluted with benzene and benzene/chloroform (1:1) is recrystallized from chloroform/hexane (1:1); MP 107° to 109°C.

(C) Preparation of 9,10-Dihydro-4H-Benzo[4,5] Cyclohepta[1,2-b] Thiophen-(4)-One: 200 ml of 85% phosphoric acid and 112 g of phosphorus pentoxide are heated to 135°C. 7.0 g of o-[2-thienyl-(2')-ethyl] benzoic acid are then introduced while stirring thoroughly over a period of 30 min. Stirring is then continued for another hour at 135°C and the reaction mixture is then stirred into 1 liter of ice water. Extraction is then effected 3 times, using 250 ml ether portions, the ethereal extract is washed with 2 N sodium carbonate solution, dried over sodium sulfate and reduced in volume by evaporation. The residue is boiled up with 55 ml of ethanol, the solution freed of resin by decanting and then stirred at room temperature for 6 hours with animal charcoal. It is then filtered off, reduced in volume in a vacuum and the residue distilled. BP 120° to 124°C/0.005 mm, $n_D^{24.5}$ = 1.6559.

(D) Preparation of 4-[1'-Methyl-Piperidyl-(4')]-9,10-Dihydro-4H-Benzo[4,5] Cyclohepta[1,2-b] Thiophen-(4)-ol: 0.94 g of magnesium filings which have been activated with iodine are covered with a layer of absolute tetrahydrofuran and etched with a few drops of ethylene bromide. A solution of 5.0 g of 1-methyl-4-chloropiperidine in 5 ml of tetrahydrofuran is then added dropwise and boiling then effected for a further hour under reflux. After cooling to room temperature, the solution of 4.5 g of 9,10-dihydro-4H-benzo[4,5] cyclohepta[1,2-b] thiophen-(4)-one in 5 ml of tetrahydrofuran is added dropwise.

Stirring is carried out first for 3 hours at room temperature and then for 2 hours at boiling temperature, it is then cooled and poured into 300 ml of ice-cold 20% ammonium chloride solution. It is then shaken out with methylene chloride, the methylene chloride solution washed with water and shaken 3 times with 30 ml portions of aqueous 2 N tartaric acid solution. The tartaric acid extract is rendered alkaline while cooling thoroughly and then extracted twice with methylene chloride. After washing with water, drying over potassium carbonate and reducing in volume by evaporation, the residue is recrystallized from ethanol. MP 197° to 199°C.

(E) Preparation of 4-[1'-Methyl-Piperidylidene-(4')]-9,10-Dihydro-4H-Benzo[4,5] Cyclohepta[1,2-b] Thiophene Hydrochloride: 2 g of 4-[1'-methyl-piperidyl-(4')]-9,10-dihydro-4H-benzo[4,5] cyclohepta[1,2-b] thiophen-(4)-ol, 60 ml of glacial acetic acid and 20 ml of

concentrated hydrochloric acid are boiled for 30 minutes under reflux. After evaporating in a vacuum, the residue is triturated with 3 ml of acetone, the precipitated hydrochloride is then filtered off and it is recrystallized from isopropanol/ether. MP 261° to 263°C (decomposition).

References

Merck Index 7389
Kleeman & Engel p. 742
DOT 9 (6) 221 (1973)
I.N. p. 786
Jucker, E., Ebnother, A., Stoll, A., Bastian, J.-M. and Rissi, E.; U.S. Patent 3,272,826; September 13, 1966; assigned to Sandoz Ltd., Switzerland

POLOXALKOL

Therapeutic Function: Pharmaceutic aid (surfactant)

Chemical Name: Poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene)

Common Name: Poloxalene

Structural Formula: $HO(CH_2CH_2O)_a[CH(CH_3)CH_2O]_b(CH_2CH_2O)_cH$

average values for a, b, c are:
a = 12; b = 34; c = 12

Chemical Abstracts Registry No.: 9003-11-6

Trade Name	Manufacturer	Country	Year Introduced
Polykol	Upjohn	U.S.	1958
Therabloat	Norden	U.S.	—

Raw Materials

Propylene glycol
Propylene oxide

Manufacturing Process

(A) In a 1-liter 3-necked round bottom flask equipped with a mechanical stirrer, reflux condenser, thermometer and propylene oxide feed inlet, there were placed 57 g (0.75 mol) of propylene glycol and 7.5 g of anhydrous sodium hydroxide. The flask was purged with nitrogen to remove air and heated to 120°C with stirring and until the sodium hydroxide was dissolved. Then sufficient propylene oxide was introduced into the mixture as fast as it would react until the product possessed a calculated molecular weight of 2,380. The product was cooled under nitrogen, the NaOH catalyst neutralized with sulfuric acid and the product filtered. The final product was a water-insoluble polyoxypropylene glycol having an average molecular weight of 1,620 as determined by hydroxyl number or acetylation analytical test procedures.

(B) The foregoing polyoxypropylene glycol having an average 1,620 molecular weight was placed in the same apparatus as described in procedure (A), in the amount of 500 g (0.308 mol), to which there was added 5 g of anhydrous sodium hydroxide. 105 g of ethylene oxide was added at an average temperature of 120°C, using the same technique

as employed in (A). The amount of added ethylene oxide corresponded to 17.4% of the total weight of the polyoxypropylene glycol base plus the weight of added ethylene oxide.

References

Merck Index 7431
I.N. p. 789
REM p. 1320
Lundsted, L.G.; U.S. Patent 2,674,619; April 6, 1954; assigned to Wyandotte Chemicals Corporation

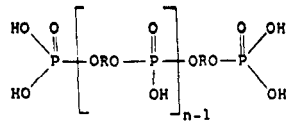
POLYESTRADIOL PHOSPHATE

Therapeutic Function: Estrogen

Chemical Name: Estradiol phosphate polymer

Common Name: Polymeric ester of phosphoric acid and estradiol

Structural Formula:



–ORO– is the estradiol radical and *n* is about 80

Chemical Abstracts Registry No.: 28014-46-2

Trade Name	Manufacturer	Country	Year Introduced
Estradurin	Ayerst	U.S.	1957
Estradurin	Abello	Spain	—
Estradurin	Leo	Sweden	—

Raw Materials

Estradiol
Phosphorus oxychloride

Manufacturing Process

3 g of estradiol was dissolved in 75 ml of anhydrous pyridine. The solution was cooled to -10°C, whereupon a solution of 1.1 ml of phosphorus oxychloride in 10 ml of anhydrous pyridine was added with agitation. After the addition, which required 7 minutes, the reaction mixture was kept at -10°C for a further period of 3 hours, and then it was left standing at room temperature for 15 hours. A clear solution thus resulted, to which finely crushed ice was then added. The resulting solution was evaporated in vacuum to dryness. After drying in a vacuum desiccator, 3.8 g of a white powder was obtained. This powder was suspended in 2 ml of pyridine, and 25 ml of 0.5 N sodium hydroxide was added, whereupon a solution was obtained which was then diluted with water to 100 ml.

The solution was then dialyzed through a cellophane membrane against 4 liters of water for 10 hours, with stirring. The dialysis was repeated 2 additional times, with fresh amounts of water. To the dialyzed solution there was added 2 ml of 1 N hydrochloric acid, whereupon polyestradiol phosphate was precipitated as a white bulky precipitate. This was centrifuged off and washed repeatedly with 0.1 N hydrochloric acid. Thereafter it was dried in a vacuum desiccator. The yield was 3 g of polyestradiol phosphate. The analysis shows 0.65% of water, 1.35% of pyridine and 9.3% of phosphorus (calculated on a dry sample).

References

Merck Index 7439
PDR p. 618
I.N. p. 790
REM p. 987

Diczfalusy, E.R., Fernö, O.B., Fex, H.J., Högberg, K.B. and Linderot, T.O.E.; U.S. Patent 2,928,849; March 15, 1960; assigned to Leo AB, Sweden

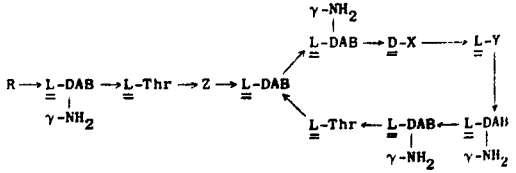
POLYMYXIN

Therapeutic Function: Antibacterial

Chemical Name: Complex antibiotic; see structural formula

Common Name: –

Structural Formula:



DAB = α,γ-diaminobutyric acid
R = alkanoyl
X,Y,Z = amino acids

Chemical Abstracts Registry No.: 1406-11-7

Trade Name	Manufacturer	Country	Year Introduced
Aerosporin	Burroughs Wellcome	U.S.	1951
Cortisporin	Burroughs Wellcome	U.S.	–
Mastimyxin	Chassot	Switz.	–
Neo-Polycin	Merrell Dow	U.S.	–
Neosporin	Burroughs Wellcome	U.S.	–
Octicair	Pharmafair	U.S.	–
Ophthocort	Parke-Davis	U.S.	–
Otobiotic	Schering	U.S.	–
Otocort	Lemmon	U.S.	–
Polyfax	Pitman-Moore	U.S.	–
Polysporin	Burroughs Wellcome	U.S.	–
Pyocidin	Berlex	U.S.	–
Topisporin	Pharmafair	U.S.	–
Tri-Thalmic	Schein	U.S.	–

Raw Materials

Bacterium *Bacillus polymyxa*
Nutrient medium
Corn meal

Manufacturing Process

As described in U.S. Patent 2,595,605, in a pilot plant tank 225 liters of a medium containing the following ingredients was prepared: 2% ammonium sulfate, 0.2% potassium di-

hydrogen phosphate, 0.05% magnesium sulfate heptahydrate, 0.005% sodium chloride, 0.001% ferrous sulfate heptahydrate, 0.5% yeast extract, 1% dextrose, 1% calcium carbonate and 3% corn meal. The fermentation medium was adjusted to pH 7.3 to 7.4. It was then sterilized for 30 minutes at 110°C. After sterilization the pH was about 7. To the medium was added 225 ml of mineral oil.

The fermentation medium was inoculated with *Bacillus polymyxa* prepared as follows: A culture of *Bacillus polymyxa* in a tube with Trypticase soybean broth was incubated overnight at 25°C. 5 ml of this culture was transferred to 100 ml of the tank medium in a 500 ml Erlenmeyer flask which was incubated for 48 hours at room temperature. This 100 ml culture served as inoculum for one tank. During the course of fermentation the medium was aerated at the rate of 0.3 volume of air per volume of mash per minute. The temperature was maintained at about 27°C. Samples of mash were taken every 8 hours in order to determine pH and the presence of contaminants and spores. After 88 hours of fermentation the pH was about 6.3 and an assay using *Escherichia coli* showed the presence of 1,200 units of polymyxin per cubic centimeter. The polymyxin was extracted and purified by removing the mycelia, adsorbing the active principle on charcoal and eluting with acidic methanol.

Polymyxin is usually used as the sulfate.

References

Merck Index 7445
Kleeman & Engel p. 743
PDR pp. 671, 732, 738, 757, 888, 1034, 1232, 1380, 1415, 1429, 1606, 1645
DOT 8 (1) 21 (1972)
I.N. p. 790
REM p. 1202
Ainsworth, G.C. and Pope, C.G.; U.S. Patent 2,565,057; August 21, 1951; assigned to Burroughs Wellcome & Co. (U.S.A.) Incorporated
Petty, M.A.; U.S. Patent 2,595,605; May 6, 1952; assigned to American Cyanamid Company
Benedict, R.G. and Stodola, F.H.; U.S. Patent 2,771,397; November 20, 1956; assigned to the U.S. Secretary of Agriculture

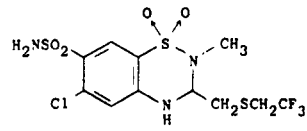
POLYTHIAZIDE

Therapeutic Function: Diuretic

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

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 346-18-9

Trade Name	Manufacturer	Country	Year Introduced
Renese	Pfizer	U.S.	1961

Trade Name	Manufacturer	Country	Year Introduced
Drenusil	Pfizer	W. Germany	1962
Renese	Pfizer	Italy	1962
Renese	Pfizer	France	1965
Envarese	Pfizer	France	–
Minizide	Pfizer	U.S.	–
Nephril	Pfizer	U.K.	–
Polyregulon	Yamanouchi	Japan	–
Toleran	Medica	Finland	–

Raw Materials

Mercaptoacetaldehyde dimethylacetal
Sodium
Trifluoroethyl iodide
4-Amino-2-chloro-5-(methylsulfamyl)benzenesulfonamide

Manufacturing Process

(A) Preparation of Trifluoroethylthioacetaldehyde Dimethylacetal: To 4.6 g (0.2 mol) of metallic sodium dissolved in 75 ml of absolute methanol is rapidly added 24.4 g (0.2 mol) of mercaptoacetaldehyde dimethylacetal followed by dropwise addition of 42.0 g (0.2 mol) of trifluoroethyl iodide.

The resulting reddish mixture is refluxed on a steam bath for one hour. One half of the alcohol is removed by concentration and the remainder diluted with several volumes of water and extracted with ether. The combined ether extracts are dried over sodium sulfate, the ether then removed at reduced pressure and the residue distilled to about 30 g (BP 82°C/25 mm).

(B) Preparation of 4-Amino-2-Chloro-5-(Methylsulfamyl)Benzenesulfonamide: The 5-substituted-2,4-disulfamyl anilines may be prepared by procedures described in the literature, for example, the general procedures in *Monatsch. Chem.* vol. 48, p 87 (1927), which involves the treatment of a m-substituted aniline with from 10 to 20 parts by weight of chlorosulfonic acid followed by the gradual addition of from about 90 to 170 parts by weight of sodium chloride. The resultant mixture is heated at approximately 150°C for about 2 hours after which the reaction mixture is poured into water and the resultant 5-substituted aniline-2,4-disulfonyl chloride is filtered and is then treated with concentrated ammonium hydroxide or suitable amine by standard procedures to obtain the corresponding disulfonamide.

(C) Preparation of 2-Methyl-3-(2,2,2-Trifluoroethyl)Thiomethyl-6-Chloro-7-Sulfamyl-3,4-Dihydro-1,2,4-Benzothiadiazine-1,1-Dioxide: To 4.6 g (0.015 mol) of 4-amino-2-chloro-5-(methylsulfamyl)benzenesulfonamide in 30 ml of the dimethyl ether of ethylene glycol is added 4.08 g (0.02 mol) of 2,2,2-trifluoroethylmercaptoacetaldehyde dimethylacetal followed by 1 ml of ethyl acetate saturated with hydrogen chloride gas. The resulting solution is refluxed for 1.5 hours, cooled and then slowly added to cold water dropwise with stirring. The crude product is filtered, dried and recrystallized from isopropanol (3.2 g), MP 202° to 202.5°C. A second recrystallization from isopropanol raised the MP to 202° to 203°C.

References

Merck Index 7457
Kleeman & Engel p. 743
PDR pp. 1409, 1421
OCDS Vol. 1 p. 360 (1977)
I.N. p. 791
REM p. 940
McManus, J.M.; U.S. Patent 3,009,911; November 21, 1961; assigned to Chas. Pfizer & Co., Inc.