O

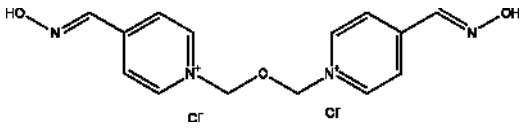
OBIDOXIME CHLORIDE

Therapeutic Function: Antidote

Chemical Name: Pyridinium, 1,1'-(oxybis(methylene))bis(4-(hydroxyimino)methyl)-, dichloride

Common Name: Obidoxime chloride

Structural Formula:



Chemical Abstracts Registry No.: 114-90-9; 7683-36-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Toksobidin	Polfa-Starogard	-	-
Toxogonin	Merck KGaA	-	-

Raw Materials

Pyridine-4-aldoxime
bis-Chloromethyl ether
α,α-Dichloro-dimethyl-ether

Manufacturing Process

2 Methods of producing of obidoxime chloride:

1. Into a boiling agitated solution of 2.44 g pyridine-4-aldoxime in 10 ml absolute ethanol is added dropwise during the course of 25 min a solution of 1.14 g bis-chloromethyl ether in 5 ml absolute ethanol. The reaction mixture is then refluxed for 35 min, and then agitated for 5 h at room temperature. The precipitate of bis-[4-hydroxyimino-methyl-pyridinium-(1)-methyl]-ether-

dichloride is thoroughly washed with absolute acetone. The yield is 3.5 g which is 98% of the theoretical, and the melting point is 229°C. If convenient, the mother liquor can be reused to make additional product.

2. 12.2 g (0.1 mole) pyridine-4-aldoxime are dissolved with heating in 125 ml chloroform. Within 25 min, 8.5 g (0.075 mole), α,α-dichlorodimethyl ether in 20 ml chloroform are dropped while stirring into the boiling solution. The reaction mixture is heated for another 35 min. After standing for several hours, the precipitate is filtered off, washed with absolute ethanol, acetone and ether and dried at 80°C. Yield: 17.0 g, 95% of the theoretical, and the melting point is 225°C (dec.).

References

Luttringhaus A. et al.; US Patent No. 3,137,702; June 16, 1964; Assigned: E. Merck, Darmstadt, Germany

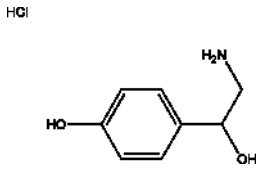
OCTOPAMINE HYDROCHLORIDE

Therapeutic Function: Hypertensive

Chemical Name: α-(Aminomethyl)-4-hydroxybenzene-methanol hydrochloride

Common Name: Norsympatol hydrochloride; Norsynephrine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 770-05-8; 104-14-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Norfen	Morishita	Japan	1975
Depot-Norphen	Byk Gulden	W. Germany	-
Norphen	Byk Gulden	W. Germany	-

Raw Materials

Phenol
Aminoacetonitrile
Hydrogen chloride
Hydrogen

Manufacturing Process

A solution of 33 grams of anhydrous aluminum chloride in 60 grams of nitrobenzene, to which a mixture of 14 grams of phenol and 9.3 grams of hydrochloride of amino-acetonitrile was added, had dry hydrochloric acid gas introduced into it for 3 hours, while stirring and cooling to keep the temperature between 20° and 30°C. The reaction mixture was then poured, with cooling, into 70 cc of water and the deposit obtained was sucked off, washed with acetone and dissolved in 300 cc of water. The solution thus prepared was decolorized with carbon, 50 grams of 30% sodium citrate solution was added to it, and then it was made slightly alkaline with ammonia. Thereupon hydroxy-4'-phenyl-1-amino-2-ethanone crystallized out in the form of leaflets. The yield was 7.7 grams.

The hydrochloride of this base, obtained by evaporation to dryness of a solution of the base in dilute hydrochloric acid and subsequent treatment of the residue with ethyl alcohol and acetone, had a chlorine content of 18.84%, (calculated, 18.90%).

This hydrochloride, on being dissolved in water and hydrogenated with hydrogen and a nickel catalyst, gave a good yield of hydrochloride of hydroxy-4'-phenyl-1-amino-2-ethanol melting, after crystallization from a mixture of ethyl alcohol and butanone-2, at from 177° to 179°C with decomposition.

References

Merck Index 6599
Kleeman and Engel p. 655
I.N. p. 699
Asscher, M.; US Patent 2,585,988; February 19, 1952

OCTREOTIDE ACETATE

Therapeutic Function: Antiulcer, Growth hormone inhibitor

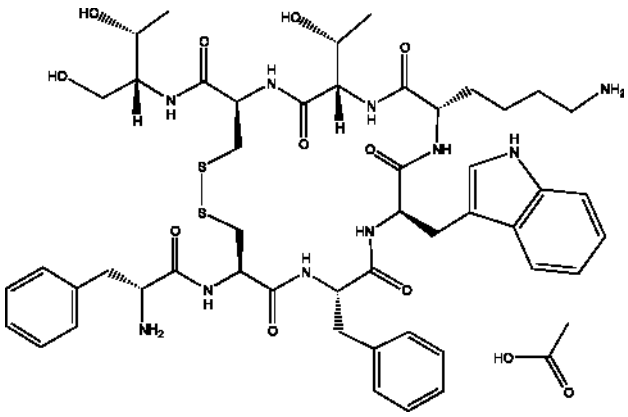
Chemical Name: L-Cysteinamide, D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-(2-hydroxy-1-(hydroxymethyl)propyl)-, cyclic(2-7)-disulfide, (R-(R*,R*))-, acetate (salt)

Common Name: Octreotide acetate

Chemical Abstracts Registry No.: 79517-01-4; 83150-76-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Sandostatin	Novartis Pharma AG	Switz.	-
Sandostatin LAR	Novartis Pharma AG	Switz.	-

Structural Formula:



Raw Materials

Threoninol
Piperidine
Tfifluoroethanol
Iodine
Threonino
Trifluoroacetic acid
N,N-Diisopropylethylamine
Diisopropylcarbodiimide
Hydroxybenzotriazole
Boc-D-Phe; Fmoc-Cys(Trt); Fmoc-Trp; Fmoc-Lys(Boc); Fmoc-Thr(tBu)

Manufacturing Process

Synthesis of octreotide and derivative thereof can be carried out by two methods. The first method is synthesized initially by fragment condensation solution phase procedures. The synthetic process of octreotide has been described by Bauer et al. (1). The second method is the synthese by solid-phase procedures. Edward et al. (2) isolated side chain protected octreotide with a total yield of 14% by cleaving the protected peptide from the resin with threoninol. Arano et al. (3) carried out another solid phase method for octreotide. and produced it in overall 31.8% yield based on the starting Fmoc-Thr(tBu)-ol-resin. The basic difference from the other procedures already described is that the introduction of the threoninol is carried out upon the protected peptidic structure (resin-free), which, when appropriately activated, leads quantitatively and without needing to make temporary protections upon the threoninol, to the protected precursor of octreotide, which in turn, with a simple acid treatment leads to octreotide with very high yields.

At first the Fmoc-Cys-Cl-trityl-resin was prepared. The incorporation of the Fmoc-Cys(trt)-OH residue upon 2Cl-Trt resin is accomplished with an excess of 1 eq. of Fmoc-Cys(Trt) and 2.5 eq. of N,N'-diisopropylethylamine (DIEA).

2.93 g (5.0 mmol) of Fmoc-Cys(Trt) are incorporated upon 5 g of resin (f = 1.28 mmol/g of resin, 6.4 mmol). The resin and the amino acid are weighed in separate containers and left to dry in a vacuum with KOH, for a minimum of two hours. A 1/1 solution of DIEA and CH_2Cl_2 (DCM) (dry on a 4A sieve) is

prepared. The already dry amino acid is dissolved with dry DCM at a concentration of 0.1 g of resin per ml, adding the minimum quantity of dry DMF to complete the dissolution. 1/3 of the 1.8 ml (12.5 mmol) DIEA solution is added to this transparent solution in 1.8 ml of DCM. This is thoroughly homogenized and added to the dry resin. It is subjected to vigorous magnetic agitation for five minutes and the rest of the DIEA is added to the reaction; the mixture is allowed to react for forty minutes more. Then, 4 ml of dry MeOH are added and allowed to react for 10 minutes, after which the resin is filtered and the washings described below are carried out.

Step	Reagent	Repetitions	Time(min)
1	DMF	3	1'
2	5% piperidine/(DMF/DCM)	1	10'
3	20% piperidine/DMF	1	15'
4	DMF	3	2'

The incorporation of the amino acids for obtaining of Boc-D-Phe-Cys-(Trt)-D-Trp-Lys(Boc)-Thr(tBu)-Cys(Trt)-2-Cl-trityl-resin is carried out following a synthesis program such as that described below, using an excess of 2.5 equivalents of Fmoc-amino acid, N-hydroxybenzotriazol (HOBt) and diisopropylcarbodiimide (DIPCDI). Later the Fmoc group is deprotected with 20% of piperidine/DMF for 1 min + 5 min.

Step	Reagent	Repetitions	Time(min)
1*	DMF	5	1'
2*	pip/DMF 20%	5	1'
3*	pip/DMF 20%	1	5'
4*	DMF	1	1'
5*	Fmoc aminoacid	-	+
6	HOBt	-	+
7	DIPCDI	-	40'
8	DMF	5	1'

[*for Thr]

Control by Ninhydrin test; if (+), return to 5; if (-) follow step 1 forward following amino acid.

The yields at the end of the synthesis are quantitative in obtaining Boc-D-Phe-Cys(Trt)-Phe-D-Trp-Lys(Boc)-Thr(tBu)-Cys(Trt)-2Cl-trityl-resin.

Preparation of Boc-D-Phe-Cys(Trt)-Phe-D-Lys(Boc)-Thr(tBu)-Cys(Trt)

250 mg (113 μmols) of Boc-D-Phe-Cys(Trt)-Phe-D-Trp-Lys(Boc)-Thr(tBu)-Cys(Trt)-2Cl-trityl-resin are treated with 6.36 ml of mixture 7/2/1 or 5.5/0.5/4 of DCM/TFE(tfifluoroethanol)/AcOH, for two hours, under magnetic agitation. The suspension is then filtered and washed 3 times with 0.2 ml of the 7/2/1 mixture of DCM/TFE/AcOH. The solution is evaporated (if it is not desired to proceed with the oxidation) until dry, at reduced pressure, and the solid obtained is washed with water. The yield is quantitative.

Obtaining of cycle $^{(2\text{-}7)}$Boc-D-Phe-Cis-Phe-D-Trp-Lys(Boc)-Thr(tBu)-Cis-OH (Oxidized 1-7 fragment).

250 mg (113 mmols) of Boc-D-Phe-Cys(Trt)-Phe-D-Trp-Lys(Boc)-Thr(tBu)-Cys(Trt)-COOH dissolved in 7 ml of the 7/2/1 mixture of DCM/TFE/AcOH, is slowly added to 290 mg (1.13 mmol) of iodine of 0.8 M concentration in the 7/2/1 mixture of DCM/TFE/AcOH. The reaction is allowed to evolve for 15 minutes. 4.3 ml of a $Na_2S_2O_7$, 1 N solution is added to eliminate the iodine excess. The aqueous phase is extracted and washed three times with 1 ml of DCM, the entirety of the organic phases is extracted with a citric acid/water solution and is evaporated at reduced pressure to dryness. The solid obtained is washed with water. The yield fluctuates between 85 and 95%.

Coupling of cycle $^{(2-7)}$Boc-D-Phe-Cis-Phe-D-Trp-Lys(Boc)-Thr(tBu)-Cis-OH (Oxidized 1-7 fragment) with Throl.

Over 250 mg (230 μmols) of $^{(2-7)}$Boc-D-Phe-Cis-Phe-D-Trp-Lys(Boc)-Thr(tBu)-Cis-OH(Oxidized 1-7 fragment), 103 mg (690 μmol) of HOBt and 72 mg (690 μmol) of threoninol are weighed out and dissolved in 10 ml of dry DMF/dry DCM (1:1); under vigorous agitation, 111 μL (690 μmols) of DIPCDI are added. The mixture is allowed to react for five hours at room temperature. It is evaporated to dryness until an oil is obtained, water is added, the mixture is well homogenized by ultrasound and lyophilized. The coupling is quantitative.

Oxidation of Boc-D-Phe-Cys(Trt)-Phe-D-Trp-Lys(Boc)-Thr(tBu)-Cys(Trt)-Throl.

Obtaining of cycle $^{(2-7)}$Boc-D-Phe-Cis-Phe-D-Trp-Lys(Boc)-Thr(tBu)-Cis-Throl(Oxidized fragment 1-8).

250 mg (147 μmols) of Boc-D-Phe-Cys(Trt)-Phe-D-Trp-Lys(Boc)-Thr(tBu)-Cys(Trt)-Throl dissolved in 8.26 ml of mixture 7/2/1 of DCM/TFE/AcOH, are slowly added to a solution of 290 mg (1.47 mmol) of iodine of 0.8 M concentration in the mixture 7/2/1 of DCM/TFE/AcOH. The reaction is allowed to evolve for 15 minutes. 4.3 ml of an $Na_2S_2O_7$ 1 N is added to eliminate the excess iodine. The aqueous phase is extracted and washed three times with 1 ml of DCM, the entirety of the organic phases is extracted with a solution of citric acid and water and is evaporated at reduced pressure to dryness. The solid obtained is washed with the help of a filter plate and water.

Removal of protecting groups. Obtention of Octreotide.

230 mmols cycle $^{(2-7)}$Boc-D-Phe-Cis-Phe-D-Trp-Lys(Boc)-Thr(tBu)-Cis-Throl (Oxidized 1-8 fragment)n are treated with 2 ml of trifluoroacetic acid (TFA) (95:5%) for five hours at ambient temperature. Later, the filtrate is dropped over 100 ml of dry and cold diethyl ether and the white precipitate obtained is once again centrifuged. The solid is resuspended in diethyl either and centrifuged again, repeating the operation five times more. The crude peptide is purified by preparative HPLC at 25% of CH_3CN/H_2O with 0.01% TFA in a 10 μml.

References

Bayer W. et al.; Eur. Patent Appl. 29,579, 1981 and Bayer W. et al.; US Patent No. 4,395,403; July 26, 1983; Assigned: Sandoz Ltd. (Basel, CH)
Edward et al.; J. Med. Chem. 1994, 37, 3749-3757

Arano et al.; Bioconjugate Chem. 1997, 8, 442-446
Obiols B. et al.; US Patent No. 6,346,601 B1; Feb. 12, 2002; Assigned to Lipotec S.A., Barcelona (ES)

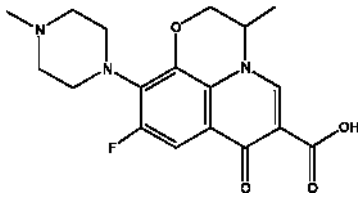
OFLOXACIN

Therapeutic Function: Antibacterial

Chemical Name: 7H-Pyrido(1,2,3-de)-1,4-benzoxazine-6-carboxylic acid, 2,3-dihydro-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-, ()-

Common Name: Mefoxacin; Ofloxacin

Structural Formula:



Chemical Abstracts Registry No.: 82419-36-1; 83380-47-6

Trade Name	Manufacturer	Country	Year Introduced
Exocin	Allergan	-	-
Floxan	Janssen-Cilag	-	-
Floxil	Cilag	-	-
Floxin	Aetna Inc.	-	-
Floxin	Janssen-Ortho Inc.	-	-
Floxin	Ortho	-	-
Floxin	McNeil	-	-
Floxstat	Jannsen-Cilag	-	-
Oflo	Unique	India	-
Oflomac	Macleods Pharmaceuticals	India	-
Oflox	Allergan	-	-
Ofloxacin	JAKA-80	Macedonia	-
Ofloxacin	Nu-Pharm Inc.	Canada	-
Ofloxacin	Ranbaxy	India	-
Ofloxacin	Chemo Iberica	Spain	-
Ofloxacin	Huanguan East Asia Chemical Co.	China	-
Ofloxin 200	Leciva	Czech Republic	-
Quinoxan	Andromaco	-	-
Tarivid	Hoechst	Germany	-

Trade Name	Manufacturer	Country	Year Introduced
Tarivid	Hoechst Marion Roussel	India	-
Uroflox	Houde	-	-
Urosin	Sifar	-	-
Zanocin	Ranbaxy Guangzhow	China	-
Zanocin	Ranbaxy Ireland	Ireland	-
Zanocin	Ranbaxy	India	-

Raw Materials

3,4-Trifluoronitrobenzene
Sodium dithionite
N-Methylpiperazine
Dimethyl sulfoxide
Ethyl polyphosphate
Diethyl ethoxymethylenemalonate

Manufacturing Process

20 g of 2,3,4-trifluoronitrobenzene was dissolved in 150 ml of dimethyl sulfoxide, and to this mixture a solution of 10% potassium hydroxide was added dropwise while keeping the temperature at 18° to 20°C. Then, the mixture was stirred for 2 hours at room temperature and one liter of water was added to this reaction mixture and the mixture was shaken with chloroform. The water layer was acidified with hydrochloric acid and was extracted with chloroform. The extract was washed with water and was dried, then chloroform layer was concentrated. The residue was purified by silica gel column chromatography to provide 5.8 g of 2,3-difluoro-6-nitrophenol as yellow oil.

7.9 g of the 2,3-difluoro-6-nitrophenol, 50.1 g of 1,2-dibromoethane and 18.7 g of potassium carbonate were added to 80 ml of dimethylformamide and the mixture was stirred for 2.5 hours at from about 80° to 100°C (bath temperature). The reaction mixture was concentrated to dryness in vacuo and the residue was distributed between ethyl acetate and water. The organic solvent layer was washed with water and was dried, then the solvent was evaporated. The residue was dissolved in benzene and was purified by silica gel column chromatography to provide 7.7 g of 2-(2-bromoethoxy)-3,4-difluoronitrobenzene as light yellow oil.

1.74 g of this product was dissolved in 30 ml of methanol and a solution of 6.44 g of sodium dithionite dissolved in 15 ml of water was added thereto. The mixture was stirred for 1 hour at room temperature. Methanol was evaporated and the residue was extracted with chloroform. After the extract was washed with water and dried, the solvent was evaporated to provide 0.44 g of 2-(2-bromoethoxy)-3,4-difluoroaniline.

1.82 g of this product and 3.03 g of potassium carbonate were added to 10 ml of dimethylformamide and the mixture was stirred for 1 hour at from about 80° to 100°C (bath temperature). The reaction mixture was added to ice-cold water and was extracted with ethyl acetate. After the extract was washed with water and dried, the solvent was distilled off at room temperature to provide 1.21 g of 7,8-difluoro-2,3-dihydro-4H-[1,4]benzoxazine with m.p. 48°-54°C.

The mixture of 1.1 g of this product and 1.38 g of diethyl

ethoxymethylenemalonate was stirred for 2 hours at from about 130° to 135°C (bath temperature). The ethanol produced was evaporated and 20 g of ethyl polyphosphate was added to the residue. Then the mixture was stirred for 1.5 hours at from about 140° to 145°C (bath temperature). The reaction mixture was added to ice-cold water and was extracted with chloroform. The extract was washed fully with water. After drying, the solvent was evaporated and the residue was recrystallized from ethyl acetate. 1.3 g of ethyl 9,10-difluoro-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylate was obtained as colorless needles with m.p. 265°-266°C.

1.15 g of this product was added to 12 ml of mixture of concentrated hydrochloric acid and acetic acid (1:4 by volume) and the mixture was stirred for 4 hours at 100° to 110°C (bath temperature). After cooling, the precipitated crystals were collected by filtration, washed with water, methanol and chloroform to give 0.78 g of 9,10-difluoro-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]-benzoxazine-6-carboxylic acid as colorless needles with m.p. above 300°C.

1.0 g of 9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid and 2.85 g of N-methylpiperazine were added to 15 ml of dimethylsulfoxide. The mixture was stirred at a temperature of from about 100° to 110°C (bath temperature) for 12 hours and the reaction mixture was concentrated to dryness in vacuo and 40 ml of water was added to the residue. Then the product was extracted with chloroform. The extract was dried and concentrated to dryness in vacuo. The residue was recrystallized from ethanol to provide 550 mg of 9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid as colorless needles with m.p. 250°-257°C (with decomposition).

References

Hayakawa I. et al.; US Patent No. 4,382,892; May 10, 1983; Assigned to Dalichi Selyaku Co., Ltd., Tokyo, Japan

OLANZAPINE

Therapeutic Function: Antipsychotic

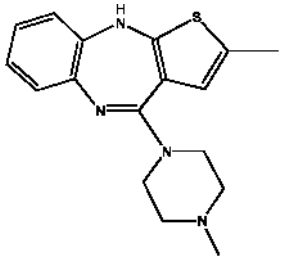
Chemical Name: 10H-Thieno(2,3-b)(1,5)benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)-

Common Name: Olanzapine

Raw Materials

Propionaldehyde
Triethylamine
2-Fluoronitrobenzene
N-Methylpiperazine
Dimethyl sulfoxide
Malononitrile
Stannous chloride

Structural Formula:



Chemical Abstracts Registry No.: 132539-06-1

Trade Name	Manufacturer	Country	Year Introduced
Joyzol	Merind Limited	India	-
Olan	Synapse (A Div. of Microlabs)	India	-
Olandus	Zydus Neurosciences	India	-
Olanex	Solus	India	-
Oleanz	Sun Pharmaceuticals Industries Ltd.	India	-
Olexa	Protech Biosystems	-	-
Onza	SPPL (Sarabhai Piramal Pharmaceuticals Ltd.)	India	-
Zyprexa	Eli Lilly	UK	-
Zyprexa Zydis	Eli Lilly	UK	-

Manufacturing Process

1. 2-Amino-5-methylthiophene-3-carbonitrile

A mixture of sulphur (217.8 g, 6.79 mol), propionaldehyde (472.5 g, 587 mL, 8.13 mol) and dimethylformamide (1350 m) was placed in a 5 liter flange-necked flask fitted with air stirrer, air condenser, thermometer and dropping funnel. Triethylamine (576 mL, 4.13 mol) was added dropwise over 30 minutes to the cooled stirred reaction mixture whilst maintaining the pot temperature between 5°-10°C with an ice-bath. After addition was complete the pot was allowed to warm up to 18°C over 50 minutes, keeping the mixture well stirred. Then a solution of malononitrile (450 g, 6.8 mol) in dimethylformamide (900 mL) was added dropwise over 70 minutes keeping the pot temperature around 20°C throughout the addition. After addition was complete the mixture was stirred at 15°-20°C for a further 45 minutes then sampled for TLC. The mixture was then poured onto ice (4 liters)/water (8 liters) with stirring and this caused the required product to precipitate. After 10 minutes the stirrer was switched off and the solid allowed to settle. The aqueous liquor was decanted away and the solid isolated by filtration. The isolated solid was well washed with water (de-ionised, 4 liters), then dried over night in vacuo at 70°-75°C to give the title compound (585 g), m.p. 100°C.

2. 2-(2-Nitroanilino)-5-methylthiophene-3-carbonitrile

To a stirred slurry of sodium hydride (14.4 g, 50% dispersion in oil, 0.3 mol) in dry tetrahydrofuran (50 mL) under nitrogen was added, dropwise, a solution of 2-fluoronitrobenzene (28.2 g, 0.2 mol) and 2-amino-5-methylthiophene3-carbonitrile (27.6 g, 0.2 mol) in dry tetrahydrofuran (250 mL). The mixture was stirred at 25°C for 24 hours, poured onto cracked ice and extracted into dichloromethane (3 times 500 mL). The combined extracts were washed with 2 N hydrochloric acid (2 times 200 mL), water (2 times 200 mL), dried over magnesium sulphate and the solvent removed under reduced pressure. The residue was crystallised from ethanol to give the title compound, (35.2 g), m.p. 99°-102°C.

3. 4-Amino-2-methyl-10H-thieno[2,3-b][1,5]benzodiazepine, hydrochloride

To a stirred slurry of 2-(2-nitroanilino)-5-methylthiophene-3-carbonitrile (3 g, 0.011 mol) in ethanol (35 mL) at 50°C was added, over 10 minutes, a solution of anhydrous stannous chloride (6.95 g, 0.037 mol) in hydrochloric acid (26 mL, 5 M). The mixture was stirred under reflux for 1 hour, concentrated under reduced pressure and allowed to crystallise over night at 5°C. The salt was filtered, washed with a small amount of water, dried (4.3 g) m.p. >250°C, and used without further purification in the next stage.

4. 2-Methyl-10-(4-methyl-1-piperazinyl)-4H-thieno[2,3-b][1,5]-benzodiazepine

Crude 4-amino-2-methyl-10H-thieno[2,3-b][1,5]benzodiazepine, hydrochloride (4.3 g) was refluxed in a mixture of N-methylpiperazine (15 mL), dimethylsulfoxide (20 mL) and toluene (20 mL) under a nitrogen atmosphere for 20 hours. The mixture was cooled to ca. 50°C, water (20 mL) added, and the product allowed to crystallise at 5°C over night. The product was filtered and crystallised from acetonitrile (30 mL) to give the title compound (1.65 g) m.p. 195°C. The structure of the compound was confirmed spectroscopically.

References

Chakrabarti J.K. et al.; US Patent No. 5,229,382; Jul. 20, 1993; Assigned to Lilly Industries, Basingstroke, England

OLEANDOMYCIN

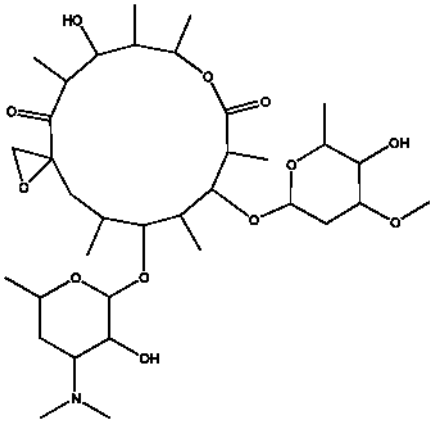
Therapeutic Function: Antibiotic

Chemical Name: Oleandomycin

Common Name: Troleandomycin

Chemical Abstracts Registry No.: 3922-90-5

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Matromycin	Pfizer	US	1956
Oleandocyn	Pfizer	W. Germany	-
Oimicina	Morgan	Italy	-
Sigmamycin	Pfizer	Japan	-
Taocin-O	Sankyo	Japan	-
TAO	Roerig	US	-
Triolmicina	Ripari-Gero	Italy	-

Raw Materials

Bacterium Streptomyces antibioticus
Dextrose
Soybean meal

Manufacturing Process

A slant of S. antibioticus ATCC 11891 was cultivated on agar under controlled conditions in order to develop spores for the purpose of inoculating a nutrient medium having the following composition: 20 g Cerelose (dextrose hydrate), 15 g soybean meal, 5 g distillers' solubles, 10 g cornmeal, and tap water, in a sufficient amount for a 1,000 ml solution, adjusted to pH 7.0 to 7.2 with potassium hydroxide.

After the pH was adjusted, 5 g of calcium carbonate was added. This inoculum medium was then subjected to heat sterilization. The medium was then cooled and 2 ml of a spore suspension of an oleandomycin-producing strain of S. antibioticus was added under aseptic conditions. The cultivation of the organism was conducted in shaken flasks at 28% for a period of 48 hours.

The mixture of broth and mycelium thus formed was then transferred under aseptic conditions to a 3-liter fermentor containing 2,000 ml of a sterile

fermentation medium having the following composition: 60 g Cerelose (dextrose hydrate), 18 g soybean meal, 5 g distillers' solubles, 12 g cornmeal and tap water in a sufficient amount for a 1,000 ml total volume, adjusted to pH 7.0 to 7.2 with potassium hydroxide.

After the pH had been adjusted, 5 g of calcium carbonate, 5 ml of soybean oil antifoam and 0.020 g of Acridine Orange dye were added. The mixture was then autoclaved at 20 psi (250°F) for 15 minutes in order to sterilize the contents, before transferring the broth and mycelium thereto.

After seeding the nutrient medium with the preformed inoculum previously described, the mixture was subjected to agitation and aeration under aseptic conditions for 72 hours; at 27°C to 28°C for the first 24 hours, then at 25°C to 26°C for the next 48 hours; during this period, the pH was in the range of 6.4 to 6.8. Aeration was accomplished by cultivation under submerged conditions at an air flow rate of one volume of air per volume of medium per minute. After termination of the process, the mycelium was removed by filtration and the filtered broth found to contain 450 γ of oleandomycin per ml of solution.

References

Merck Index 6703
Kleeman & Ensel P. 657
I.N. p. 701
Sobin, B.A., Routien, J.B. and Lees, T.W.; US Patent 2,757,123; July 31, 1956; assigned to Chas. Pfizer & Co., Inc.
Ratajak, E.J. and Nubel, R.C.; US Patent 2,842,481; July 8, 1958; assigned to Chas. Pfizer & Co., Inc.

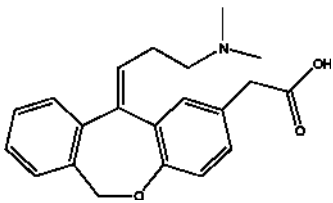
OLOPATADINE

Therapeutic Function: Antiallergic

Chemical Name: 11-((Z)-3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid

Common Name: Doxepadine; Olopatadine

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Patanol	Alcon	UK	-

Chemical Abstracts Registry No.: 113806-05-6

Raw Materials

Phthalide	p-Hydroxyphenyl acetic acid
$POCl_3$	Boron trifluoride-ethylether complex
Butyl lithium	Methyltriphenylphosphonium bromide
Sodium permanganate	Triphenylchloromethane
Magnesium	3-Dimethylaminopropyl chloride
Dibromoethane	Trifluoroacetic anhydride

Manufacturing Process

402.4 g of phthalide and 200 g of sodium chloride and equal molecular quantity of p-hydroxyphenyl acetic acid are mixed with one another and stirred at 150°C for 6 hours. After completion of the reaction, the mixture is cooled until the temperature is brought back to room temperature, 4 L of aqueous 10% acetic acid solution is added thereto and the mixture is allowed to stand at room temperature overnight. After stirring the mixture at room temperature for 3 hours, deposited crystals are separated by filtration, and 6 L of water is added thereto. After stirring the mixture at room temperature for 30 minutes, the deposited crystals are separated by filtration. After the addition of 3 L of toluene to the crystals, the mixture is stirred at room temperature for one hour. The crystals are separated by filtration and dried over heating under reduced pressure to yield of 2-(4-acetoxyphenoxy)benzoic acid.

266.0 g of trifluoroacetic anhydride is added to the equal molecular quantity of 2-(4-acetoxyphenoxy)benzoic acid suspended in 5.0 L of methylene chloride and thereto. After stirring the mixture at room temperature for one hour, 19.4 g of boron trifluoride-ethylether complex is added thereto and the mixture is stirred at room temperature for two hours. The reaction solution is poured into ice water. After an organic solvent layer is separated from the mixture, the organic layer is washed with diluted aqueous sodium hydroxide solution and water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain 335.3 g of methyl 11-oxodibenz[b,e]oxepin-2-carboxylate as a white crystal melting point 130°-132°C

Methyl 11-methylene-6,11-dihydrodibenz-[b,e]oxepin-2-acetate.

In 100 ml of tetrahydrofuran is suspended 25 g of methyltriphenylphosphonium bromide and 40 ml of 1.6 N n-butyl lithium hexane solution is dropwise added thereto under a nitrogen atmosphere and ice-cooling. After stirring the mixture under ice-cooling for 30 minutes, a solution obtained by dissolving equal molar quantity of 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid in 250 ml of tetrahydrofuran is dropwise added thereto and the mixture is stirred at room temperature for two hours. The solvent is distilled away under reduced pressure and the residue is purified by column chromatography on silica gel (eluent: hexane:ethyl acetate = 3:1) to obtain the desired product as a colorless oily

matter.

(11-(3-Dimethylaminopropylidene)-2-(2-triphenylmethyloxymethyl)-6,11-dihydrodibenz[b,e]oxepin.

Process A: 11-Hydroxy-2-(2-hydroxyethyl)-6,11-dihydrodibenz [b,e]oxepin

In this process, 20 g of methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetate is dissolved in 500 ml of tetrahydrofuran. To the solution is added 6.0 g of lithium aluminum hydride and the mixture is stirred at room temperature for one hour. After decomposing an excess of the reagent by the addition of water to the solution, the mixture is filtered to remove an inorganic salts and the filtrate is concentrated to dryness under reduced pressure to obtain 17.7 g of the desired product as a white solid. Melting point: 132°-136°C.

Process B: 11-Hydroxy-2-(2-triphenylmethyloxyethyl)-6,11-dihydrodibenz[b,e]oxepin

In this process, 17.2 g of 11-hydroxy-2-(2-hydroxyethyl)-6,11-dihydrodibenz[b,e]oxepin is dissolved in 50 ml of pyridine. To the solution is added 30 g of triphenylchloromethane and the mixture is stirred at 50°C for 5 hours. After adding water and stirring the mixture for 2 hours, the solvent is distilled away under reduced pressure. The mixture is extracted with 1000 ml of ethyl acetate, washed with saturated aqueous sodium chloride solution, and dried over anhydrous sodium sulfate. The solvent is distilled away under reduced pressure and the resultant residue is purified by column chromatography on silica gel (eluent: hexane:ethyl acetate = 3:1) to obtain 21.7 g of the desired product as a colorless amorphous.

Process C: 11-Oxo-2-(2-triphenylmethyloxyethyl)-6,11-dihydrodibenz[b,e]oxepin

In this process, 10 g of 11-hydroxy-2-(2-triphenylmethyloxyethyl)-6,11-dihydrodibenz[b,e]oxepin is dissolved in a solution comprising 800 ml of acetone, 1000 ml of water, 20 ml of saturated aqueous magnesium sulfate solution and 0.2 g of disodium phosphate. To the solution is dropwise added 2.6 g of aqueous sodium permanganate solution and the mixture is stirred at room temperature for 4.5 hours. Then, 100 ml of methanol is added thereto and the mixture is heated at reflux for 3 hours. After allowing the mixture to stand for cooling, the mixture is filtered and the filtrate is extracted with 1000 ml of ethyl acetate, washed with saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. The solvent is distilled away under reduced pressure and the resultant crude product is recrystallized from isopropanol to obtain 8.0 g of the desired product having melting point of 132°-134°C as a white crystal.

Process D: 11-(3-Dimethylaminopropyl)-11-hydroxy-2-(2-triphenylmethyloxyethyl)-6,11-dihydrodibenz[b,e]oxepin

To a solution of 3-dimethylaminopropyl magnesium chloride obtained by reacting 0.2 g of magnesium with 1.0 g of 3-dimethylaminopropyl chloride in 10 ml of tetrahydrofuran under a nitrogen atmosphere using dibromoethane as a catalyst, is dropwise added a solution obtained by dissolving 2.0 g of 11-

oxo-2-(2-triphenylmethyloxyethyl)-6,11-dihydrodibenz[b,e]oxepin in 10 ml of tetrahydrofuran under ice cooling and the mixture is stirred at room temperature for one day. Aqueous ammonium chloride solution is added thereto and the pH of the mixture is adjusted to 7.0 with aqueous 4 N hydrochloric acid solution. The solvent is distilled away under reduced pressure. The mixture is extracted with 200 ml of methylene chloride and washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution in order. After drying the extract over anhydrous sodium sulfate, the solvent is distilled away under reduced pressure. The resultant residue is purified by column chromatography on silica gel (eluent: hexane:ethyl acetate:triethylamine = 10:10:1) to obtain 1.2 g of the desired product as a colorless amorphous.

Process E: 11-(3-Dimethylaminopropylidene)-2-(2-triphenylmethyloxyethyl)-6,11-dihydrodibenz[b,e]oxepin

In this process, 1.2 g of 11-(3-dimethylaminopropyl)-11-hydroxy-2-(2-triphenylmethyloxyethyl)-6,11-dihydrodibenz[b,e]oxepin is dissolved in 50 ml of pyridine. To the solution is dropwise added 0.8 g of phosphorusoxychloride under a nitrogen atmosphere and ice-cooling. After stirring the mixture at room temperature for one hour, the solvent is distilled away under reduced pressure. The residue is extracted with 100 ml of methylene chloride, and washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution in order. After drying the mixture over anhydrous sodium sulfate, the solvent is distilled away under reduced pressure. The resultant residue is purified by column chromatography on silica gel (eluent: hexane:ethylacetate:triethylamine = 10:10:1) to obtain 0.82 g of the desired product as a colorless oily matter.

11-(3-Dimethylaminopropylidene)-2-(2-hydroxyethyl)-6,11-dihydrodibenz[b,e]oxepin

0.92 g of 11-(3-dimethylaminopropylidene)-2-(2-triphenylmethyloxyethyl)-6,11-dihydro dibenz[b,e]oxepin is dissolved in a mixed solvent of 20 ml of water and 20 ml of dioxane. To the solution is added 60 mg of p-toluene sulfonic acid and the mixture is heated at reflux for two hours. The solvent is distilled away under reduced pressure and the residue is extracted with 200 ml of ethylacetate, washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium hydrochloride solution in oder and dried over anhydrous sodium sulfate. The solvent is distilled away under reduced pressure. The resultant residue is purified by column chromatography on silica gel (eluent: ethylacetate triethylamine = 10:1) to obtain 0.4 g of the desired product. Cis form white solid. Melting point: 100°-102°C (diethylether).

11-(3-Dimethylaminopropylidene)-6,11-dihydrodibenz [b,e]oxepin-2-acetic acid

2.2 g of 11-(3-dimethylaminopropylidene)-2-(2-hydroxyethyl)-6,11-dihydrodibenz[b,e]oxepin is dissolved in 100 ml of acetone. The Jones reagent ($Na_2Cr_2O_7$+ H_2SO_4) is added to the solution until the reaction solution shows an orange color and the mixture is stirred at room temperature for one hour. Sodium bicarbonate is added thereto and an inorganic substance is removed by filtration. The solvent of the filtrate is distilled away under reduced

pressure to obtain the desired product, 11-(3-Dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid. Cis form white crystal. Melting point: 118°-120°C (Isopropanol).

References

Oshima et al.; US Patent No. 5,116,863; May 26, 1992; Assigned to Kyowa Hakko Kogyo Co., Ltd., Tokyo, Japan

Hayakawa E. et al.; US Patent No. 5,641,805, Jun. 24, 1997; Assigned to Alcon Laboratories, Inc. (Fort Worth, TX); Kyowa Hakko Kogyo Co. Ltd. (Tokyo, JP)

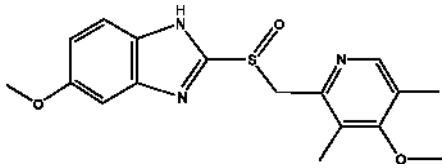
OMEPRAZOLE

Therapeutic Function: Antiulcer

Chemical Name: 1H-Benzimidazole, 5-methoxy-2-(((4-methoxy-3,5-dimethyl-2-pyridinyl)methyl)sulfinyl)-

Common Name: Omeprazole

Structural Formula:



Chemical Abstracts Registry No.: 73590-58-6

Trade Name	Manufacturer	Country	Year Introduced
Fordex	Leti	-	-
Gastrium	Ache	-	-
Gastrotem	Temis Lostalo	-	-
Helicid 10	Leciva	Czech Republic	-
Helicid 11	Colins Laboratories Ltd.	India	-
Lenar	Chemica	-	-
Lomak	Cipla Limited	India	-
Losec	Astra	Sweden	-
Losec MUPS	AstraZeneca	Sweden	-
Lozol	Medinfar	-	-
Norpramin	Cepa	-	-
Ocid	Cadila Healthcare	India	-
Omegast	Lifesource Healthcare	India	-
Omegast	Agio Pharmaceuticals Ltd.	India	-
Omepar	Nabros Pharma	India	-

Trade Name	Manufacturer	Country	Year Introduced
Omeprazole	Balkanpharma	Bulgaria	-
Omeprazole	New Life Pharmaceuticals	India	-
Omeprazole	Chemo Iberica	Spain	-
Omeprazole	Aurobindo	India	-
Omeprazole-Richter	Lyconsa	Spain	-
Omeprol	Zdravle	Yugoslavia	-
Omez	Dr. Reddy's Laboratories Ltd.	India	-
Omizac	Torrent	India	-
OMZ	Dexa Medica	-	-
Osiren	Chemia	-	-
Pamoxan	Italmex	-	-
Pepticum	Laboratorios Andromaco	Spain	-
Prazol	Tecnoquimicos	-	-
Proseptin	Beximco	-	-
Sanamidol	Inkeysa	-	-
Ulceral	Tedec-Meiji	-	-
Ultop	Krka	Slovenia	-
Ulzol	Pliva	Horvatia	-
Zerocid	Sun Pharmaceuticals Industries Ltd.	India	-
Zolcer	Aurobindo	India	-

Raw Materials

3,5-Lutidine
Dimethyl sulfate
Thionyl chloride
Phthalic anhydride
Hydrogen peroxide
Ammonium persulfate
5-Methyl-2-mercaptobenzimidazole
Benzylammonium chloride

Manufacturing Process

3,5-Lutidine-N-Oxide

Hydrogen peroxide (45%, 200 ml) was added dropwise at 60°-70°C during 2 hours to a mixture of 3,5-Lutidine (125 g, 1.16 mole) and acetic acid (400 ml). The mixture was heated to 90°C and maintained at 90°-100°C for 2 hours after which it was cooled to 60°C. Again hydrogen peroxide (45%, 200 ml) was added dropwise at 60°-70°C during 1 hour and then the mixture was heated to 90°C and maintained at 90°-100°C for 6 hours. Thereafter, acetic acid and water was distilled off under reduced pressure and the distillation residue obtained was used as a starting product for the nitration.

3,5-Dimethyl-4-nitropyridine-N-oxide

To the distillation above obtained residue was added sulphuric acid (146 ml). Thereafter, a nitrating mixture consisting of sulphuric acid (250 ml) and nitric acid (280 ml) was added dropwise during 4 hours at 90°-100°C. The reaction

mixture was heated further at 90°-100°C for 6 hours, after which it was cooled and poured over crushed ice (4 kg), Caustic lye (50%, 1150 ml) was added to the yellow solution and the precipitated crystalline compound was filtered under suction. The cake was washed with water and dried in vacuuo oven to yield the product which melted at 171°-173°C. Yield 78.5%. A sample crystallized from acetone had a melting point of 174°-174.5°C.

3,5-Dimethyl-4-nitropyridine-N-oxide-dimethyl sulfate adduct

To a suspension of 3,5-dimethyl-4-nitropyridine-N-oxide (150 g, 0.80 mole) in acetone (450 ml) was added dimethyl sulfate (90 ml, 0.95 mole). The mixture was heated to reflux until a clear solution was obtained and then allowed to cool to ambient temperature. An off-white crystalline solid separated out, which was filtered, washed with acetone and dried to yield 220 g of the adduct. Yield was 83.8% of theoretical.

3,5-Dimethyl-2-hydroxymethyl-4-nitropyridine

3,5-Dimethyl-4-nitropyridine-N-oxide-dimethyl sulfate adduct (220 g, 0.75 mole) was dissolved in methanol (1.0 ltr) and the solution heated to reflux. A solution of ammonium persulfate (140 gm) in water (200 ml) was added dropwise over 4 hours after which reflux was continued for 4 hours. Methanol was distilled off under reduced pressure and the residue was basified to pH 10 by addition of caustic lye (105 ml). The mixture was extracted with dichloromethane (2 times 400 ml). The dichloromethane layer was dried over sodium sulfate and filtered. The product was used as its solution in dichloromethane for the next reaction.

2-Chloromethyl-3,5-dimethyl-4-nitropyridine hydrochloride

To the cooled dichloromethane solution of 3,5-dimethyl-2-hydroxymethyl-4-nitropyridine was added thionyl chloride (60 ml, 0.85 mole) dropwise over a period of 2 hours and stirring was continued for a further 2 hours. Methanol (10 ml) was added to destroy excess thionyl chloride and separated product was filtered under suction and washed with dichloromethane. The cake was dried in vacuum oven to yield 55 g of a cream colored product. Melting point was 124°-126°C.

5-Methoxy-2-[(3,5-dimethyl-4-nitro-2-pyridinyl)methylthio]-1H-benzimidazole

To a suspension of 5-methyl-2-mercaptobenzimidazole (36 g, 0.2 mole), 2-chloromethyl-3,5-dimethyl-4-nitropyridine hydrochloride (47.4 g, 0.2 mole) and triethyl benzylammonium chloride (5 g) in a dichloromethane (500 ml) was added dropwise a solution of NaOH (17.6 gm, 0.44 mole) in water (30 ml). The addition was exothermic and the temperature was observed to rise to 40°C with reflux of dichloromethane - the reaction mixture was stirred for further 6 hours at ambient temperature and filtered. The cake was washed with water and dried in vacuum oven to yield 55.8 g of cream color product. Yield 81.1%; melting point 124°-128°C.

5-Methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridinyl)methylthio]-1H-benzimidazole

5-Methoxy-2-[(3,5-dimethyl-4-nitro-2-pyridinyl)methylthio]-1H-benzimidazole(50 g, 0.145 mole) was dissolved in methanol and heated to 45°C. A solution of sodium methoxide (50 g, 0.925 mole) in methanol (150 ml) was added dropwise over a period of 3 hours at 45°-60°C. Stirring was continued for another 2 hours and then methanol was distilled off under reduced pressure. To the cooled residue was added water (200 ml) followed by concentrated HCl (65 ml) until the pH of the mixture was 7.5. The reaction mixture was extracted with dichloromethane and the dichloromethane layer was washed with water (2 times 100 ml). The dichloromethane layer was dried over sodium sulfate and concentrated to yield the product as an amber color syrup. Yield was 40.1 gm, about 83.8% of theoretical. A solid sample was obtained by trituration of the syrup several times with petroleum ether. Melting point was 87°-90°C.

5-Methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridinyl)methylthio]-1H-benzimidazolehydrochloride

HCl gas was bubbled into a cooled solution of 5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridinyl)methylthiol]-1H-benzimidazole (50 g) in dichloromethane (250 ml) until no more precipitation was observed. The reaction mixture was warmed to 40°C and again cooled to 10°C. The solid was filtered under suction and washed with dichloromethane to yield the product (49 g) as a cream colored fine granular solid. Yield was 88.2% of theoretical. Melting point 144°-148°C.

Omeprazole from 5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridinyl)methylthiol]-1H-benzimidazole

To a solution of 5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridinyl)methylthio]-1H-benzimidazole (32.9 g, 0.1 mole) in dichloromethane (200 ml) was added phthalic anhydride (20 g, 0.135 mole) and cooled in an ice salt bath. This was followed by addition of sodium carbonate (18 g, 0.17 mole) and water (20 ml). Hydrogen peroxide (12 ml, 45%, 0.16 mm mole) was added dropwise at -5°-0°C and the reaction mixture was stirred at the same temperature. When the reaction was complete as indicated by TLC, water (200 ml) was added, cooling bath was removed and the reaction mixture was stirred for 10 mins. The organic layer was separated and washed with 5% sodium carbonate solution. The separated dichloromethane solution was charcoalised and filtered through celite. The filtrate was concentrated to 100 ml and ethyl acetate 100 ml was added thereto. The separated solid was filtered, washed with ethyl acetate and dried in vacuum oven to yield 28.20 g of omeprazole. Yield 82.4% of theoretical. Melting point was 158°-160°C (dec.).

References

Singh S. et al.; US Patent No. 6,245,913 B1; Jun. 12, 2001; Assigned to Wockhardt Europe Limited, Dublin (IE)

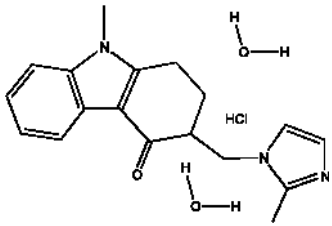
ONDANSETRON HYDROCHLORIDE DIHYDRATE

Therapeutic Function: Serotonin antagonist

Chemical Name: 4H-Carbazol-4-one, 1,2,3,9-tetrahydro-9-methyl-3-((2-methyl-1H-imidazol-1-yl)methyl)-, hydrochloride, hydrate (1:1:2)

Common Name: Ondansetron hydrochloride dihydrate

Structural Formula:



Chemical Abstracts Registry No.: 103639-04-9; 99614-02-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Ondansetron hydrochloride	Chemo Iberica	Spain	-
Zofran	GlaxoSmithKline	UK	-

Raw Materials

Diethyl oxalate
Sodium
2-Methylimidazole
9-Methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one
Formol solution

Manufacturing Process

Preparation of 3-ethoxalyl-9-methyl-1,2,3,9-tetrahydro-4H-carbozol-4-one

3.0 g (0.13 mole) of sodium metal are portionwise added to a stirred mixture containing 19.93 g (0.1 mole) of 9-methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one, 19.0 g (0.13 mole) of diethyl oxalate, 2 g of ethanol and 200 ml of dioxane. The slightly warming reaction mixture is stirred at 40° to 50°C for 4 hours, then 16 g of glacial acetic acid and finally 200 ml of water are added thereto at room temperature. After filtering off the yellow crystalline suspension, the precipitate is washed with water and dried to give the title compound in a yield of 24 g (80.2%), m.p. 118°-120°C.

Preparation of 3-hydroxymethyl-9-methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one-3-glyoxylic acid lacton

After adding 0.1 g of triethylamine to a stirred suspension containing 3.00 g (0.01 mole) of the 3-ethoxalyl-9-methyl-1,2,3,9-tetrahydro-4H-carbazol-4-

one, in 20 ml of acetone, 1.13 g (0.015 mole) of formol solution are dropwise added to the mixture. The suspension becomes clear within 1 to 2 minutes and crystals begin to precipitate. After further stirring at 35° to 40°C for one hour, the reaction mixture is cooled down to room temperature, filtered off, the precipitate is washed with 50% acetone and dried to give 2.10 g (74.2%) of the title compound, m.p. 242°-244°C.

Preparation of ondansetron base (chemically 9-methyl-3-[(2-methyl-1-H-imidazol-1-yl)methyl]-1,2,3,9-tetrahidro-4-H-carbazol-4-one)

A mixture containing 2.83 g (0.01 mole) of 3-hydroxymethyl-9-methyl-2,3,9-tetrahydro-4H-carbazol-4-one-3-glyoxylic acid lactone, 15 ml of dioxane, 1.32 g of triethylamine, 1.0 g of ethanol and 1.64 g (0.02 mole) of 2-methylimidazole is boiled under reflux while stirring for 5 hours. Thereafter, the reaction mixture is diluted with 45 ml of water and cooled down. The precipitate is filtered off, washed with aqueous dioxane and dried to obtain 2.56 g (87.3%) of the title compound, m.p. 220°-223°C.

Preparation of 9-methyl-3-[(2-methyl-1-H-imidazol-1-yl)methyl]-1,2,3,9-tetrahydro-4H-carbazol-4-one hydrochloride dihydrate The process above described is followed, except that after cooling down the reaction mixture to room temperature after boiling, 20 ml of 37% aqueous hydrochloric acid are added thereto. Then, the precipitate is filtered off, washed with isopropanol and dried to obtain 2.40 g (65.6%) of the title salt, m.p. 178°-180°C. The active agent content of the product was found to be 100.3% based on potentiometric titration with sodium hydroxide solution. The theoretical water content is 9.85% (calculated for $C_{18}H_{19}N_3OHCl_2H_2O$).The water content measured is 10.03%.

References

Bod P. et al.; US Patent No. 5,478,949; Dec. 26, 1995; Assigned to Richter Gedeon Vegyeszeiti Gyar Rt., Budapest, Hungary

OPIPRAMOL

Therapeutic Function: Antidepressant, Antipsychotic

Chemical Name: 4-[3-(5H-Dibenz[b,f]azepin-5-yl)propyl]-1-piperazine-ethanol

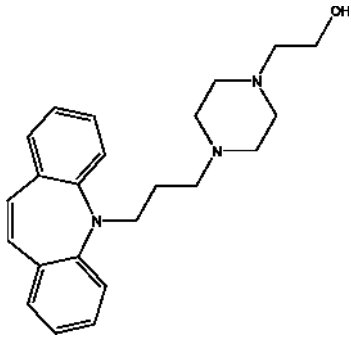
Common Name:-

Chemical Abstracts Registry No.: 315-72-0; 909-39-7 (Dihydrochloride salt)

Raw Materials

5-(3-Toluene-p-sulfonyloxypropyl)dibenzazepine
1-(2-Hydroxyethyl)piperazine

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Insidon	Geigy	W. Germany	1962
Insidon	Geigy	France	1962
Insidon	Geigy	Italy	1962
Deprenil	Yurtoglu	Turkey	-
Ensidon	Ciba Geigy	US	-
Oprimol	Taro	Israel	-
Pramolan	Polfa	Poland	-

Manufacturing Process

A solution of 5-(3-toluene-p-sulfonyloxypropyl)dibenzazepine (9.2g) and 1-(2-hydroxyethyl)piperazine (8.6g) in anhydrous toluene (50 cc) is heated at boiling point under reflux for 4 hours.

After cooling, distilled water (75 cc) is added. The aqueous phase is decanted. The toluene solution is washed with distilled water (25 cc) and then extracted with N hydrohloric acid (40 cc). The hydrochloric acid solution is made alkaline to phenolphthalein with sodium hydroxide (d = 1.33).The base which separates is extracted with chloroform (50 cc). The chloroform solution is dried over anhydrous sodium sulfate and then evaporated to dryness. There are obtained 5-[3-(4-β-hydroxyethylpiperazino)propyl]dibenzazepine (7.95g), the dihydrochloride of which, crystallized from ethanol, melts at about 210°C.

References

Merck Index 6727
Kleeman & Ensel P. 657
I.N. p. 703
Gaillot, P. and Gaudechon, J.; British Patent 881,398; November 1, 1961; assigned to Societe des Usines Chimiques Rhone-Poulenc

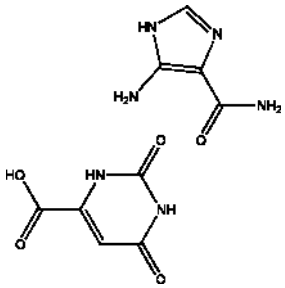
ORAZAMIDE

Therapeutic Function: Hepatoprotectant

Chemical Name: 5-Aminoimidazole-4-carboxamide orotate

Common Name: AICA orotate

Structural Formula:



Chemical Abstracts Registry No.: 2574-78-9

Trade Name	Manufacturer	Country	Year Introduced
Aicamine	Labaz	France	1971
Aicurat	Mack	W. Germany	1962
Aicamin	Crinos	Italy	1977
Aicamin	Fujisawa	Japan	-

Raw Materials

4-Amino-5-imidazolecarboxamide
Orotic acid

Manufacturing Process

14.4 grams of 4-amino-5-imidazolecarboxamide (monohydrate) and 17.4 grams of orotic acid (monohydrate) were dissolved with heating in 600 cc of water. The solution is decolorized with Norit, cooled and then filtered off. 28.8 grams of a white crystalline salt (dihydrate) is obtained with MP 284°C (decomposition).

References

Merck Index 6739
Kleeman & Engel p. 658
I.N. p. 704
Haraoka, R. and Kamiya, T.; US Patent 3,271,398; September 6, 1966; assigned to Fujisawa Pharmaceutical Co., Ltd., Japan

ORGOTEIN

Therapeutic Function: Antiinflammatory

Chemical Name: See Structural Formula

Common Name: Ormetein

Structural Formula: Orgotein is a complex protein with a molecular weight of about 33,000. It is a divalent metal (Mg, Cu, Zn) chelated structure

Chemical Abstracts Registry No.: 9016-01-7

Trade Name	Manufacturer	Country	Year Introduced
Ontosein	Gruenenthal	W. Germany	1980
Peroxinorm	Protochemie	Switz.	1982
Peroxinorm	Gruenenthal	Japan	1982
Oxinorm	Zambeletti	Italy	-

Raw Materials

Beef blood
Ethanol
Chloroform

Manufacturing Process

Fresh beef blood was centrifuged, e.g., at about 2,600 to 5,000 x g for 10 minutes at 0°C and the plasma decanted. The red blood cells were then washed at least twice and preferably repeatedly with 2 to 3 volumes of 0.9% saline solution. The washed red blood cells were lysed by mixing with 1.1 volumes of cold deionized water containing 0.02% detergent (Saponin). After a minimum of 30 minutes at 4°C with stirring, 0.25 volume (per volume of hemolysate) of ethyl alcohol at -15°C was slowly added while stirring followed by 0.31 volume (per volume of hemolysate) of chloroform, also at -15°C. Stirring was continued for about 15 minutes at -5°C or below, at which time, the mixture was a thick paste. The hemoglobin precipitation was carried out in a cold bath which was kept at below -10°C. After the paste had stood for a further 15 minutes at 4°C, 0.2 volume of cold 0.15 M NaCl solution was added, giving an easily poured suspension. The precipitate and excess chloroform were removed by centrifuging at about 12,000 to 20,000 x g at about -10°C for 10 minutes. The supernatant liquid was removed and if desired, filtered and briefly dialyzed against cold-deionized water, prior to lyophilization.

The alcohol chloroform precipitate was dislodged, chloroform was removed, the pellet broken up and reextracted with about an equal amount of deionized water by blending the precipitate and the water in a blender and thereafter centrifuging. The reextraction solution was dialyzed and lyophilized with the main extract. If the process proceeds normally, the reextraction of the precipitated hemoglobin usually yields up to 30% of protein mixture present in the original supernatant. An additional reextraction may give an additional

5 to 15%.

The lyophilized material was redissolved in 0.025 M tris-glycine buffer containing 0.001 M Mn^{2+} at pH 7.5 (usually to a concentration of 20 mg/ml). The solution was heated at or near 65°C for about 15 minutes. This step removes the carbonic anhydrase and other heat labile proteins from the solution. After heating, the solution was rapidly cooled in an ice bath to 5°C. The solution was then centrifuged at 20,000 x g at 0°C for 10 minutes to remove the precipitate. Filtration through "Versapore" works equally well. The supernatant was thoroughly dialyzed against deionized water to remove excess metal ions and buffer and then lyophilized. The resulting solid consists largely of orgotein.

References

Merck Index 6742
DOT 9 (1) 34 (1973) 11 (3) 103 (1975) and 13 (3) 105 (1977)
I.N. p. 705
Huber, W.; US Patent 3,579,495; May 18, 1971; assigned to Diagnostic Data, Inc.
Huber, W.; US Patent 3,687927; August 29, 1972; assigned to Diagnostic Data, Inc.

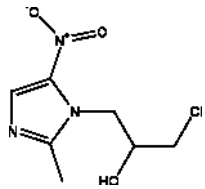
ORNIDAZOLE

Therapeutic Function: Antiinfective

Chemical Name: α-(Chloromethyl)-2-methyl-5-nitro-1H-imidazole-1-ethanol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 16773-42-5

Trade Name	Manufacturer	Country	Year Introduced
Tiberal	Roche	W. Germany	1977
Tiberal	Roche	Italy	1981
Tiberal	Roche	France	1981
Tiberal	Roche	Switz.	1982

Trade Name	Manufacturer	Country	Year Introduced
Tiberal	Roche	Australia	1983
Kolpicid	Roche	Sweden	1983
Madelen	Finadiet	Argentina	-
Ornidal	Selvi	Italy	-

Raw Materials

1-(2,3-Epoxypropyl)-2-methyl-5-nitroimidazole
Hydrogen chloride

Manufacturing Process

5g of 1-(2,3-epoxypropyl)-2-methyl-5-nitroimidazole was added to 30 ml of concentrated aqueous hydrochloric acid. The solution was heated to the boiling point for 20 minutes, chilled, diluted with 30 ml of water and carefully neutralized with ammonia to a pH of 7 to 8. It was then saturated with ammonium sulfate. The precipitated oil crystallized after several days. Recrystallized from toluene, there was obtained the 1-(3-chloro-2-hydroxypropyl)-2-methyl-5-nitroimidazole product melting at 77°C to 78°C.

References

Merck Index 6746
OCDS Vol. 3 p. 131 (1984)
DOT 11 (9) 369 (1975)
I.N. p. 706
REM p. 1224
Hoffer, M.; US Patent 3,435,049; March 25, 1969; assigned to Hoffmann-LaRoche, Inc.

ORNIPRESSIN

Therapeutic Function: Vasoconstrictor

Chemical Name: 8-L-Ornithinevasopressin

Common Name: -

Chemical Abstracts Registry No.: 3397-23-7

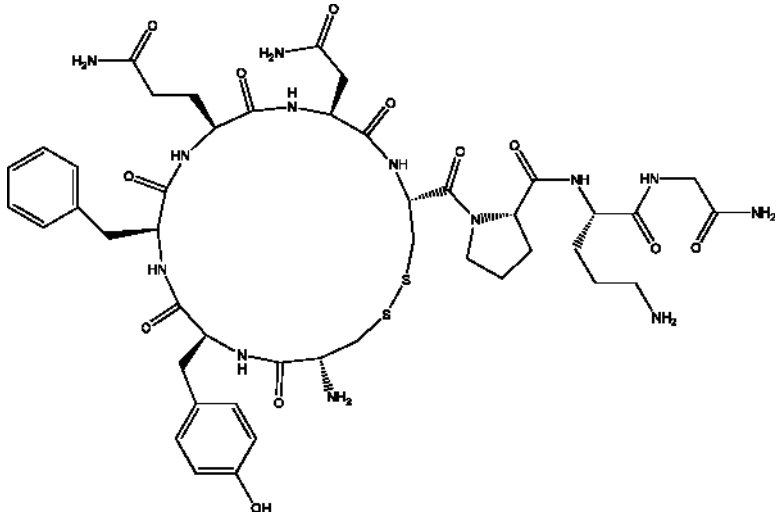
Trade Name	Manufacturer	Country	Year Introduced
POR-8	Sandoz	W. Germany	1977

Raw Materials

N-α-Carbobenzoxy-N-δ-toluenesulfonyl-L-ornithine
Glycine ethyl ester

N-Carbobenzoxy-L-proline
N-Carbobenzoxy-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-azide
N-Carbobenzoxy-S-benzyl-L-cysteinyl-L-tyrosyl-L-phenylalanine azide
Sodium
Ammonia

Structural Formula:



Manufacturing Process

(a)N-α-carbobenzoxy-N-δ-p-toluenesulfonyl-L-ornithyl-glycine ethyl ester: 104 g of N-α-carbobenzoxy-N-δ-p-toluenesulfonyl-L-ornithine and 27 g of glycine ethyl ester are dissolved in 450 cc of acetonitrile, the mixture is cooled at 0°C, 51 g of dicyclohexyl carbodiimide are added and the mixture is shaken at room temperature for 4 hours. Precipitated dicyclohexyl urea is filtered off and washed with acetonitrile. The whole filtrate is evaporated in a vacuum. The residue crystallizes after the addition of petroleum ether. After recrystallization from n-propanol, 93 g of N-α-carbobenzoxy-N-δ-toluenesulfonyl-L-ornithyl-glycine ethyl ester are obtained; melting point 136°C; $[\alpha]_D^{22}$ = -6.5° (96% ethanol).

(b) N-carbobenzoxy-L-prolyl-N-δ-p-toluenesulfonyl-L-ornithyl-glycinamide: 90 g of N-α-carbobenzoxy-N-δ-p-toluenesulfonyl-L-ornithyl-glycine ethyl ester are dissolved in 800 cc of anhydrous acetic acid which has been saturated with hydrogen bromide. The mixture is left to stand for one hour at 20°C, evaporated in a vacuum at a temperature below 40°C and the residue washed carefully with diethyl ether. The residue is dissolved in 500 cc of acetonitrile, 25 cc of triethylamine and 43 g of N-carbobenzoxy-L-proline are added, cooling is effected at 0°C, 355 g of dicyclohexyl carbodiimide are then added and the mixture shaken overnight at 20°C. After filtering off dicyclohexyl urea, the filtrate is evaporated in a vacuum at 30°C, the residue dissolved in ethyl acetate and this solution is washed with dilute sulfuric acid and aqueous

ammonia. After drying over sodium sulfate, the ethyl acetate is removed by evaporation in a vacuum and the residue dissolved in 1 liter of absolute ethanol. The solution is cooled at 0°C, saturated with ammonia and left to stand overnight at 20°C. After evaporating in a vacuum at 30°C, the residue is recrystallized from dimethylformamide/ethyl acetate. 58 g of N-carbobenzoxy-L-prolyl-N-δ-p-toluenesulfonyl-L-ornithyl-glycinamide are obtained: melting point 122°C (with decomposition).

(c) N-carbobenzoxy-L-glutaminyl-L-asparaginyl-S-benzyl-L-cystsinyl-L-prolyl-N-δ-p-toluenesulfonyl-L-ornithyl-glycinamide: 100 g of N-carbobenzoxy-L-prolyl-N-δ-p-toluenesulfonyl-L-ornithyl-glycinamide are dissolved in 500 cc of anhydrous acetic acid which has been saturated with hydrogen bromide, the solution is left to stand for one hour at 20°C and is evaporated in a vacuum at a temperature below 40°C. The residue is carefully washed with diethyl ether and then added to a solution of 100 g of N-carbobenzoxy-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-azide and 26 cc of triethylamine in 1,000 cc of dimethylformamide. The mixture is left to stand overnight at 20°C, 3,000 cc of ethyl acetate are added thereto, the precipitate is filtered off and washing is effected with ethyl acetate. 105 g of N-carbo-benzoxy-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-N-δ-p-toluenesulfonyl-L-ornithyl-glycinamide are obtained; melting point 193°C; $[\alpha]_D^{20}$ = -38.5°(dimethylformamide).

(d) N-carbobenzoxy-S-benzyl-L-cysteinyl-L-tyrosyl-L-phenyl-alanyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-N-δ-p-toluenesulfonyl-L-ornithyl-glycinamide: 50 g N-carbobenzoxy-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-N-δ-p-toluenesulfonyl-L-ornithyl-glycinamide are dissolved in 250 cc of anhydrous acetic acid which has been saturated with hydrogen bromide and the solution is left to stand for one hour at 20°C. After evaporating the solvent in a vacuum at a temperature below 40°C, the residue is carefully washed with diethyl ether and a solution of 31.5 g of N-carbobenzoxy-S-benzyl-L-cysteinyl-L-tyrosyl-L-phenylalanine-azide and 7.5 cc of triethylamine in 250 cc of dimethylformamide is added thereto. The mixture is left to stand for 2 days at 20°C. 1,000 cc of ethyl acetate are subsequently added and the precipitate is washed with ethyl acetate. After drying in a vacuum at 30°C. the product is washed with warm methanol. 45 g of N-carbobenzoxy-S-benzyl-L-cysteinyl-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-N-δ-p-toluenesulfonyl-L-ornithyl-glycinamide are obtained; melting point 224°C.

(e) L-cysteinyl-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparaginyl-L-cysteinyl-L-prolyl-L-ornirhyl-glycinamide: The necessary amount of sodium or potassium metal is added to a solution of 5 g of N-carbobenzoxy-S-benzyl-L-cysteinyl-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-N-δ-p-toluenesulfonyl-L-ornithyl-glycinamide in 1,200 cc of dry liquid ammonia, while stirring at the boiling temperature of the solution, to give a stable blue coloration. After the addition of 3 g of ammonium chloride, the solution is evaporated to dryness. The residue contains L-cysteinyl-L-tyrosyl-L-phenyl-alanyl-L-glutaminyl-L-asparaginyl-L-cysteinyl-L-prolyl-L-ornithyl-glycinamide.

References

Merck Index 6747

DOT 13 (11) 498 (1977)
I.N. p. 706
Boissonnas, R. and Huguenin, R.; US Patent 3,299,036; January 17, 1967; assigned to Sandoz Ltd. (Switzerland)

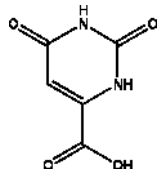
OROTIC ACID

Therapeutic Function: Hepatoprotectant

Chemical Name: 4-Pyrimidinecarboxylic acid, 1,2,3,6-tetrahydro-2,6-dioxo-

Common Name: Acide orotique; Acidum oroticum; Animal galactose factor; Orotic acid; Vitamin B13; Whey factor

Structural Formula:



Chemical Abstracts Registry No.: 65-86-1

Trade Name	Manufacturer	Country	Year Introduced
Lactinium	Roland	-	-

Raw Materials

Ketene	Trichloroacetyl chloride
Urea	Acetic acid
Sulfuric acid	Sodium hydroxide

Manufacturing Process

91.7 g (0.5 mol) of trichloroacetyl chloride was cooled to -35°C in a glass vessel by means of a cooling brine. In the course of 3 h, 27.0 g (0.06 mol) of pure ketene was introduced through a tube. After completion of the reaction, the vessel was immediately put under dry nitrogen to prevent penetration of moisture. So γ,γ,γ-trichloroacetoacetylchloride was produced.

The reaction mixture containing the γ,γ,γ-trichloroacetoacetyl chloride was transfered under nitrogen to a dropping funnel and in the course of 15 min was added with vigorous agitation to a suspension of 69.0 g (1.15 mole) of urea in 90.0 g of anhydrous acetic acid. Water cooling was used so that the reaction temperature would not exceed 40°C. After completion of the addition, the reaction mixture was heated as rapidly as possible to 115°C, and held at

this temperature for 30 min.

Subsequently there was cooling and one more 99.0 g of glacial acetic acid and 180.0 g of water were added. The precipitated 6-trichloromethyluracil was filtered off and dried at 60°C in a vacuum drying cabinet. The yield was 91.0 g or 80%.

In a glass vessel equipped with an agitator, thermometer and pH electrode, 500 ml of water was placed and heated to 80°C. 50 g of 6-trichloromethyluracil was then added. By means of the pH electrode, the addition of sodium hydroxide was automatically controlled so that the pH value throughout the whole hydrolysis was 6.5. Into, 165 ml of 5 N NaOH was consumed. Finally, the hydrolysis solution was cooled and the precipitated sodium orotate filtered off.

The crude sodium orotate was again suspended at 80°C in water and brought into solution (pH 10.5) by addition of 30 ml of 5 N NaOH. After treatment with active charcoal, the solution was acidified with 30.0 g of 50% sulfuric acid. The solution was then cooled. The orotic acid was filtered off and carefully washed with water. After drying, 20.5 g of orotic acid, having a purity of 99.3% (titration) was obtained. This corresponds to a 60% yield.

References

Jackson B; US Patent No. 4,064,126; Dec. 20, 1977; Assigned: Lonza, Ltd., Gampel, Switzerland

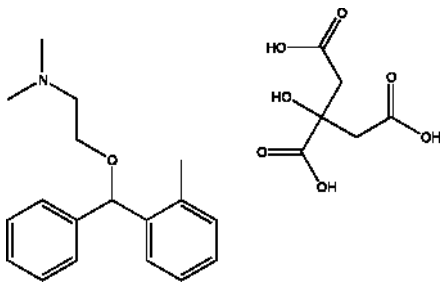
ORPHENADRINE CITRATE

Therapeutic Function: Muscle relaxant

Chemical Name: N,N-Dimethyl-2-[(2-methylphenyl)phenylmethoxy] ethanamine citrate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 4682-36-4; 83-98-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Norflex	Riker	US	1959
Neocyten	Central	US	1975
X-Otag	Tutag	US	1976
Banflex	O'Neal Jones	US	1980
Bio-Flex	Foy	US	-
Flexin	Taro	Israel	-
Mioflex	Formenti	Italy	-
Myotrol	Legere	US	-
Norgesic	Riker	US	-
Ro-Orphena	Robinson	US	-
Tega-Flex	Ortega	US	-

Raw Materials

o-Methylbenzhydryl bromide
β-Dimethylaminoethanol
Citric acid

Manufacturing Process

As described in US Patent 2,567,351, o-methylbenzhydryl bromide is added slowly to β-dimethylaminoethanol at refluxing temperature. After the addition has been completed the mixture is refluxed and stirred for an additional 16 hours. The mixture is cooled and the bottom layer consisting of the crude hydrobromide salt of β-dimethylaminoethanol is drawn off. The excess amino alcohol is distilled from the upper layer in vacuo and the residue is reacted with citric acid.

References

Merck Index 6752
Kleeman & Engel p. 661
PDR pp. 1033, 1452
OCDS Vol. 1 p. 42 (1977)
DOT 9 (6) 247 (1973) and 18 (2) 90 (1982)
I.N. p. 707
REM p. 932
Rieveschi, G. Jr.; US Patent 2,567,351; September 11, 195 : assigned to Parke, Davis & Company
Harms, A.F.; US Patent 2,991,225; July 4, 1961 ; assigned 1 NV Koninklijke Pharmaceutische Fabrieken, Netherlands

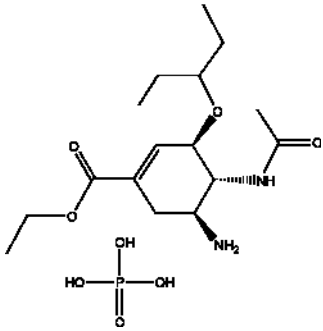
OSELTAMIVIR PHOSPHATE

Therapeutic Function: Antiviral

Chemical Name: 1-Cyclohexene-1-carboxylic acid, 4-(acetylamino)-5-amino-3-(1-ethylpropoxy)-, ethyl ester, (3R,4R,5S)-, phosphate (1:1)

Common Name: Oseltamivir phosphate

Structural Formula:



Chemical Abstracts Registry No.: 204255-11-8; 196618-13-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Tamiflu	Hoffmann-La Roche Inc.	-	-

Raw Materials

Shikimic acid	Boron trifluoride diethyl etherate
Sodium azide	1,8-Diazabicyclo[5.4.0]undec-7-ene
Dimethoxypropane	4-Toluenesulfonic acid
Triethylamine	Methanesulfonyl chloride
Trityl chloride	N,N-Diisopropylethylamine
Triphenylphosphine	Chloromethyl methyl ether
Acetic anhydride	Potassium hydroxide
Ethanol	Ammonium chloride
Phosphoric acid	Dimethylaminophenol

2-(Diethylamino)ethyl(bicyclohexyl)-1-carboxylate

Manufacturing Process

To a suspension of shikimic acid (25 g, 144 mmol, Aldrich) in methanol (300 ml) was added p-toluenesulfonic acid (274 mg, 1.44 mmol, 1 mol %) and the mixture was heated to reflux for 2 h. After adding more p-toluenesulfonic acid (1 mol %) the reaction was refluxed for 26 h and was evaporated. The crude methyl ester (28.17 g) was suspended in acetone (300 ml) and was treated with dimethoxypropane (35 ml, 288 mmol) and was stirred at room temperature for 6 h and then was evaporated. The crude product was dissolved in ethyl acetate (400 ml) and was washed with saturated $NaHCO_3$ (3 times 125 ml) and saturated NaCl. The organic phase was dried ($MgSO_4$), filtered, and evaporated to afford crude 7-hydroxy-2,2-dimethyl-3a,6,7,7a-

tetrahydro-benzo[1,3]dioxole-carboxylic acid methyl ester (about 2.94 g).

To a solution of 7-hydroxy-2,2-dimethyl-3a,6,7,7a-tetrahydro-benzo[1,3]dioxole-carboxylic acid methyl ester (29.4 g, 141 mmol) in CH_2Cl_2, (250 ml) at 0°C was added triethylamine (29.5 ml, 212 mmol) followed by the addition of methanesulfonyl chloride (13.6 ml, 176 mmol) over a period of 10 min. The reaction was stirred at 0°C for 1 h and ice cold water (250 ml) was added. After transfer to a separatory funnel, the organic phase was washed with water, 5% citric acid (300 ml), saturated $NaHCO_3$ (300 ml) and was dried ($MgSO_4$), filtered, and evaporated. The crude product was filtered through a short plug of silica gel on a fritted glass funnel eluting with ethyl acetate. The filtrate was evaporated to afford 7-methanesulfonyloxy-2,2-dimethyl-3a,6,7,7a-tetrahydro-benzo[1,3]dioxole-carboxylic acid methyl ester (39.5 g, 91%) as a viscous oil.

To a solution of 7-methanesulfonyloxy-2,2-dimethyl-3a,6,7,7a-tetrahydro-benzo[1,3]dioxole-carboxylic acid methyl ester (35.85 g, 117 mmol) in methanol (500 ml) was added p-toluenesulfonic acid (1.11 g, 5.85 mmol, 5 mol %) and the solution was refluxed for 1.5 h and was evaporated. The residue was redissolved in methanol (500 ml) and was refluxed an additional 4 h. The solvent was evaporated and the crude oil was triturated with diethyl ether (250 ml). After completing the crystallization overnight at 0°C, the solid was filtered and was washed with cold diethyl ether, and dried to afford 3,4-dihydroxy-5-methanesulfonyloxy-cyclohex-1-enecarboxylic acid methyl ester (24.76 g) as a white solid. Evaporation of the filtrate and crystallization of the residue from methanol/diethyl ether gave an additional 1.55 g. Obtained 26.3 g (85%) of the 3,4-dihydroxy-5-methanesulfonyloxy-cyclohex-1-ene-1-carboxylic acid methyl ester.

A suspension of 3,4-dihydroxy-5-methanesulfonyloxy-cyclohex-1-ene-1-carboxylic acid methyl ester (20.78 g, 78 mmol) in tetrahydrofuran (400 ml) at 0°C was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (11.7 ml, 78 mmol) and was stirred at room temperature for 9 h at which time the reaction was complete. The reaction was evaporated and the crude residue was dissolved in CH_2Cl_2 (200 ml) and was washed with saturated NaCl (300 ml). The aqueous phase was extracted with CH_2Cl_2 (2 times 200 ml). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated. The crude product was purified on silica gel (ethyl acetate) to afford 5-hydroxy-7-oxa-bicyclo[4.1.0]hept-3-ene-3-carboxylic acid methyl ester (12 g, 90%) as a white solid.

To a solution of 5-hydroxy-7-oxa-bicyclo[4.1.0]hept-3-ene-3-carboxylic acid methyl ester (4 g, 23.5 mmol) in CH_2Cl_2 (100 ml) was added N,N'-diisopropylethylamine (12.3 ml, 70.5 mmol) followed by chloromethyl methyl ether (3.6 ml, 47 mmol, distilled from tech. grade). The solution was refluxed for 3.5 h and the solvent was evaporated. The residue was partitioned between ethyl acetate (200 ml) and water (200 ml). The aqueous phase was extracted with ethyl acetate (100 ml). The combined organic extracts were washed with saturated NaCl (100 ml), dried ($MgSO_4$), filtered, and evaporated to afford 4.9 g of a solid residue of 5-methoxymethoxy-7-oxa-bicyclo[4.1.0]hept-3-ene-3-carboxylic acid methyl ester which was of suitable purity to use directly in the next step: melting point 62°-65°C (crude); melting point 64°-66°C (diethyl ether/hexane).

To a solution of 5-methoxymethoxy-7-oxa-bicyclo[4.1.0]hept-3-ene-3-carboxylic acid methyl ester (4.9 g, 22.9 mmol) in 8/1-MeOH/H_2O (175 ml, v/v) was added sodium azide (7.44 g, 114.5 mmol) and ammonium chloride (2.69 g, 50.4 mmol) and the mixture was refluxed for 15 h. The reaction was diluted with water (75 ml) to dissolve precipitated salts and the solution was concentrated to remove methanol. The resulting aqueous phase containing a precipitated oily residue was diluted to a volume of 200 ml with water and was extracted with ethyl acetate (3 times 100 ml). The combined organic extracts were washed with saturated NaCl (100 ml), dried ($MgSO_4$), filtered and evaporated. The crude was purified on silica gel (1/1-hexane/ethyl acetate) to afford 5-azido-4-hydroxy-3-methoxymethoxy-cyclohex-1-ene-1-carboxylic acid methyl ester (5.09 g, 86%) as a pale yellow oil. Subsequent preparations of 5-azido-4-hydroxy-3-methoxymethoxy-cyclohex-1-ene-1-carboxylic acid methyl ester provided material which was of sufficient purity to use in the next step without further purification.

To a solution of 5-azido-4-hydroxy-3-methoxymethoxy-cyclohex-1-ene-1-carboxylic acid methyl ester (6.47 g, 25.2 mmol) in CH_2Cl_2 (100 ml) at 0°C was added first triethylamine (4.4 ml, 31.5 mmol) then methanesulfonyl chloride (2.14 ml, 27.7 mmol). The reaction was stirred at 0°C for 45 min then was warmed to room temperature stirring for 15 min. The reaction was evaporated and the residue was partitioned between ethyl acetate (200 ml) and water (100 ml). The organic phase was washed with water (100 ml), saturated $NaHCO_3$ (100 ml), saturated NaCl (100 ml). The water washes were extracted with a single portion of ethyl acetate which was washed with the same $NaHCO_3$/NaCl solutions. The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated. The 5-azido-4-methansulfonyloxy-3-methoxymethoxy-cyclohex-1-ene-1-carboxylic acid methyl ester was of suitable purity to be used directly in the next step.

To a solution of 5-azido-4-methansulfonyloxy-3-methoxymethoxy-cyclohex-1-ene-1-carboxylic acid methyl ester (8.56 g, 25 mmol) in THF (150 ml) at 0°C was added Ph_3P (8.2 g, 31 mmol), initially adding a third of the amount while cooling and then after removing the ice bath adding the remainder of the Ph_3P over a period of 10-15 min. After complete addition of the Ph_3P the reaction was stirred at room temperature for 3 h with the formation of a white precipitate. To this suspension was added triethyl amine (5.2 ml, 37.5 mmol) and water (10 ml) and the mixture was stirred at room temperature for 12 h. The reaction was concentrated to remove THF and the residue was partitioned between CH_2Cl_2 (200 ml) and saturated NaCl (200 ml). The aqueous phase was extracted with several portions of CH_2Cl_2 and the combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to afford a crude product which was purified on silica gel (10% MeOH/EtOAc) to afford 5-methoxymethoxy-7-aza-bicyclo[4.1.0]hept-3-ene-3-carboxylic acid methyl aster (4.18 g, 78%) as an oil which typically contained trace amounts of triphenylphosphine oxide impurity.

To a solution of 5-methoxymethoxy-7-aza-bicyclo[4.1.0]hept-3-ene-3-carboxylic acid methyl aster (3.2 g, 15 mmol) in DMF (30 ml) was applied a vacuum on a rotary evaporator (40°C) for several minutes to degas the solution. To the solution was added sodium azide (4.9 g, 75 mmol) and ammonium chloride (1.6 g, 30 mmol) and the mixture was heated at 65°-

70°C for 21 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (about 100 ml) and was filtered. The filtrate was evaporated and the residue was partitioned between diethyl ether (100 ml) and saturated NaCl (100 ml). The organic phase was washed again with saturated NaCl (100 ml), dried ($MgSO_4$), filtered, and was evaporated. Additional crude product was obtained from the aqueous washings by extraction with ethyl acetate and treated in the same manner as described above. The crude product was purified on silica gel (5% MeOH/CH_2Cl_2) to afford 4-amino-5-azido-3-methoxymethoxy-cyclohex-1-ene-1-carboxylic acid methyl ester (2.95 g) as an oil which contained a small amount of triphenylphosphine oxide impurity from the previous step.

4-Amino-5-azido-3-methoxymethoxy-cyclohex-1-ene-1-carboxylic acid methyl ester (2.59 g, 10.2 mmol) was dissolved in 5% HCl/MeOH (30 ml) and the solution was stirred for 3 h at room temperature. Additional 5% HCl/MeOH (10 ml) was added stirring 1 h and the solvent was evaporated to afford 2.52 g of the HCl salt as a tan solid after high vacuum. To a suspension of the HCl salt in CH_2Cl_2 (50 ml) at 0°C was added triethylamine (3.55 ml, 25.5 mmol) followed by the addition of solid trityl chloride (5.55 g, 12.8 mmol) in one portion. The mixture was stirred at 0°C for 1 h and then was warmed to room temperature stirring for 2 h. The reaction was cooled to 0°C, triethylamine (3.6 ml, 25.5 mmol) was added and methane sulfonyl chloride (0.97 ml, 12.5 mmol) was added, stirring the resulting mixture for 1 h at 0°C and for 22 h at room temperature. The reaction was evaporated and the residue was partitioned between diethyl ether (200 ml) and water (200 ml). The organic phase was washed with water (200 ml) and the combined aqueous phases were extracted with diethyl ether (200 ml). The combined organic extracts were washed with water (100 ml), saturated NaCl (200 ml) and were dried (Na_2SO_4), filtered, and evaporated. The crude product was purified on silica gel (1/1-hexane/CH_2Cl_2) to afford 5-azido-7-trityl-7-aza-bicyclo[4.1.0]hept-2-ene-3-carboxylic acid methyl ester (3.84 g, 86%) as a white foam.

BF_3Et_2O (43 μl, 0.35 mmol) was added to a solution of 5-azido-7-trityl-7-aza-bicyclo[4.1.0]hept-2-ene-3-carboxylic acid methyl ester (104 mg, 0.24 mmol) in 3-pentanol (2.0 ml) under argon with stirring at room temperature. The pale solution was heated at 75°C for 1.5 h and then concentrated in vacuo to give a brown residue which was dissolved in dry pyridine (2.0 ml) and treated with acetic anhydride (235 ml) and a catalytic amount of dimethylaminophenol (few crystals) at 0°C. The reaction was allowed to warm to room temperature and stirred for 1.5 h, concentrated in vacuo and partitioned between ethyl acetate and brine. The organic layer was separated and washed sequentially with dilute HCl, saturated sodium bicarbonate, brine and dried over $MgSO_4$. Concentration in vacuo followed by flash chromatography of the residue on silica gel (50% hexanes in ethyl acetate) gave 41 mg (53%) of the 4-acethylamino-5-azido-3-(1-ethyl-propoxy)-cyclohex-1-ene-1-carboxylic acid methyl ester.

To a solution of 4-acethylamino-5-azido-3-(1-ethyl-propoxy)-cyclohex-1-ene-1-carboxylic acid methyl ester (268 mg, 0.83 mmol) in THF (7.0 ml) was added aqueous KOH (1.60 ml of a 1.039 N solution) at room temperature. After stirring for 19 h at room temperature the reaction was acidified to pH 4.0 with Amberlite IR-120 (H^+) acidic resin. The resin was filtered and washed with water and ethanol. Concentration in vacuo gave the crude 4-

acethylamino-5-azido-3-(1-ethyl-propoxy)-cyclohex-1-ene-1-carboxyllic acid as a pale orange foam which was used for the next reaction without any further purification.

To a solution of 4-acethylamino-5-azido-3-(1-ethyl-propoxy)-cyclohex-1-ene-1-carboxyllic acid (crude from previous reaction, assume 0.83 mmol), ethyl alcohol (150 ml), and catalytic dimethylaminophenol in (CH_2Cl_2 (6.0 ml) was added 2-(diethylamino)ethyl(bicyclohexyl)-1-carboxylate (172 mg, 0.83 mmol) in one portion at room temperature. After several minutes a precipitate formed and after an additional 1 h of stirring the reaction was filtered and washed with CH_2Cl_2. Concentration in vacuo afforded a pale solid which was purified by flash chromatography on silica gel (50% hexanes in ethyl acetate) to give 272 mg (96%) of 4-acethylamino-5-azido-3-(1-ethyl-propoxy)-cyclohex-1-ene-1-carboxyllic acid ethyl ester as a white solid.

Triphenylphosphine (342 mg, 1.30 mmol) was added in one portion to a solution of 4-acethylamino-5-azido-3-(1-ethyl-propoxy)-cyclohex-1-ene-1-carboxyllic acid ethyl ester (272 g, 0.80 mmol) in THF (17 ml) and water (1.6 ml). The reaction was then heated at 50°C for 10 h, cooled and concentrated in vacuo to give a pale white solid. Purification of the crude solid by flash chromatography on silica gel (50% methanol in ethyl acetate) gave 242 mg (96%) of the 4-acethylamino-5-amino -3-(1-ethyl-propoxy)-cyclohex-1-ene-1-carboxyllic acid ethyl ester as a pale solid.

The racemic mixture are separated into their individual, substantially optically pure isomers through well-known techniques such as, for example, the separation of diastereomeric salts formed with optically active adjuncts, e.g. acids or bases followed by conversion back to the optically active substances. So the 4-acethylamino-5-amino-3-(1-ethyl-propoxy)-cyclohex-1-ene-1-carboxyllic acid ethyl ester,(3α,4β,5α) was obtained.

The 4-acethylamino-5-amino-3-(1-ethyl-propoxy)-cyclohex-1-ene-1-carboxyllic acid ethyl ester, (3α,4β,5α) is dissolved in H_3PO_4 to give the corresponding water soluble salt form.

References

Bischofberger N.W. et al.; US Patent No. 5,763,483; June 9, 1998; Assigned: Gilead Sciences, Inc., Foster City. Calif.

OTILONIUM BROMIDE

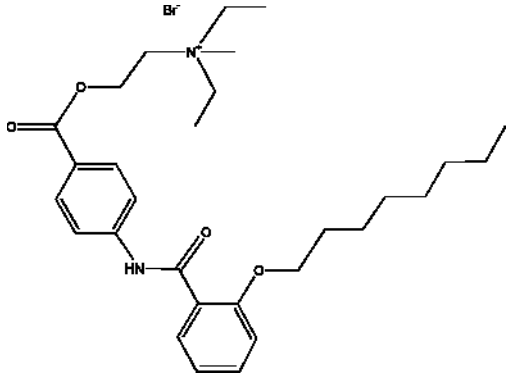
Therapeutic Function: Anticholinergic, Spasmolytic

Chemical Name: Ammonium, diethyl(2-hydroxyethyl)methyl-, bromide, p-(o-(octyloxy)benzamido)benzoate

Common Name: Octylonium bromide; Otilnium bromide

Chemical Abstracts Registry No.: 26095-59-0; 105360-89-2 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Spasmomen	Minapharm Co.	-	-
Spasmomen 40	A.Menarini Pharmaceutical Industre's Group Ltd.	-	-
Doralin	Menarini Hellas A.E.	-	-
Menoctyl	Menarini	-	-
Pasminox 40	Beta	-	-
Spasen	F.I.R.M.A. S.p.A.	-	-
Spasmoctyl	Menarini	-	-

Raw Materials

Sodium hydroxide
N-Diethylaminoethanol
Methyl bromide
2-Diethylamine-ethyl-p-aminobenzoate
o-Octyloxybenzoyl chloride
2-Diethylaminoethyl chloride

Manufacturing Process

3 Methods of producing of p-[2-(n-octyloxy)benzoyl]aminobenzoate of N-diethylammoniumethanol:

1. 21.20 g (0.1 mole) of o-octyloxybenzoyl chloride and aqueous 10% NaOH are added at room temperature, with stirring and by slow dropping to 23.63 g (0.1 mole) of 2-diethylamine-ethyl-p-aminobenzoate in 100 ml of water, in such a manner as to keep the reaction mixture slightly alkaline. After concluding the slow dropping the solution is kept under stirring for 1 h and then the precipitate is collected. This precipitate, p-[2-(n-octyloxy)benzoyl] aminobenzoate of N-diethylammoniumethanol dried and recrystallized from hexane, has a melting point of 81°-82°C.

2. To 31.3 g (0.1 mole) of p-[2-(n-octyloxy)benzoyl]aminobenzoate acid in 300 ml of ethanol, are added 4.0 g (0.1 mole) of finely ground NaOH and the whole is heated to reflux for 1 h. Then 20.25 g (0.15 mol) of 2-

diethylaminoethyl chloride are slowly dropped under stirring and the heating is continued for 4 h. After cooling, the sodium chloride formed is filtered off and the solvent is separated by distillation, and the excess of the base, under a reduced pressure. The residue of p-[2-(n-tyloxy)benzoyl]aminobenzoate of N-diethylammoniumethanol, recrystallized from hexane, has a melting point of 81°-82°C.

3. 11.7 g (0.1 mole) of N-diethylaminoethanol in 200 ml of anhydrous pyridine are added by careful dropping, 34.7 g (0.1 mole) of the chloride of p-[2-(n-octyloxy)benzoyl]aminobenzoate acid and the mixture is heated in a water-bath for 3 h. The solvent is then separated by vacuum concentration, the residue is taken up with water, alkalinized and extracted with ether. The collected ether extracts, anhydridised owing to the separation of the solvent, leave a residue of p-[2-(n-tyloxy)benzoyl]aminobenzoate of N-diethylammoniumethanol which, recrystallized from hexane, has a melting point of 81°-82°C.

p-[2-(n-Octyloxy)benzoyl]aminobenzoate of N-diethylmethylammoniumethyl bromide may be prepared by reaction of the p-[2-(n-octyloxy) benzoylaminobenzoate of N-diethylammoniumethanol with methylating agents such as methylbromide.

References

Chelardoni M. et al.; US Patent No. 3,536,723; Oct. 27, 1970; Assigned: A. Menarini Societa in Accomandita Semplice, Florence, Italy, a Italian corporate body

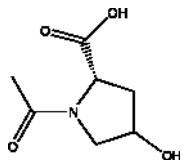
OXACEPROL

Therapeutic Function: Antirheumatic

Chemical Name: N-Acetyl-4-hydroxy-L-proline

Common Name: Aceprolinum

Structural Formula:



Chemical Abstracts Registry No.: 33996-33-7

Trade Name	Manufacturer	Country	Year Introduced
Jonctum	Merrell	France	1970
AHP-2000	Chephasaar	W. Germany	1975

Trade Name	Manufacturer	Country	Year Introduced
Jonctum	Merrell	Italy	1978
Tejuntivo	Valderrama	Spain	-

Raw Materials

L-Hydroxyproline
Acetic anhydride

Manufacturing Process

16.7 g (0.127 mol) of L-hydroxyproline are dissolved in 400 ml of pure boiling acetic acid. With vigorous boiling and agitation, a mixture of 13.7 ml (0.154 mol) of rectified acetic anhydride and 250 ml of pure acetic acid is added during 25 minutes. Without discontinuing the stirring, contents of the flask are cooled by simply causing fresh air to circulate externally round the flask until the temperature of the mixture is reduced to about 35°C. The acetic acid is removed by using a rotary evaporator without exceeding 35°C under a vacuum of about 15 mm Hg. After one hour, 20 ml of anhydrous toluene are added, then 10 ml of anhydrous acetone; the mixture is homogenized and concentrated again as above during 30 minutes. Then 25 ml of acetone are added again, and subsequently 20 ml of toluene, the product being concentrated again; gradually the solution is converted into an amber-colored crystallized paste. Finally, 30 ml of acetone are added to the residue, and stirring is carried out until the oily fraction surrounding the crystals is dissolved. The product is then cooled in an ice chamber, centrifuged, washed with anhydrous acetone and eventually dried, After recrystallization from acetone, crystals are obtained, melting point 132°C.

References

Merck Index 90
Kleeman & Engel p. 662
DOT 12 (1) 9 (1976)
I.N. p. 709
Coirre, P. and Coirre, B.; British Patent 1,246,141; September 15, 1971

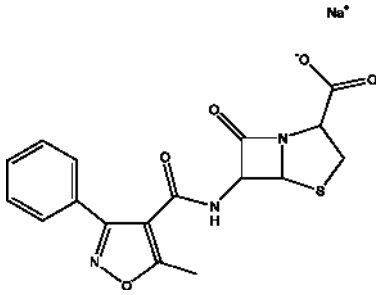
OXACILLIN SODIUM

Therapeutic Function: Antibacterial

Chemical Name: 3,3-Dimethyl-6-(5-methyl-3-phenyl-4-isoxazolecarboxamido)-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, sodium salt

Common Name: 6-(5-Methyl-3-phenyl-2-isoxazoline-4-carboxamido) penicillanic acid, sodium salt; 5-Methyl-3-phenyl-4-isoxazolylpenicillin, sodium salt

Structural Formula:



Chemical Abstracts Registry No.: 7240-38-2; 66-79-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Resistopen	Squibb	US	1962
Prostaphlin	Bristol	US	1962
Cryptocillin	Hoechst	W. Germany	1962
Bristopen	Bristol	France	1963
Penstapho	Bristol	Italy	1966
Bactocill	Beecham	US	1972
Oxabel	Sarva	Belgium	-
Penistafil	Antibioticos	Spain	-
Stapenor	Bayer	W. Germany	-
Staphcillin V	Banyu	Japan	-

Raw Materials

Benzaldehyde
Thionyl chloride
Hydroxylamine
6-Aminopenicillanic acid
Chlorine
Sodium bicarbonate
Ethyl acetoacetate

Manufacturing Process

(A) Benzaldoxime: (Reference, Vogel, Textbook of Practical Organic Chemistry, page 883) -Materials: (Theoretical yield, 121.1 grams of free oxime), 106.1 grams (1.0 mol) of benzaldehyde (NF grade), 69.5 grams (1.0 mol) of hydroxylamine hydrochloride (practical grade), 68.0 grams (1.7 mol) of sodium hydroxide (pellet).

Procedure: The sodium hydroxide is dissolved in 200 ml water and the benzaldehyde is added. With continued stirring the hydroxylamine hydrochloride is added in portions. Some heat is developed and eventually the benzaldehyde dissolves. The solution is stirred for 15 minutes and then cooled in an ice-bath. A waxy, crystalline mass separates, and after further cooling it is collected by suction and dried in air. Yield is 86 to 149 grams. This crude material is suitable for step (B).

(B) Benzohydroximic Chloride: [Reference, G.W. Perrold et al, J. Am. Chem. Soc., 79, 462 (1957)] - Materials: 121 grams (0.77 mol) of crude benzaldoxime from step (A), 500 ml of 8.3 N hydrochloric acid, chlorine.

Procedure: The crude product from (A) is suspended in the hydrochloric acid, cooled in an ice-salt mixture, and chlorine is passed into the mixture with stirring for ½ to 1 hour. Transient blue and green colors may be noticed in the mixture during this time. The temperature will probably rise to 3° to 5°C. The solid is collected by suction filtration and dried for an hour or so on the filter before use in (C). If at all possible, it should be used on the day of preparation. Yield is 71 grams (after 1½ hours on the filter).

(C) 5-Methyl-3-Phenyl-4-Isoxazolecarboxylic Acid: [Reference, A. Quilico and R. Rusco, Gazz. Chim. Ital. 67, 589 (1937); C.A. 32, 2117[7]] - Materials: 71 grams (0.45 mol) of crude benzohydroximic chloride from (E), 78 grams (0.60 mol) of ethyl acetoacetate (practical grade), 34 grams (0.60 mol) of sodium methoxide (95% minimum), 400 ml of methanol (reagent grade).

Procedure: The sodium methoxide is cautiously added in portions to 200 ml of methanol with stirring. Some heat is evolved. To this warm solution is rapidly added the ethyl acetoacetate with continued stirring. The solution is stirred for 10 minutes and then cooled in an ice-salt-acetone mixture (-25°C). If desired a Dry Ice-acetone cooling bath may be used to shorten the addition time. The crude material from (B) is dissolved in 200 ml of methanol. At this point it is probably easier to filter this mixture by suction to remove a large amount of insoluble solid, which is probably sodium chloride. The solid may be rinsed with more methanol.

The filtrate is chilled in ice-water and added to the cooled methanolic solution of the sodium derivative of ethyl acetoacetate at a rate which keeps the temperature of the re. action mixture below 0°C. The addition time will be 15 to 20 minutes if ice-salt-acetone is used as a coolant. This reaction is extremely exothermic.

The reaction mixture is stirred overnight at room temperature and filtered to remove the sodium chloride. The filtrate is stripped in vacuo and the crude ester (literature reports MP 48°C) is dissolved in 150 ml of ethanol; 28 grams (0.70 mol of sodium hydroxide in 90 ml of water is added and the solution is refluxed for 2 hours. After removal of the ethanol in vacuo the residue is dissolved in water and extracted twice with ether. Dissolved ether is removed from the aqueous solution in vacuo and it is acidified to pH 2 with concentrated hydrochloric acid.

The crystalline crude acid is dried briefly and then recrystallized from acetonitrile to give 32 grams of white product; MP 193° to 194.5°C (literature reports 189° to 190°C). Concentration of the mother liquor gives an additional 5 grams of material having a MP of 192.5 to 194°C. The 37 grams of material represents an 18% overall yield from benzaldehyde.

(D) The acid is converted to the acid chloride by reaction with thionyl chloride.

(E) 5-Methyl-3-Phenyl-4-Isoxazolylpenicillin: A solution of 4.43 grams of 5-methyl-3-phenylisoxazole-4-carbonyl chloride in 120 ml acetone was added

gradually to a stirred solution of 4.32 grams of 6-aminopenicillanic acid in 168 ml of 3% aqueous sodium bicarbonate and 50 ml acetone. When addition was complete the mixture was stirred at room temperature for 4 hours and then extracted with ether (2 x 200 ml), only the aqueous phase being retained. This aqueous solution was covered with 50 ml ether and adjusted to pH 2 by the addition of N hydrochloric acid. After separating the layers, the aqueous phase was extracted with two further 50 ml portions of ether. The combined ether solutions (which at this stage contained the free penicillin acid) were washed with water and then neutralized by shaking with 20 ml N sodium bicarbonate solution. The aqueous phase was separated, washed with ether, and evaporated at low temperature and pressure to leave the crude sodium salt of 5-methyl-3-phenyl-4-isoxazolylpenicillin as a white solid, which was finally dried in vacuo over phosphorus pentoxide and found to weigh 7.34 grams.

References

Merck Index 6777
Kleeman & Engel p. 662
PDR pp. 673, 708, 1606
OCDS Vol. 1 p. 413 (1977)
DOT 1 (3) 115 (1965)
I.N. p. 709
REM p. 1197
Doyle, F.P. and Nayler, J.H.C.; US Patent 2996,501; August 15, 1961

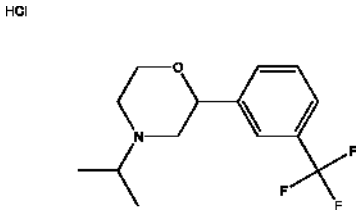
OXAFLOZANE HYDROCHLORIDE

Therapeutic Function: Antidepressant

Chemical Name: 2-(3-Trifluoromethyl)phenyl-4-isopropyl-tetrahydro-1,4-oxazine hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 26629-86-7; 26629-87-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Conflictan	Sarbach	France	1982
Conflictan	Riom Lab	France	-

Raw Materials

Bromine
Isopropylamine
(3-Trifluoromethyl)phenyl magnesium bromide
2-Chloroethylvinyl ether
Hydrogen chloride

Manufacturing Process

(1) 1,2-Dibromo-2-(2-chloro)ethoxyethane: 640 g of bromine (4 mols) are added dropwise, with stirring, to 426 g (4 mols) of 2-chloroethylvinyl ether dissolved in 1,040 ml of chloroform maintained at -10°C.

When addition is ended, the solvent and then the residue are distilled in vacuum to obtain 690 g of product. Yield = 65%.

(2) 2-(3-Trifluoromethyl)-2-(2-chloro)ethoxy-1-bromoethane: (3-Trifluoromethyl)phenyl magnesium bromide is prepared under the normal conditions for magnesium derivatives, from 48.6 g of magnesium turnings and 455.7 g of (3-trifluoromethyl)bromobenzeneand 1.5 liters anhydrous ether.

To the solution of the magnesium compound so obtained the following solution is added dropwise, with stirring so as to maintain a slight reflux of ether: 1,2-dibromo-2-(2-chloro)-ethoxyethane: 550 g. Anhydrous ether: 300 ml.

After the addition, reflux heating is continued for two hours, cooling is carried out and there is hydrolysis by the mixture: Ice: 500 g. Concentrated HCl: 200 ml.

The organic phase is decanted, washed in NaCl saturated water and dried on anhydrous Na_2SO_4; the ether is distilled and the residue is rectified in vacuum to obtain 361 g of the product. Yield = 54%.

According to gas phase chromatography, the product so obtained is about 95% pure and it can be used in further reactions without a second rectification.

(3) 2-(3-Trifluoromethyl)phenyl-4-isopropyl tetrahydro-1,4-oxazine hydrochloride: The following mixture is heated in an autoclave at 100°C; 2-(3-trifluoromethyl)-2-(2-chloro)-ethoxy-1-bromoethane: 33.15 g (0.1 mol); isopropylamine: 20 g (0.34 mol); toluene: 100 ml.

After filtration of the isopropylamine hydrochloride and bromohydrate, the solvent is stripped and the residue is admixed with ~ 4 N HCl and the aqueous phase is washed with ether. The aqueous phase is treated with 50% aqueous NaOH, the amine is ether-extracted and, after drying on anhydrous Na_2SO_4, the ether is distilled and the residue is rectified in vacuum to obtain 14 g of the product. Yield = 50%.

The hydrochloride is crystallized by adding ethyl acetate to the base and then adding the necessary amount of pure alcohol saturated in dry HCl. Melting point 164°C.

References

Merck Index 6780
DFU 3 (9) 667 (1978)
Kleeman & Engel p. 663
DOT 18 (10) 536 (1982)
I.N. p. 709
Mauvernay, R.Y., Busch, N., Moleyre, J. and Simond, J.; US Patent 3,637,680; January 25, 1972; assigned to Societe Anonyme: Centre Europeen De Recherches Mauvernay

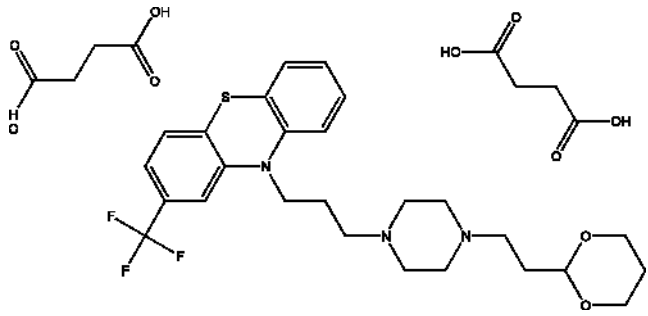
OXAFLUMAZINE DISUCCINATE

Therapeutic Function: Neuroleptic, Antihistaminic, Spasmolytic

Chemical Name: N-3-(2-Trifluoromethyl-10-phenothiazinyl)-propyl-N'-2-[2-(1,3-dioxanyl)]ethyl-piperazine disuccinate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 41761-40-4; 16498-21-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Oxaflumine	Diamant	France	1970

Raw Materials

N-[2-(3,1-Dioxanyl)ethyl]piperazine
2-Trifluoromethylphenothiazine
Succinic acid
1-Bromo-3-chloropropane
Sodium

Manufacturing Process

Preparation of N-(3-chloropropyl)-N'-[2-(1,3-dioxanyl)-ethyl]-piperazine: A solution of 30 g (0.15 mol) of N-[2-(1,3-dioxanyl)-ethyl]-piperazine and 11.8 g (0.075 mol) of 1-bromo-3-chloropropane in 150 ml of dry benzene was refluxed with stirring for 5 hours. After cooling, the N-[2-(1,3-dioxanyl)-ethyl]-piperazinium bromide which had precipitated was filtered off, the filtrate was concentrated in vacuo and the residual oil was distilled. 14.1 g (68%yield) of N-(3-chloropropyl)-N'-[2-1,3-dioxanyl)-ethyl]-piperazine which occurred as a light yellow oil were obtained. Boiling point: 152°C to 155°C under 0.07 mm Hg (n_D^{23} = 1.4940). The disuccinate prepared in acetone and recrystallized from acetone melts at 104°C to 105°C on a hot stage microscope.

The sodium derivative of the 2-trifluoromethylphenothiazine was prepared from 26.7 g (0.1 mol) of 2-trifluoromethylphenothiazine and 2.3 g (0.1 g atom) of sodium in 500 ml of liquid ammonia. After the reaction was completed, the ammonia was driven off and 500 ml of dry toluene were added. A solution of 25 g (0.09 mol) of N-(3-chloropropyl)-N'-[2-(1,3-dioxanyl)-ethyl]-piperazine in 200 ml of toluene was added drop by drop to this solution which was then refluxed with stirring for 18 hours. After cooling, the precipitate which had formed was filtered and the filtrate was washed with water, dried and concentrated in vacuo. 33 g of brown oil, the N-3-(2-trifluoromethyl-10-phenothiazinyl)-propyl-N'-2-[2-(1,3-dioxanyl)]-ethyl-piperazine, were obtained.

A warm solution of 4.4 g of the base obtained in 100 ml of acetonitrile was added to a warm solution of succinic acid in 200 ml of acetonitrile. After standing for 15 hours at 0°C. the crystalline product was obtained, melting point 138°C.

References

Merck Index 6781
Kleeman & Engel p. 663
DOT 6 (3) 89 (1970)
I.N. p. 709
Societe Industrielle Pour La Fabrication Des Antibiotiques (S.I.F.A.); British Patent 1,103,311; February 14, 1968

OXAMETACINE

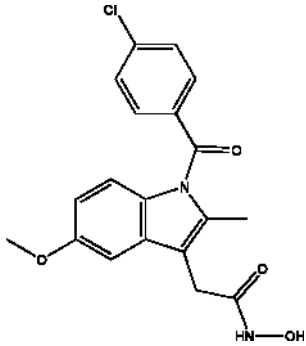
Therapeutic Function: Antiinflammatory

Chemical Name: 1-(4-Chlorobenzoyl)-N-hydroxy-5-methoxy-2-methyl-1H-indole-3-acetamide

Common Name: Indoxamic acid

Chemical Abstracts Registry No.: 27035-30-9

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Flogar	A.B.C.	Italy	1976
Flogar	U.C.B.	France	1981
Dinulcid	Pharmascience	France	1983

Raw Materials

1-p-Chlorobenzoyl-2-methyl-5-methoxy-3-indoleacetic acid
Thionyl chloride
Hydroxylamine hydrochloride

Manufacturing Process

1 g of 1-p-chlorobenzoyl-2-methyl-5-methoxy-3-indoleacetic acid [J. Am. Chem. Soc. 85, 488-489 (1963)] is treated in a nitrogen stream with 10 ml thionyl chloride in which it promptly dissolves. The solution is quickly evaporated in vacuum and the residue (which typically is of a deep brown-green color) is distempered, twice or three times, with a few ml anhydrous benzene which is removed in vacuum each time. The resulting residue is thoroughly distempered with 5 ml anhydrous ether which dissolves most of the color impurities, and separated by filtering, purified by crystallizing from plenty of anhydrous ether, yielding a crystalline mass of needles of straw-yellow color, melting point 124°C to 127°C. Yield: 0.700 g. Found: Cl % 18.62 (calculated 18.84).

The product is relatively stable towards water and aqueous alkalies in which it proves to be insoluble even after dwelling therein several hours at room temperature. It reacts, better if at elevated temperature, with lower alcohols with which it forms the corresponding esters, and with ammonia under suitable conditions for forming the amide (melting point 219°C to 221°C).

A solution of 1.330 g sodium hydroxide in 20 ml water is slowly admixed with 2.330 g hydroxylamine hydrochloride while cooling, whereupon 1 g chloride of 1-p-chlorobenzoyl-2-methyl-5-methoxy-3-indoleacetic acid is distempered in this neutral or slightly alkaline solution by vigorously stirring during a few minutes.

The acid chloride reacts with the free hydroxylamine with considerable rapidity apparently without dissolving. The reaction is completed when a sample of the suspension shows to become clear on adding aqueous alkali. The crystalline pale-yellow mass of product is separated by filtering, lavishly washed with water and dried in vacuum. The crude product yield is actually quantitative. The product is purified with excellent yields by repeatedly crystallizing from hot dioxane and washing with ether: melting point 181°C to 182°C (dec.).

References

Merck Index 6788
I.N. p. 710
De Martlis, F., Arrigoni-Martelli, E. and Tamietto, T.; US Patent 3,624,103; November 30, 1971; assigned to Instituto Biologico Chemioterapico (A.B.C.) SpA (Italy)

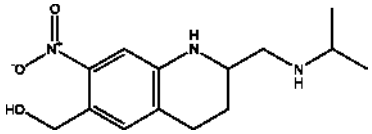
OXAMNIQUINE

Therapeutic Function: Antischistosomal

Chemical Name: 1,2,3,4-Tetrahydro-2-[[(1-methylethyl)amino]methyl]-7-nitro-6-quinolinemethanol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 21738-42-1

Trade Name	Manufacturer	Country	Year Introduced
Vansil	Pfizer	US	1980
Vansil	Pfizer	France	1981

Raw Materials

Bacterium Aspergillus sclerotiorum Huber
Soybean meal
Glucose
2-Isopropylaminomethyl-6-methyl-7-nitro-1,2,3,4-tetrahydroquinoline

Manufacturing Process

(1) Four fermenters are set up, each one of which contained 2.0 liters of the

following medium, sterilized for 35 minutes at 15 psi, respectively:

Soybean meal	5 grams
Glucose	20 grams
NaCl	5 grams
K_2HPO_4	5 grams
Yeast extract	5 grams
Tap water to	1 liter

pH adjusted with sulfuric acid to 6.5

The fermenters are inoculated with 7.5% by volume of a 24-hour old culture of Aspergillus sclerotiorum Huber grown at 28°C in 50 ml aliquots of the above described soybean-glucose medium contained in 300 ml Erlenmeyer flasks, placed on a shaker rotating at approximately 230 rpm. The inoculated fermenters are agitated at 1,380 rpm and each aerated with 1 liter of air per minute and at a temperature of 28°C for 47 hours. A silicone antifoam is added when required. At the end of the 47 hour period, the pH of the fermentation broth rose to 6.8 to 6.9. Sulfuric acid is then added with sterile precautions to restore the pH to 6.5.

(2) 0.75 g of 2-isopropylaminomethyl-6-methyl-7-nitro-1,2,3,4-tetrahydroquinoline as hydrogen maleate, dissolved in 75 ml of sterile water, is added to each of the four fermenters and agitation and aeration are continued for a further 23 hours. The whole fermentation broths from each fermenter are pooled, the pH adjusted to 8.0 with sodium hydroxide and the 8.2 liters of fermentation broth thus obtained are extracted by agitating vigorously with 16.4 liters of methylene chloride for 10 minutes. The solvent extract is then dried over anhydrous sodium sulfate and subsequently evaporated to dryness at a temperature below 40°C (dry weight 5.567 g).

(3) The dark brown residue from (2) is extracted four times with methanol at room temperature, decanting the solution from the insoluble material. The combined methanol extracts, total volume about 200 ml, are then filtered and treated with 3 g of sodium borohydride, added in portions over a period of 30 minutes with stirring, to reduce any 6-formyl compound present to the 6-hydroxymethyl compound. The methanol solution is then allowed to stand overnight at room temperature and is thereafter diluted with 1 liter of ether. The solution is washed 4 times with 500 ml of water and the resulting pale yellow ethereal solution is dried over magnesium sulfate. The ether is next removed by vacuum distillation from a water bath at 40°C. The residue is dissolved in about 75 ml of isopropanol at 50°C, filtered to remove any insoluble particles and cooled overnight in the refrigerator. The product is collected and dried in vacuo to yield 0.5 g of 6-hydroxymethyl-2-isopropylaminomethyl-7-nitro-1,2,3,4-tetrahydroquinoline as pale yellow crystals of melting point 147°C to 149°C. A further 0.5 g of crude material is obtained from the mother liquors of the recrystallization. Total yield is therefore 1.0 g (0.0036 mol) from 3.0 g (0.0079 mol) of starting material, i.e., 45% of the theoretical amount.

References

Merck Index 6791
OCDS Vol. 2 p. 372 (1980)

DOT 17 (4) 152 (1981)
I.N. p. 710
REM p. 1236
Richards, H.C.; US Patent 3,821,228; June 28, 1974; assigned to Pfizer, Inc.

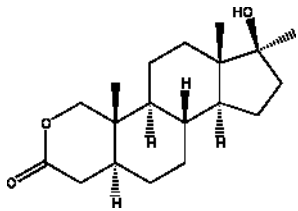
OXANDROLONE

Therapeutic Function: Androgen

Chemical Name: 17β-Hydroxy-17-methyl-2-oxa-5α-androstan-3-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 53-39-4

Trade Name	Manufacturer	Country	Year Introduced
Anavar	Searle	US	1964
Anatrophill	Searle	France	1965
Vasorome	Kowa	Japan	1969
Oxandrolone Spa	SPA	Italy	1979
Lonavar	Searle	Italy	-

Raw Materials

17β-Hydroxy-17α-methyl-5α-androst-1-en-3-one
Lead tetraacetate
Sodium borohydride

Manufacturing Process

To a solution of 6.36 parts of 17β-hydroxy-17α-methyl-5α-androst-1-en-3-one in 95 parts of acetic acid and 12 parts of water is added 40 parts of lead tetracetate and 0.6 part of osmium tetroxide. This mixture is stored at room temperature for about 24 hours, then is treated with 2 parts of lead tetracetate. Evaporation to dryness at reduced pressure affords a residue, which is extracted with benzene. The benzene extract is washed with water, and extracted with aqueous potassium bicarbonate. The aqueous extract is washed with ether, acidified with dilute sulfuric acid, then extracted with ethyl

acetate-benzene. This organic extract is washed with water, dried over anhydrous sodium sulfate, and concentrated to dryness in vacuo. To a solution of the residual crude product in 20 parts of pyridine is added 10 parts of 20% aqueous sodium bisulfite and the mixture is stirred for about 20 minutes at room temperature.

This mixture is then diluted with water, washed with ethyl acetate, acidified with dilute sulfuric acid, and finally extracted with benzene. The benzene extract is washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness at reduced pressure to produce crude 17β-hydroxy-17α-methyl-1-oxo-1,2-seco-A-nor-5α-androstan-2-oic acid, which after recrystallization from aqueous isopropyl alcohol melts at about 166° to 173°C (decomposition).

An aqueous slurry of 6 parts of 17β-hydroxy-17α-methyl-1-oxo-1,2-seco-A-nor-5α-androstan-2-oic acid in 200 parts of water is made alkaline to pH 10 by the addition of dilute aqueous sodium hydroxide, then is treated with 6 parts of sodium borohydride. This mixture is allowed to react at room temperature for about 3 hours. Benzene is added and the resulting mixture is acidified carefully with dilute hydrochloric acid. The benzene layer is separated, and the aqueous layer is further extracted with benzene. The combined benzene extracts are washed successively with aqueous potassium bicarbonate and water, dried over anhydrous sodium sulfate, then evaporated to dryness in vacuo. The resulting residue is triturated with ether to afford pure 17β-hydroxy-17α-methyl-2-oxa-5α-androstan-3-one, MP about 235° to 238°C, according to US Patent 3,128,283.

References

Merck Index 6794
Kleeman & Engel p. 664
PDR p. 1677
OCDS Vol. 1 p. 174 (1977)
I.N. p. 710
REM p. 999
Pappo, R.; US Patent 3,128,283; April 7, 1964; assigned to G.D. Searle and Co.
Pappo, R.; US Patent 3,155,684; November 3, 1964; assigned to G.D.Searle 81 Co.

OXAPROZIN

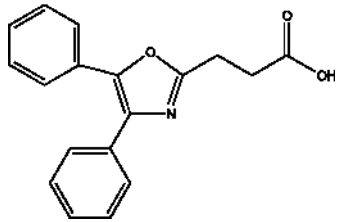
Therapeutic Function: Antiinflammatory

Chemical Name: 2-Oxazolepropanoic acid, 4,5-diphenyl-

Common Name: Oxaprozin

Chemical Abstracts Registry No.: 21256-18-8

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Danoprox	TRB Chemedica	Switz.	-
Daypro	Pfizer	-	-
Daypro	Pharmacia	-	-
Dayrun	CSC Pharmaceuticals	Austria	-
Duraprox	Gerolymatos	Greece	-
Duraprox	Aventis Pasteur	France	-
Oxaprozin	Apotex Inc.	-	-
Oxaprozin	Dr. Reddy's Laboratories Ltd.	India	-

Raw Materials

Pyridine
Benzoin
Succinic anhydride
Acetic acid

Manufacturing Process

A clean dry reactor of 20 gallon (91 liters) capacity was charged with pyridine (9.25 kg), benzoin (16.5 kg) and succinic anhydride (11.7 kg.). The reactor was purged with nitrogen and a nitrogen atmosphere was maintain throughout the process. The mixture was heated without agitation until it became liquid at 85°C. Agitation was commenced and the mixture was heated at 90°-95°C for 1.5 hours. A solution of ammonium acetate (12.0 kg) in glacial acetic acid (35.0 kg) was charged to the header of the reactor and added to the reaction mixture over 15 minutes, maintaining the temperature between 90° and 95°C. The container for the solution and the header were washed with glacial acetic acid (4.0 kg) and the washing liquid was added to the reaction mixture. The reaction mixture was held at 90°-95°C for 2 hours. The reaction mixture was cooled to 50°C and transferred via a line filter to a reactor of 50 gallon (227 liters) capacity. The first reactor, lines and filter were washed with glacial acetic acid (4.0 kg.) which was combined with the reaction mixture. The reaction mixture was heated with agitation to 90°-95°C over 30 minutes and water (21.0 kg.) was added maintaining the temperature at 90°-95°C. The reaction mixture was then cooled to 20°-25°C over 55 minutes by means of water in the jacket of the reactor and then cooled to 10°-15°C by means of brine in the jacket and left overnight. The product was filtered on a ceramic filter and sucked well dry. The product on the filter was washed with a pre-filtered mixture of glacial acetic acid (25.5 kg.) and water (12.5 kg) and

sucked well dry. Pre-filtered water (50.0 kg) and the filter cake were added to a reactor of 50 gallon (227 liters) capacity. The mixture was stirred at room temperature for 30 minutes and filtered on a ceramic filter and the product was sucked well dry. The product on the filter was washed twice with pre-filtered water (10 kg each time) and sucked well dry. The product was then dried in a Mitchell oven at 80°C for 16-18 hours. The yield of crude β-(4,5-diphenyloxazol-2-yl)propionic acid was 15.9 kg (69.8%). This material only just failed specification for acceptable purity because although TLC analysis showed only very faint trace impurities.

Recrystallisation of crude β-(4,5-Diphenyloxazol-2-yl)propionic acid

Methanol (62.0 kg) was added to a reactor of 50 gallon capacity (227 liters). 15.9 kg of the crude oxazole above prepared was added with agitation. The mixture was heated to reflux. All the solid dissolved. The mixture was then cooled to 50°C and transferred to a reactor of 20 gallon (91 liters) capacity. The larger reactor and transfer lines were washed through with methanol at about 40°C twice (3 kg each time). The mixture was cooled over 1 hour 50 minutes with agitation, gradually at first, to 15°-20°C by means of cooling water on the jacket of the reactor. The product was then filtered on a ceramic filter and sucked well dry. The product on the filter was washed twice with methanol (5 kg each time) and sucked well dry. The wash liquors were combined with the filtration liquors and retained. The product from the filter was dried in an air oven at 55°-60°C for 18 hours. The yield of β-(4,5-diphenyloxazol-2-yl)propionic acid was 12.1 kg. TLC investigation showed the product to be pure. Melting point 160.5°-161.5°C.

Another crop of product was obtained from the methanol liquors as follows. The liquors were added to a reactor of 20 gallon (91 liters) capacity and the solvent was distilled off for 9 hours until solid appeared. The mixture was then cooled to 15° to 20°C over 1 3/4 hours using cooling water in the jacket of the reactor. The mixture was cooled to 10°C using brine in the jacket and stirred at this temperature for 30 minutes. The product was then filtered on a ceramic filter and sucked well dry. The product on the filter was washed twice with methanol (5 kg each time) and sucked well dry. The product was dried in an air oven at 55°-60°C for 18 hours. The yield was 2.14 kg. This product may also have been acceptably pure but its purity was not investigated. It was therefore retained as crude product to be resubjected to recrystallisation with methanol. The yield for the recrystallisation was thus 12.1 kg from a consumption of 13.76 kg of crude product, that is 88%. The overall yield of pure product is 69.8% times 88%, that is, 61.4%.

References

Weston G.O.; US Patent No. 4,190,584; Feb. 26, 1980; Assigned to John Wyeth and Brother Limited, Maidenhead, England

Brown K.; US Patent No. 3,578,671; May 11, 1971; Assigned to John Wyeth and Brother Limited, Taplow, Maidenhead, Berkshire, England

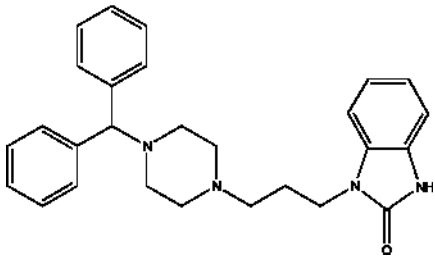
OXATOMIDE

Therapeutic Function: Antiallergic

Chemical Name: 1-[3-[4-(Diphenylmethyl)-1-piperazinyl]propyl]-2-benzimidazolone

Common Name: Oxatimide

Structural Formula:



Chemical Abstracts Registry No.: 60607-34-3

Trade Name	Manufacturer	Country	Year Introduced
Tinset	Janssen	W. Germany	1981
Tinset	Janssen	UK	1982
Tinset	Janssen	Switz.	1983
Finsedyl	Microsules	Argentina	-

Raw Materials

1-(3-Chloropropyl)-2H-benzimidazol-2-one
1-(Diphenylmethyl)piperazine

Manufacturing Process

A mixture of 53 parts of 1-(3chloropropyl)-2H-benzimidazol-2one, 5 parts of 1-(diphenylmethyl)piperazine, 6.4 parts of sodium bicarbonate and 200 parts of 4-methyl-2-pentanone is stirred and refluxed overnight with water-separator. After cooling, water is added and the layers are separated. The 4-methyl-2pentanone phase is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and 5% of methanol as eluent. The pure fractions are collected and the eluent is evaporated. The oily residue is crystallized from a mixture of 2,2'-oxybispropane and a small amount of 2-propanol. The product is filtered off and dried, yielding 1-[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]-2H-benzimidazole-2-one; melting point 153.6°C.

References

Merck Index 6798

DFU 3 (6) 465 (1978)
OCDS Vol. 3 p. 173 (1984)
DOT 16 (7) 219 (1980); 18 (7) 341 and (9) 440 (1982)
I.N. p. 711
Vandenberk, J., Kennis, L.E.J., Van der Aa, M.J.M.C. and Van Heertum, A.H.M.T.; US Patent 4,200,641; April 29, 1980; assigned to Janssen Pharmaceutica N.V.

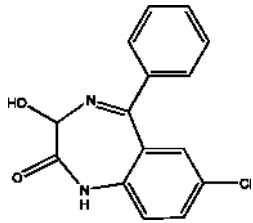
OXAZEPAM

Therapeutic Function: Tranquilizer

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

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 604-75-1

Trade Name	Manufacturer	Country	Year Introduced
Serax	Wyeth	US	1965
Adumbran	Thomae	W. Germany	1965
Seresta	Wyeth Byla	France	1966
Praxiten	Wyeth	UK	1966
Serpax	Wyeth	Italy	1967
Anxiolit	Gerot	Austria	-
Aplakil	Aristegui	Spain	-
Aslapax	Asla	Spain	-
Benzotran	Protea	Australia	-
Droxacepam	Jeba	Spain	-
Durazepam	Durachemie	W. Germany	-
Enidrel	Syncro	Argentina	-
Hilong	Banyu	Japan	-
Iranil	Iltas	Turkey	-
Isochin	Tosi	Italy	-
Limbial	Chiesi	Italy	-

Trade Name	Manufacturer	Country	Year Introduced
Nesontil	Promeco	Argentina	-
Noctazepam	Brenner	W. Germany	-
Oxpam	I.C.N.	Canada	-
Propax	Cipan	Portugal	-
Psicopax	Bama-Geve	Spain	-
Psiquiwas	Wassermann	Spain	-
Purata	Lennon	S. Africa	-
Quen	Ravizza	Italy	-
Quilibrex	Isnardi	Italy	-
Sedokin	Geymonat Sud	Italy	-
Serepax	Ferrosan	Denmark	-
Sigacalm	Siegfried	Switz.	-
Sobile	Lafarquin	Spain	-
Uskan	Desitin	W. Germany	-
Vaben	Rafa	Israel	-
Wakazepam	Wakamoto	Japan	-

Raw Materials

7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one-4-oxide
Acetic anhydride
Sodium hydroxide

Manufacturing Process

(A) Suspend 10 g of 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide in 150 ml of acetic anhydride and warm on a steam bath with stirring until all the solid has dissolved. Cool and filter off crystalline, analytically pure 3-acetoxy-7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one, melting point 242°C to 243°C.

(B) Add to a suspension of 3.4 g of 3-acetoxy-7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one in 80 ml of alcohol.6 ml of 4 N sodium hydroxide. Allow to stand after complete solution takes place to precipitate a solid. Redissolve the solid by the addition of 80 ml of water. Acidify the solution with acetic acid to give white crystals. Recrystallize from ethanol to obtain 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-2H-1,4-benzodiazepin-2-one, melting point 203°C to 204°C.

References

Merck Index 6799
Kleeman & Engel p. 664
PDR p. 1980
OCDS Vol. 1 p. 366 (1977) and 2, 402 (1980)
DOT 1 (3) 102 (1965) and 9 (6) 238 (1973)
I.N. p. 711
REM p. 1063
Bell, S.C.; US Patent 3,296,249; January 3, 1967; assigned to American Home Products Corp.

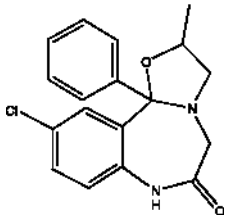
OXAZOLAM

Therapeutic Function: Tranquilizer

Chemical Name: 7-Chloro-5-phenyl-5'-methyltetrahydrooxazolo[5.4-b]-2,3,4,5-tetrahydro-1H-1,4-benzodiazepin-2-one

Common Name: Oxazolazepam

Structural Formula:



Chemical Abstracts Registry No.: 24143-17-7

Trade Name	Manufacturer	Country	Year Introduced
Serenal	Sankyo	Japan	1970
Quiadon	Merck	W. Germany	1980
Convertal	Roemmers	Argentina	-
Hializan	Pharma-investi	Spain	-
Tranquit	Promonta	W. Germany	-

Raw Materials

5-Chloro-2-chloroacetylaminobenzophenone
Isopropanolamine

Manufacturing Process

To a solution of 12.0 g of 5-chloro-2-chloroacetylaminobenzophenone and 3.2 g of isopropanolamine in 100 ml of ethanol was added 3.3 g of sodium acetate.

The resulting mixture was heated under reflux with stirring for 12 hours. After completion of the reaction, the solvent was distilled off and the residue was extracted with dichloromethane. The extract was washed with water, dried over anhydrous sodium sulfate and the solvent was distilled off.

The residue was recrystallized from ethanol to give 10.6 g of the desired product melting at 186°C to 188.5°C.

References

Merck Index 6801

DOT 8 (1) 18 (1972) and 9 (6) 239 (1973)
I.N. p. 712
REM p. 1064
Tachikawa, R., Takagi, H., Kamioka, T., Midayera, T., Fukunaga, M. and Kawano, Y.; US Patents 3,772,371; November 13, 1973; and 3,914,215; October 21, 1975; both assigned to Sankyo Co., Ltd.

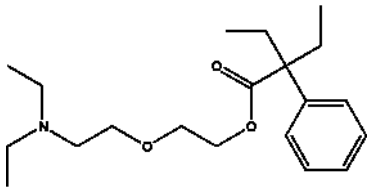
OXELADIN

Therapeutic Function: Antitussive

Chemical Name: α,α-Diethylbenzeneacetic acid 2-[2-(diethylamino)ethoxy] ethyl ester

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 468-61-1; 16485-39-5 (Citrate)

Trade Name	Manufacturer	Country	Year Introduced
Silopentol	Schulte	W. Germany	1970
Ethochlon	Hokuriku	Japan	1970
Fustopanox	Ottia Pharm.	Japan	1970
Paxeladine	Beaufour	France	1974
Dorex	Woelm	W. Germany	-
Hihustan	Maruko	Japan	-
Hustopan	Ohta	Japan	-
Marukofon	Maruko	Japan	-
Neoasdrin	Toa	Japan	-
Neobex	Lampugnani	Italy	-
Neusedan	Nippon Zoki	Japan	-
Pectamol	Malesci	Italy	-
Pectussil	Kwizda	Austria	-
Tussilisin	Ibirn	Italy	-
Tussimol	B.D.H.	UK	-

Raw Materials

Phenylacetonitrile	Ethyl chloride
Sodium	β,β'-Dichlorodiethyl ether
Potassium hydroxide	Diethylamine

Manufacturing Process

Preparation of Diethylphenylacetonitrile: 25 grams of sodium was dissolved in 300 ml liquid ammonia containing 0.3 gram ferric chloride and 59 grams phenylacetonitrile was added slowly with stirring. After about 15 minutes a cooled solution of 80 grams of ethyl chloride in 200 ml dry ether was added and the mixture stirred for 1 hour. The ammonia was then allowed to evaporate, water added and the ether layer separated, dried, concentrated and the residual oil distilled in vacuo to yield diethylphenylacetonitrile as an oil, BP 85°C/1 mm.

Preparation of Diethylphenylacetic Acid: 46 grams of the foregoing nitrile was added to 140 ml ethylene glycol containing 36 grams potassium hydroxide and the mixture refluxed with stirring for about 20 hours. The mixture was diluted with water, extracted with light petroleum (BP 60° to 80°C) to remove traces of impurities and then acidified to yield diethylphenylacetic acid which was recrystallized from dilute ethanol (40% v/v ethanol in water).

Preparation of 2-(β-Chloroethoxy)Ethyl Diethylphenylacetate: 19.2 grams of the foregoing acid was added to a solution of 4 grams of sodium hydroxide in 40 ml ethylene glycol. 28.6 grams β,β'-dichlorodiethyl ether was added and the mixture refluxed for 1 hour. After removal of solvent under reduced pressure, 150 ml water was added to the residue and the product extracted with ether. The ethereal solution was dried, concentrated and the residue distilled in vacuo to yield the product as an oil, BP 140°C/0.7 mm.

Preparation of 2-(β-Diethylaminoethoxy)Ethyl Diethylphenylacetate: A mixture of 21 grams of 2-(β-chloroethoxy)ethyl diethylphenylacetate and 14 grams diethylamine was heated under pressure in a sealed tube at 140°C for 5 hours. After cooling, the mixture was dissolved in dilute hydrochloric acid and extracted with ether to remove traces of neutral impurities. The acid layer was then made alkaline with 10% w/v sodium hydroxide solution with cooling, and re-extracted with two portions of ether. The ether extract was dried, the ether distilled off and the residue distilled in vacuo to yield the product as an oil, BP 140°C/0.1 mm.

References

Merck Index 6803
Kleeman & Engel p. 665
OCDS Vol. 1 p. 90 (1977)
I.N. p. 712
Petrow, V., Stephenson, O. and Wild, A.M.; US Patent 2,885,404; May 5, 1959; assigned to The British Drug Houses Limited, England

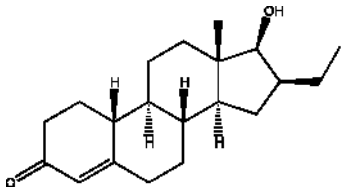
OXENDOLONE

Therapeutic Function: Antiandrogen

Chemical Name: 16β-Ethyl-17β-hydroxyestr-4-ene-3-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 33765-68-3

Trade Name	Manufacturer	Country	Year Introduced
Prostetin	Takeda	Japan	1981

Raw Materials

Ethyl orthoformate
16β-Ethylestra-4-ene-3,17-dione
Sodium borohydride
Hydrogen chloride

Manufacturing Process

To a solution of 3.0 g of 16β-ethylestra-4-ene-3,17-dione dissolved in 150 ml of dioxane, are added 15 g of ethyl orthoformate and 0.1 g of p-toluenesulfonic acid, followed by stirring for 2 hours at room temperature. The reaction solution is poured into 300 ml of a 5% aqueous solution of sodium hydrogen carbonate and the resultant mixture is extracted with ether. The ether layer is washed with water and dried, followed by evaporation of the solvent to give crude crystals of 3-ethoxy-16β-ethylestra-3,5-diene-17-one. The crystals are recrystallized from ether to give 3.0 g of the compound melting at 114°C to 115°C.

To a solution of 3.0 g of the enol-ether compound obtained above in 50 ml of methanol, is added 1.5 g of sodium borohydride. After standing for 1.5 hours at room temperature, the reaction solution is poured into 300 ml of water. The resulting precipitates are collected by filtration and recrystallized from ether to give 2.8 g of 3-ethoxy-16β-ethylestra-3,5-dien-17β-ol melting at 131°C to 133°C.

To a solution of 2.5 g of 3-ethoxy-16β-ethylestra-3,5-diene-17β-ol dissolved in

50 ml of methanol is added 1.2 ml of concentrated hydrochloric acid, followed by stirring for 10 minutes. The reaction solution is poured into 250 ml of water. The precipitated crystals are collected by filtration and recrystallized from ether to give 2.3 g of 16β-ethyl-17β-hydroxyestra-4-en-one melting at 152°C to 153°C.

References

Merck Index 6804
DFU 5 (9) 44 (1980)
I.N. p. 712
Hiraga, K., Yoshioka, K., Goto, G., Nakayama, R. and Masuoka, M.; US Patent 3,856,829; December 24, 1974; assigned to Takeda Chemical Industries, Ltd.

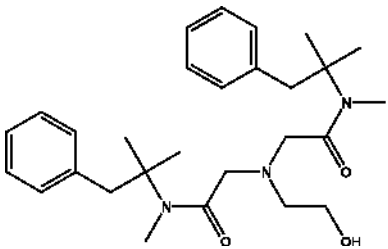
OXETHAZINE

Therapeutic Function: Local anesthetic

Chemical Name: 2,2'-[(2-Hydroxyethyl)imino]bis[N-(1,1-dimethyl-2-phenylethyl)-N-methylacetamide]

Common Name: Oxetacaine

Structural Formula:



Chemical Abstracts Registry No.: 126-27-2; 13930-31-9 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Oxaine	Wyeth	US	1960
Emoren	Wassermann	Italy	-
Mucaine	Wyeth	UK	-
Mutesa	Wyeth Byla	France	-
Stomacain	Teisan-Pfizer	Japan	-
Strocain	Eisai	Japan	-
Tepilta	Wyeth	W. Germany	-
Topicain	Chugai	Japan	-

Raw Materials

Chloro-N-methyl-N-ω-phenyl-tert-butyl acetamide
Ethanolamine

Manufacturing Process

Chlor-N-methyl-N-ω-phenyl-tert-butyl acetamide (23.95 g) (0.1 mol) is added to n-butanol (150.0 cc) containing anhydrous potassium carbonate (50.0 g). To the stirred refluxing solution is added dropwise freshly distilled ethanolamine (3.1 g) (0.05 mol). Stirring and refluxing is maintained for twenty hours. Upon cooling the solution is filtered; the residue is washed with n-butanol. The combined filtrates are washed with aqueous sodium carbonate solution then water and finally dried over anhydrous magnesium sulfate. The solvent is distilled under vacuum leaving a dry solid residue. The residue is dissolved in dry benzene to which is added n-hexane to crystallize the product melting at 104°C to 104.5°C. Yield 71-73%. Analysis-Carbon: calc. 71.9%; found 71.93%; hydrogen: calc. 8.8%; found 8.9%; nitrogen: calc. 9.0%; found 9.0%.

To make the hydrochloride salt, the bisacetamide or, by another name, 1,11-diphenyl-2,2,3,9,10,10-hexamethyl-4,8-diketo-6-(β-hydroxyethyl)-3,6,9-triazaundecane is dissolved in n-butanol. The solution is chilled and then dry hydrogen chloride gas is passed into the solution causing an oil to separate. To the heavy oil ether is added and then stirred causing crystallization to occur. MP 146°C to 147°C. Analysis for nitrogen: calc. 83%. found 8.2%.

To make the acetate salt, the bisacetamide (4.7 g) (0.01 mol) is dissolved in ethyl acetate to which is added glacial acetic acid (0.6 g) (0.01 mol). Ether is added to precipitate the acetate as a gum which is washed with hexane, and finally added to dry ether. Allow to stand for crystallization. MP 141°C. Analysis for nitrogen: calc. 8.0%; found 8.2%.

Other salts are: sulfate, MP 56°C; acid oxalate, MP 127°C; tartrate, MP 45°C; picrate, MP 151°C to 152°C.

References

Merck Index 6806
Kleeman & Engel p. 666
OCDS Vol. 1 p.72 (1977)
I.N. p. 712
Seifter, J., Hanslick, R.S. and Freed, M.E.; US Patent 2,780,646; February 5, 1957;assigned to American Home Products Corp.

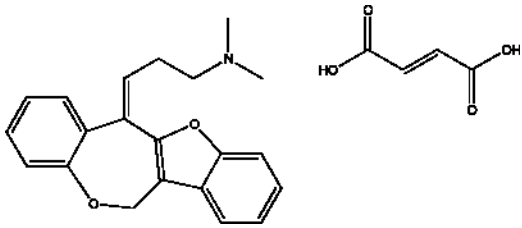
OXETORONE FUMARATE

Therapeutic Function: Serotonin antagonist, Antihistaminic

Chemical Name: 6-(3-Dimethylamino-1-propylidene)-12H-benzofuro[2,3-e] benz[b]oxepin fumarate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 34522-46-8; 26020-55-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Nocertone	Labaz	France	1975
Nocertone	Labaz	W. Germany	1976
Oxedix	Labaz	-	-

Raw Materials

Ethyl iodide	γ-Dimethylaminopropyl chloride
Magnesium	6-Oxo-benzo[b]benzofurano[2,3-e]oxepin
Sulfuric acid	Fumaric acid

Manufacturing Process

(A) Preparation of 6-(3-dimethylaminopropyl)-6-hydroxybenzo[b]benzofurano [2,3-e]oxepin - In a 250 ml flask equipped with a vertical condenser, a dropping-funnel, a dip thermometer and a stirrer, 1.5 g of magnesium turnings and a crystal of iodine were heated until vaporization of the iodine and then cooled, after which 20 ml of dry tetrahydrofuran were added.

The mixture was heated under reflux and a solution of 0.2 g of ethyl iodide in 5 ml of dry tetrahydrofuran was allowed to flow into the reaction medium. When the reaction started, a solution of 6.2 g of γ-dimethylaminopropyl chloride in 20 ml of dry tetrahydrofuran was added and the mixture so obtained was heated under reflux until the complete disappearance of the magnesium turnings. The reaction medium was then cooled in an ice bath, after which there was added thereto a solution in 45 ml of tetrahydrofuran of 7 g of 6-oxo-benzo[bl]-benzofurano[2,3-e]oxepin. The reaction mixture was allowed to stand for 20 hours at a temperature of 20°C, and was then poured into a saturated aqueous solution of ammonium chloride maintained at a temperature of 5°C. The mixture was extracted with ether and the organic portion was washed and dried over anhydrous sodium sulfate. After evaporation of the solvent, 9.4 g of crude product were obtained, which after recrystallization from isopropanol, provided 6.7 g of pure 6-(3-dimethylaminopropyl)-6-hydroxybenzo[b]benzofurano[2,3-e]oxepin, melting

point 160°C (yield, 71%).

(8) Preparation of 6-(3-dimethylaminopropylidene)-benzo[b]benzofurano[2,3-e]oxepin and its fumarate -In an Erlenmeyer flask 6.2 g of 6-(3-dimethylaminopropyl)-6-hydroxybenzo[b]benzofurano[2,3-e]oxepin prepared as described above were dissolved in 108 ml of a 10% solution of sulfuric acid. The solution obtained was heated to boiling point for 15 minutes. After cooling, 100 ml of chloroform were added and the solution was made alkaline with a 5% solution of sodium hydroxide. The solution was then extracted with chloroform, washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated and the resulting oily residue composed of 6-(3-dimethylaminopropylidene)-benzo[b]benzofurano[2,3-e]oxepin was then directly treated with a solution of fumaric acid in isopropanol to give 6.5 g of 6-(3-dimethylaminopropylidene)-benzo[b]benzofurano[2,3-e]oxepin fumarate (yield, 85%). The fumarate had a melting point of 160°C when recrystallized from isopropanol.

References

Merck Index 6807
Kleeman & Engel p. 667
OCDS Vol. 3 p. 247 (1984)
DOT 11 (1) 19 (1975)
I.N. p. 712
Binon, F. and Descamps, M.L.V.; US Patent 3,651,051; March 21, 1972; assigned to Labora. toires Labaz

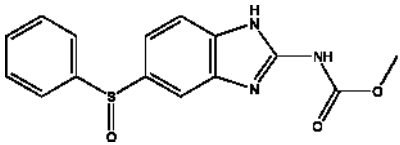
OXFENDAZOLE

Therapeutic Function: Anthelmintic

Chemical Name: Carbamic acid, (5-(phenylsulfinyl)-1H-benzimidazol-2-yl)-, methyl ester

Common Name: Oxfendazole

Structural Formula:



Chemical Abstracts Registry No.: 53716-50-0

Trade Name	Manufacturer	Country	Year Introduced
Autoworm	Coopers	-	-
Oxfendazole	AroKor Holdings Inc.	-	-

Trade Name	Manufacturer	Country	Year Introduced
Benzelmin	Syntex	-	-
Benzelmin	Wyeth Sante animale	-	-
Repidose	Agrovet	-	-
Interzol	Werfft	-	-
Oxfenil	Sanofi	-	-

Raw Materials

Sodium hydride	2-Amino-4-chloro-1-nitrobenzene
Thiophenol	Sodium phenyl mercaptide
Sulfuric acid	Sodium bicarbonate
Acetic anhydride	1,3-Bismethoxycarbonyl-S-methylisothiourea
Sodium acetate	Palladium on carbon
Hydrogen	Peracetic acid
Sodium bisulfite	Acetic acid

Manufacturing Process

5.0 g of 2-amino-4-chloro-1-nitrobenzene is added to a solution of sodium phenyl mercaptide, prepared under nitrogen from 2.53 g 57% sodium hydride and 6.2 ml thiophenol in 20 ml dimethylformamide, with a 10 ml dimethylformamide rinse. The mixture is stirred under nitrogen for 3 h at 20°-30°C and then diluted with water. The crude product is washed with water and hexane, then recrystallized from methanol, yielding 2-amino-4-phenylthio-1-nitrobenzene.

6.0 g of 2-amino-4-phenylthio-1-nitrobenzene is dissolved in 80 ml acetic anhydride and treated with a few drops of sulfuric acid. The mixture is left at 20°-30°C for 2 h then a little sodium acetate added and the solvent removed under vacuum. The residue is treated with water, filtered and recrystallized from methanol yielding 2-acetamido-4-phenylthio-1-nitrobenzene.

7.0 g of 2-acetamido-4-phenylthio-1-nitrobenzene is dissolved in 70 ml chloroform and treated, at -20°C to -15°C, with a solution of 5.0 g 40% peracetic acid in 10 ml methanol. The mixture is allowed to warm slowly to 20°C and stirred for 4 h. The reaction mixture is extracted with sodium bisulfite solution, then sodium bicarbonate solution, dried and evaporated. The residual gum of 2-acetamido-4-phenylsulfinyl-1-nitrobenzene is treated with 20 ml 5 N sodium hydroxide and 40 ml methanol at 20°-25°C for 1 h. Water is then added and essentially pure 2-amino-4-phenyl-sulfinyl-1-nitrobenzene filtered off. Recrystallization may be effected from benzene.

5.4 g of 2-amino-4-phenylsulfinyl-1-nitrobenzene is hydrogenated at 1 atmosphere pressure in 500 ml methanol in the presence of 5.0 g 5% palladized carbon, until the theoretical uptake of hydrogen has occurred. The catalyst is removed by filtration and the filtrate stripped under vacuum. The residue is recrystallized from methanol-benzene, yielding 1,2-diamino-4-phenylsulfinylbenzene.

A mixture of 5.5 g of 1,2-diamino-4-phenylsulfinylbenzene, 4.3 g of 1,3-bis-methoxycarbonyl-S-methylisothiourea and 1.2 ml acetic acid in 100 ml

ethanol and 100 ml water is refluxed for 4 h. The mixture is cooled and essentially pure 6-phenylsulfinyl-2-carbomethoxyaminobenzimidazole filtered off and washed with methanol. Recrystallization may be effected from methanol-chloroform (melting point 253°C, dec.).

References

Beard C.C. et al.; US Patent No. 3,929,821; Dec. 30, 1975; Assigned: Syntex (U.S.A.) Inc., Palo Alto, Calif.

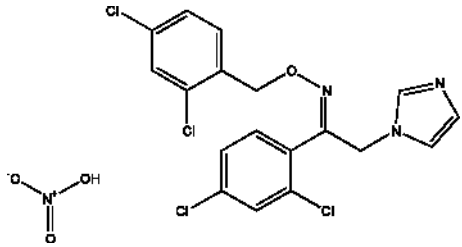
OXICONAZOLE NITRATE

Therapeutic Function: Antifungal

Chemical Name: 1-(2,4-Dichlorophenyl)-2-(1H-imidazol-1-yl)-O-(2,4-dichlorobenzyl)-ethanone oxime nitrate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 64211-46-7

Trade Name	Manufacturer	Country	Year Introduced
Myfungar	Siegfried	Switz.	1983
Oceral	Roche	Switz.	1983

Raw Materials

1-(2,4-Dichlorophenyl)-2-(1H-imidazol-1-yl)ethanone oxime
Sodium hydride
2,4-Dichlorobenzyl chloride
Nitric acid

Manufacturing Process

13.5 g of 1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)-ethanone oxime are dissolved in 100 ml dimethylformamide (DMF) and 1.2 g of sodium hydride are mixed in, whereupon an exothermic reaction is allowed to take place on

its own with stirring. After cessation of evolution of hydrogen, a solution of 9.8 g of 2,4-dichlorobenzyl chloride in 10 cc DMF is added dropwise with continuous stirring and the stirring is carried on for 2 hours further. The reaction is then taken to completion at a bath temperature of 80°C, after which the reaction mixture is evaporated in a rotation evaporator under reduced pressure and the residue is dissolved in 100 ml ethanol. After filtering off of undissolved matter, the solution is stirred with 300 ml 2N nitric acid for the conversion of free base to the nitrate.

The liquid standing over the heavy deposits which have separated out is separated off by decanting, whereupon an isomer is obtained which after recrystallization from ethanol is obtained in a yield of 5.2 g and having a melting point of 137°C to 138°C.

References

DFU 6 (2) 99 (1981)
DOT 19 (12) 884 (1983)
I.N. p. 713
Mixich, G., Thiele, K. and Fischer, J.; US Patent 4,124,767; November 7, 1978; assigned to Siegfried AG.

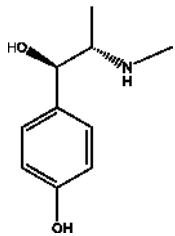
OXILOFRINE

Therapeutic Function: Sympathomimetic, Analeptic

Chemical Name: Benzenemethanol, 4-hydroxy-α-(1-(methylamino)ethyl)-, (R*,S*)-

Common Name: Hydroxyephedrine; Methyloxedrine; Methylsynephrine; Oxilofrine; Oxyephedrine

Structural Formula:



Chemical Abstracts Registry No.: 365-26-4

Trade Name	Manufacturer	Country	Year Introduced
Carnigen	Aventis Pharma Deutschland GmbH	-	-

Raw Materials

Sodium
Bromine
Caustic soda
Palladium
Ethanol absolute
p-Hydroxypropiophenone
Benzyl bromide
Methylbenzylamine
Hydrogen

Manufacturing Process

The p-benzyloxypropiophenone used for the transformation is prepared by adding to a solution of 6.9 g of sodium in 230 ml of absolute alcohol 45.0 g of p-hydroxypropiophenone and 54.0 g of benzyl bromide, and boiling for 1 h in a reflux apparatus. The excess of alcohol is then distilled and the residue is extracted with ether and water. After drying it the ethereal solution is evaporated and the residue is recrystallized from alcohol of 95% strength. The yield amounts to 60.0 g. The p-benzyloxypropiophenone melts at 100°-101°C.

55.0 g of p-benzyloxypropiophenone are dissolved in 250 ml of methylene chloride and brominated with 38.0 g of bromine. As soon as all of the bromine has been introduced drop by drop, the methylene chloride solution is washed with caustic soda solution and water. The solvent is eliminated in a vacuum and the residue is dissolved in petroleum ether. The crystalline mass which soon separates is filtered by suction and washed with petroleum ether. When recrystallized from hexahydrobenzene the p-benzyloxybromopropiophenone melts at 80°C.

40.0 g of p-benzyloxybromopropiophenone are then transformed in an alcoholic solution with 30.0 g of methylbenzylamine. After the whole has been allowed to stand for 1 day, the excess of alcohol is distilled in a vacuum and the residue is dissolved with ether. By washing with water, the benzylmethylamine hydrobrornide then formed is eliminated and the ether is removed by evaporation. The ether residue soon begins to crystallize and the p-benzyloxymethylbenzylaminopropriophenone is obtained with a good yield; when recrystallized from petroleum ether of low boiling point it melts at 58°-60°C.

15.0 g of p-benzyloxymethylbenzylaminopropriophenone are dissolved in alcohol and the solution is hydrogenated with palladium and hydrogen. As soon as the required quantity of hydrogen has been absorbed the palladium is filtered by suction and the alcohol is evaporated in a vacuum The residue is recrystallized and the p-hydroxyphenylmethylaminopropanol is obtained.

References

Bockmuhl M. et al.; US Patent No. 1,877,756; September 20, 1932

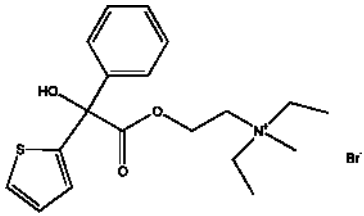
OXITEFONIUM BROMIDE

Therapeutic Function: Anticholinergic, Spasmolytic

Chemical Name: Ammonium, diethyl(2-hydroxyethyl)methyl-, bromide, α-phenyl-2-thiopheneglycolate

Common Name: Oxitefonium bromide; Oxytefonium bromide

Structural Formula:



Chemical Abstracts Registry No.: 17989-37-6

Trade Name	Manufacturer	Country	Year Introduced
Oxitefonium bromide	Sintofarm Group	-	-

Raw Materials

Phenyl-(α-thienyl)hydroxyacetic acid
2-Diethylaminoethyl chloride
Methyl bromide

Manufacturing Process

Phenyl-(α-thienyl)hydroxyacetic acid (4.86 g), 2-diethylaminoethyl chloride (2.85 g) and 75 ml of isopropyl alcohol were refluxed for 15 h. After the addition of 50 ml of absolute alcohol to the cold mixture, it was treated with Norite (activated charcoal) at room temperature, filtered, and the solvents removed under reduced pressure. The residue crystallised when triturated with absolute ether. After recrystallisation from absolute alcohol, the phenyl-(α-thienyl)hydroxyacetate of 2-diethylaminoethyl hydrochloride melted at 181-182°C.

The producing of phenyl-(α-thienyl)hydroxyacetate of 2-diethylmethylaminoethyl bromide may be carried out by methylation of phenyl-(α-thienyl)hydroxyacetate of 2-diethylaminoethyl hydrochloride with methylbromide.

References

Blicke F.F., Arbor A.; US Patent No. 2,541,025; Feb. 13, 1951; Assigned: Regents of The University of Michigan, Ann Arbor, Mich., a corporation of Michigan

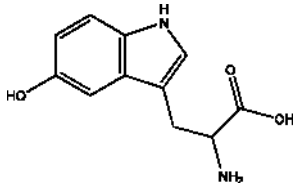
OXITRIPTAN

Therapeutic Function: Antidepressant, Antiepileptic

Chemical Name: 5-Hydroxytryptophan

Common Name: 5-Hydroxytryptophan

Structural Formula:



Chemical Abstracts Registry No.: 56-69-9

Trade Name	Manufacturer	Country	Year Introduced
Levotonine	Panmedica	France	1973
Pretonine	Arkodex	France	1973
Tript-Oh	Sigma Tau	Italy	1980
Levothym	Karlspharma	W. Germany	-
Quietim	Nativelle	France	-
Stimolomens	Irbi	Italy	-
Telesol	Lasa	Spain	-

Raw Materials

β-(5-Benzyloxyindolyl-3)-α-acetylamino-α-methylthiopropionic acid methanethiol ester
Hydrogen
Sulfuric acid

Manufacturing Process

β-(5-Benzyloxyindolyl-3)-α-acetylamino-α-methylthiopropionic acid methanethiol ester (449 mg) was added to 10 ml of ethanol and further 1 ml of triethylamine was added to the mixture. Then, the reaction mixture was refluxed for 17 hours, after condensation under reduced pressure and subsequent separation of the residue by column chromatography (silica gel, ethyl acetate), 353 mg of methyl β-(5-benzyloxyindolyl-3)-α-acetylamino-α-methylthiopropionate was obtained as colorless glasslike substance in the yield of 81.5%. Recrystallization of the substance from methanol water afforded 287 mg of crystals.

Raney nickel (3.5 cc) was suspended in 10 ml of ethanol and 356 mg of methyl β-(5-benzyloxyindolyl-3)-α-aminoacetyl-α-methylthiopropionate was added to the mixture together with 20 ml of ethanol. Then, the reaction

mixture was stirred for 1 hour at room temperature and thereafter filtered to remove insoluble substances. The residue was washed with 100 ml of ethanol and 50 ml of acetone and both the filtrate and the wash liquid were combined and concentrated under reduced pressure. By column chromatography (silica gel and acetone), 210 mg of methyl β-(5-hydroxyindolyl-3)-α-acetylaminopropionate as colorless glasslike substance in the yield of 90%.

To 430 mg of methyl β-(5-hydroxyindolyl-3)-α-acetylaminopropionate was added 50 ml of 10% sulfuric acid and the reaction mixture was refluxed under heating for 10 hours. After condensation under reduced pressure to 15 ml volume, the reaction solution was neutralized with ammonia to pH 4, to afford the extract. The resulting extract was filtered and washed with water to afford 265 mg of 5-hydroxytryptphan in the yield of 78%.

References

Merck Index 4771
Kleeman and Engel p. 668
I.N. p. 714
Tsuchihashi, G. and Ogura, K.; U.S. Patent 4,001,276; January 4,1977; assigned to Sagami Chemical Research Center (Japan)

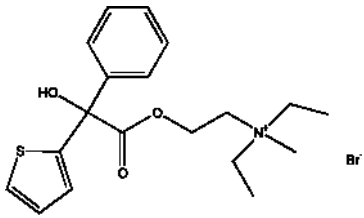
OXITROPIUM BROMIDE

Therapeutic Function: Anticholinergic bronchodilator

Chemical Name: (-)-N-Ethylnorscopolamine methobromide

Common Name: OTB

Structural Formula:



Chemical Abstracts Registry No.: 30286-75-0

Trade Name	Manufacturer	Country	Year Introduced
Ventilat	Boehringer Ingelheim	W. Germany	1983

Raw Materials

(-)-Norscopolamine
Ethyl bromide
Methyl bromide
Sodium carbonate

Manufacturing Process

14.5 g (0.05 mol) of (-)-norscopolamine and 5.4 g (0.05 mol) of ethyl bromide were dissolved in 300 cc of acetonitrile, 5.3 g (0.05 mol) of anhydrous sodium carbonate were suspended in the solution, and the suspension was heated at the boiling point for 10 hours. After a boiling time of 2.5 and 5 hours, respectively, the supply of ethyl bromide and sodium carbonate in the reaction mixture was replenished by adding each time 5.4 g (0.05 mol) of ethyl bromide and 5.3 g (0.05 mol) of anhydrous sodium carbonate. At the end of 10 hours of boiling, the inorganic sodium salts which had separated out were separated by vacuum filtration, the filter cake was washed with acetonitrile, and the acetonitrile was distilled out of the filtrate. The distillation residue was dissolved in ether, the solution was extracted with a small amount of water and then dried, and the ether was distilled off, yielding raw (-)-N-ethylnorscopolamine.

7.0 g (0.022 mol) of (-)-N-ethylnorscopolamine were dissolved in acetonitrile, 10.4 g (0.11 mol) of methyl bromide were added to the solution, and the mixture was allowed to stand at room temperature. The crystalline precipitate formed thereby was collected and recrystallized from acetonitrile.8.9 g (97.8% of theory) of white crystalline (-)-N-ethylnorscopolamine methobromide, melting point 203°C to 204°C (decomposition), were obtained.

References

Merck Index A-10
DFU4 (2) 117 (1979)
DOT 19 (7) 416 and (8) 444 (1983)
Zeile, K., Banholzer, R., Walther, G., Schulz, W. and Wick, H.; US Patent 3,472,861; Oct. 14, 1969; assigned to Boehringer Ingelheim GmbH.

OXOLAMINE CITRATE

Therapeutic Function: Antitussive, Antiinflammatory

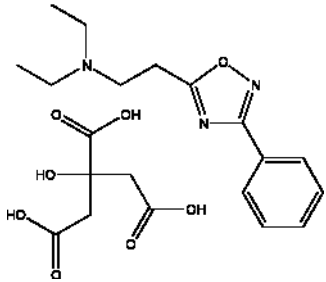
Chemical Name: 1,2,4-Oxadiazole, 5-(2-(diethylamino)ethyl)-3-phenyl-, citrate

Common Name: Oxolamine citrate

Raw Materials

3-Chloropropionyl chloride
N-Hydroxybenzamidine
Diethyl amine

Structural Formula:



Chemical Abstracts Registry No.: 1949-20-8 ; 959-14-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Bredon	Organon	-	-
Broncatar	Pulitzer	-	-
Perebron	Angelini Francesco	-	-
Prilon	Cassenne	-	-
Flogobron	Intersint	-	-
Oxolamine citrate	Milen	-	-
Oxolamine citrate	Yick-Vic Chemicals and Pharmaceuticals (HK) Ltd.	-	-
Oxolamine citrate	Shanghai Lansheng Corporation	-	-
Kalamin	Ilsan Ilac	-	-
Oxadron	Fustery	-	-
Regal	Andromaco	-	-
Aledron	IQFA	-	-

Manufacturing Process

18.7 g 3-chloro-propionyl chloride in 50 ml of dry ether was added dropwise with stirring to the cooled with ice solution 40 g of N-hydroxybenzamidine in 450 ml dry ester. A dense precipitate had fallen. The mixture was stirred 0.5 hour at room temperature and then was filtered off. The precipitate was thoroughly washed with water for a removal hydrochloride of starting N-hydroxybenzamidine whereas N-(amino)phenylmethylene-3-Cl-propionamide didnt solve. It was dried in vacuum over P_2O_5. Yield of clean product 94% from theoretical. MP: 98°-99°C. The solution of 9.2 g diethyl amine in 50 ml dry benzene was added dropwise to a suspension of above prepared N-(amino)phenylmethylene-3-Cl-propionamide in dry benzene with stirring and cooling.

The mixture was warmed and stirred else 2 hours after adding. Then it was cooled, washed two times with water and dried over $CaCl_2$. Then the solvent was removed. The residue was distilled in vacuum. Diethyl-[2-(3-phenyl[1,2,4]oxadiasol-5)ethyl]amine (oxolamine) had BP: 127°C/0.4 mm. Yield 10.5 g.

In practice it is usually used as citrate.

References

Angelini F.; D.B. Patent No. 1,097,998; Sept. 30, 1959

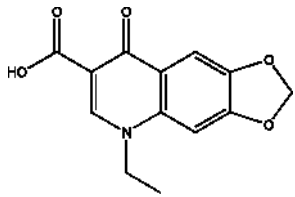
OXOLINIC ACID

Therapeutic Function: Antibacterial (urinary)

Chemical Name: 1-Ethyl-1,4-dihydro-4-oxo-1,3-dioxolo[4,5-g]quinoline-3-carboxylic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 14698-29-4

Trade Name	Manufacturer	Country	Year Introduced
Prodoxol	Warner	UK	1974
Urotrate	Substantia	France	1974
Ossian	Bioindustria	Italy	1974
Utibid	Warner Lambert	US	1975
Nidantin	Sasse/Goedecke	W. Germany	1978
Decme	Poli	Italy	-
Emyrenil	Emyfar	Spain	-
Gramurin	Chinoin	Hungary	-
Oksaren	Belupo Ltd.	Yugoslavia	-
Ossion	Bioindustria	Italy	-
Oxoboi	B.O.I.	Spain	-
Oxoinex	Inexfa	Spain	-
Oxol	Casen	Spain	-
Oxolin	Prodes	Spain	-
Pietil	Argentia	Argentina	-
Tilvis	Scharper	Italy	-
Tropodil	Elea	Argentina	-
Urinox	Syncro	Argentina	-
Uro-Alvar	Alvarez-Gomez	Spain	-

Trade Name	Manufacturer	Country	Year Introduced
Uropax	Lefa	Spain	-
Uroxol	Ausonia	Italy	-

Raw Materials

3,4-Methylenedioxyaniline
Diethyl ethoxymethylenemalonate
Sodium hydroxide
Ethyl iodide

Manufacturing Process

A mixture of 27 parts by weight of 3,4-methylenedioxyaniline and 43 parts by weight of diethyl ethoxymethylenemalonate is heated at 80° to 90°C for 3 hours. The mixture is then heated at 80° to 90°C for 1 hour under about 15 mm pressure to remove the byproduct ethyl alcohol formed. The residue is recrystallized from ligroin (BP 60° to 90°C) to give diethyl[(3,4-methylenetlioxyanilino)methylene] malonate as a yellow solid melting at 100° to 102°C. The analytical sample from ligroin melts at 101° to 102°C.

A mixture of 48 parts by weight of diethyl[(3,4-methylenedioxyanilino) methylene] malonate and 500 parts by weight of diphenyl ether is refluxed for 1 hour. The mixture is allowed to cool to about 25°C with stirring and 500 parts by weight of petroleum ether are added. Filtration gives 3-carbethoxy-6,7-methylenedioxy-4-hydroxy-quinoline as a brown solid, MP 276° to 281°C. Several recrystallizations from dimethylformamide gives almost colorless analytical material, MP 285° to 286°C, (decomposes).

A mixture of 26 parts of 3-carbethoxy-6,7-methylenedioxy-4-hydroxy-quinoline,16 parts of sodium hydroxide and 50 parts of dimethylformamide is heated at 70° to 75°C for 2 hours, then 31 parts of ethyl iodide is added over 1 hour with continued heating and stirring. After an additional 3 to 4 hours of heating (at 70° to 75°C) and stirring, the mixture is diluted with 500 parts of water, refluxed for 3 to 4 hours, acidified with concentrated hydrochloric acid and filtered to yield 18 to 22 parts of 1-ethyl-1,4-dihydro-6,7-methylene-dioxy-4-oxo-3-quinoline-carboxylic acid, MP 309° to 314°C (decomposes). The analytical sample from dimethylformamide melts at 314° to 316°C (decomposes).

References

Merck Index 6814
Kleeman & Engel p. 670
OCDS Vol. 2 pp. 370, 387(1980) and 3, 185 (1984)
I.N. p. 34
Kaminsky, D. and Meltzer, R.I.; US Patent 3,287,458; November 22, 1966; assigned to Warner-Lambert Pharmaceutical Company

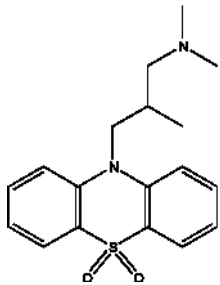
OXOMEMAZINE

Therapeutic Function: Antihistaminic

Chemical Name: N,N,β-Trimethyl-10-H-phenothiazine-10-propanamine 5,5-dioxide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 3689-50-7; 4784-40-1 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Doxergan	Specia	France	1964
Imakol	Rhone Poulenc	W. Germany	1965
Dysedon	Meiji	Japan	-
Rectoplexil	Specia	France	-
Toplexil	Specia	France	-

Raw Materials

Phenothiazine
Sodium amide
3-Dimethylamino-2-methylpropyl chloride
Hydrogen peroxide

Manufacturing Process

Phenothiazine is reacted with 3-dimethylamino-2-methylpropyl chloride in the presence of sodium amide to give 3-(10-phenthiazinyl)-2-methyl-1-dimethylaminopropane. 11.9 g of of this intermediate is dissolved with agitation in glacial acetic acid (120 cc). Pure sulfuric acid (d = 1.83; 0.5 cc) is added and a mixture of glacial acetic acid (10 cc) and hydrogen peroxide (8.5 cc of a solution containing 38 g of hydrogen peroxide in 100 cc) is then run in over 20 minutes. The temperature rises from 25°C to 35°C and is then kept at 60°C for 18 hours. The mixture is cooled and water (150 cc) is added and, with cooling, aqueous sodium hydroxide (d = 1.33; 220 cc). The resulting

mixture is extracted with ethyl acetate (3 x 100 cc), the solvent is evaporated on a water bath and the residue is recrystallized from heptane (150 cc). 3-(9,9-dioxy-10-phenthiazinyl)-2-methyl-1-dimethylaminopropane (78 g) is obtained, MP 115°C.

The corresponding hydrochloride prepared in ethyl acetate and recrystallized from a mixture of ethanol and isopropanol melts at 250°C.

References

Merck Index 6815
Kleeman & Engel p. 670
DOT 2 (4)145 (1966)
I.N. p. 715
Jacob, R.M. and Robert, J.G.; US Patent 2,972,612; February 21, 1961; assigned to Societe des Usines Chimiques Rhone-Poulenc (France)

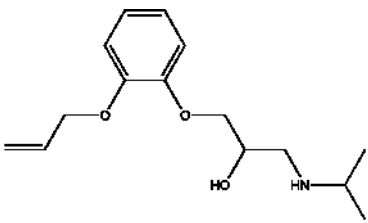
OXPRENOLOL

Therapeutic Function: Antiarrhythmic

Chemical Name: 1-[(1-Methylethyl)amino]-3-[2-(2-propenyloxy)phenoxy]-2-propanol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 6452-71-7; 6452-73-9 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Trasicor	Ciba Geigy	Italy	1970
Trasicor	Ciba Geigy	W. Germany	1971
Trasicor	Ciba Geigy	UK	1972
Trasicor	Ciba Geigy	France	1975
Trasacor	Ciba Geigy	Japan	1976
Captol	Protea	Australia	-
Cordexol	Lagap	Switz.	-
Coretal	Polfa	Poland	-

Raw Materials

Epichlorohydrin
Isopropylamine
Pyrocatechol monoallyl ether

Manufacturing Process

75 grams of pyrocatechol monoallyl ether, 75 grams of epichlorohydrin, 75 grams of potassium carbonate and 400 ml of acetone are stirred and heated at the boil for 12 hours. The potassium carbonate is then filtered off. The solvent is distilled off in a water-jet vacuum. The residual oil is dissolved in ether and agitated with 2 N sodium hydroxide solution. The ether is separated, dried and distilled off. The residue is distilled in a water-jet vacuum. 3-(ortho-allyloxy-phenoxy)-1,2-epoxypropane passes over at 145° to 157°C under 11 mm Hg pressure. A solution of 15 grams of 3-(ortho-allyloxy-phenoxy)-1,2-epoxypropane and 15 grams of isopropylamine in 20 ml of ethanol is refluxed for 4 hours. The excess amine and the alcohol are then distilled off under vacuum, to leave 1-isopropylamino-2-hydroxy-3-(ortho-allyloxy-phenoxy)-propane which melts at 75° to 80°C after recrystallization from hexane.

References

Merck Index 6820
Kleeman & Engel p. 671
OCDS Vol.1 p.117 (1977) and 2, 109 (1980)
DOT 6 (1) 25 (1970)
I.N. p. 716
Ciba Limited, Switzerland; British Patent 1,077,603; August 2, 1967

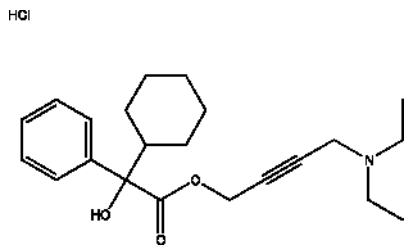
OXYBUTYNIN CHLORIDE

Therapeutic Function: Spasmolytic

Chemical Name: α-Cyclohexyl-α-hydroxybenzeneacetic acid 4-(dietylamino)-2-butynyl ester hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 1508-65-2; 5633-20-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Ditropan	Marion	US	1975
Ditropan	Scharper	Italy	-

Raw Materials

Methyl phenylcyclohexylglycolate
4-Diethylamino-2-butynyl acetate
Sodium methylate

Manufacturing Process

A mixture of 394.2 grams of methyl phenylcyclohexylglycolate and 293.1 grams of 4-diethylamino-2-butynyl acetate was dissolved with warming in 2.6 liters of n-heptane. The solution was heated with stirring to a temperature of 60° to 70°C and 8.0 grams of sodium methoxide were added. The temperature of the mixture was then raised until the solvent began to distill. Distillation was continued at a gradual rate and aliquots of the distillate were successively collected and analyzed for the presence of methyl acetate by measurement of the refractive index. The reaction was completed when methyl acetate no longer distilled, and the refractive index observed was that of pure heptane (n_D^{26} = 1.3855). About 3½ hours were required for the reaction to be completed.

The reaction mixture was then allowed to cool to room temperature, washed with water, and extracted with four 165 ml portions of 2 N hydrochloric acid. The aqueous extracts were combined and stirred at room temperature to permit crystallization of the hydrochloride salt of the desired product. Crystallization was completed by cooling the slurry in an ice bath, and the product was collected by filtration, pressed dry, and recrystallized from 750 ml of water. Yield of pure crystalline material, 323 grams.

References

Merck Index 6823
Kleeman & Engel p. 672
PDR p. 1076
OCDS Vol. 1 p. 93 (1977)
I.N. p. 716
REM p.919
Mead Johnson and Company; British Patent 940, 540; October 30, 1963

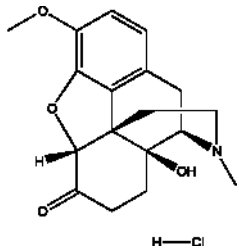
OXYCODONE HYDROCHLORIDE

Therapeutic Function: Narcotic analgesic

Chemical Name: Morphinan-6-one, 4,5α-epoxy-14-hydroxy-3-methoxy-17-methyl- hydrochloride

Common Name: Dihydrohydroxycodeinone hydrochloride; Hydrooxycodeinona; Hydroxydihydrocodeinonum hydrochloricum; Ossicodone; Oxiconum; Oxikon; Oxycodeinone hydrochloride; Oxycodone hydrochloride; Thecodin

Structural Formula:



Chemical Abstracts Registry No.: 76-42-6 (Base); 124-90-3

Trade Name	Manufacturer	Country	Year Introduced
Oxyfast	Purdue Pharma, L.P.	-	-
Endone	Boots	-	-
Oxynorm	Mundipharma	-	-
Roxicodone	Roxane	-	-
Percodan	Endo Pharmaceuticals Inc.	-	-
Codeinona	Higiene	-	-

Raw Materials

Dibutylurea	Codeine sulfate trihydrate
t-BuMe_2SiCl	Ammonium hydroxide
Peracetic acid	Aluminum isopropoxide
Acetic acid	Potassium sodium tartrate tetrahydrate
Hydrogen	Palladium on carbon

Manufacturing Process

Preparation of codeinone from codeine:

Codeinone was prepared by oxidation of codeine sulfate trihydrate. A reaction mixture was prepared containing codeine sulfate trihydrate (10.4 g), deionized water (20 g) and isopropyl acetate (87.2 g) at ambient temperature. The reaction mixture was agitated and the resultant mixture cooled to about 20°C. Concentrated ammonium hydroxide (18.0 g) was added in several portions and the mixture was maintained at a temperature of about 20°C with stirring. Sting was continued for about 15 min, and then a small portion of the aqueous layer was withdrawn to check for pH value, which was to be advantageously maintained between 11.0 and 12.0. The aqueous layer was

then separated and reextracted with isopropyl acetate (35 g). The combined organic layers (isopropyl acetate) were concentrated in vacuo to near dryness at temperature 45°C. The residual isopropyl acetate solvent was chased by adding 18 g of toluene. The concentration process was then repeated in vacuo. Codeine free base dissolved in a mixture of toluene (177 g) and cyclohexanone (47.4 g) at 45°C was then transferred to the reaction flask which was equipped with magnetic stirrer, thermocouple, Dean-Stark trap with condenser attached, addition funnel with an extender (about 4 inches height), and a nitrogen inlet adapter. The mixture was heated to boiling temperature (about 116-118°C) under a nitrogen atmosphere and 26 g (30 ml) of distillate were collected in the Dean-Stark trap. A solution of aluminum isopropoxide (3.5 g) in 35.5 g (41 ml) of toluene was then added to the addition funnel. The heating rate was adjusted and the aluminum isopropoxide/toluene solution was added into the reaction mixture at such a rate that the total volume was added over a 10-20 min period [approximately the same volume (41 ml) of distillate was collected in the Dean-Stark trap]. After completion of the addition, collection of the distillate was continued such that 57 g (66 ml) of distillate was collected in the Dean-Stark trap at a similar distillation rate. The heat source was removed and the mixture allowed to cool down to ambient temperature (under nitrogen atmosphere) over a period of about 30 min. Reaction completeness was determined by withdrawing a small sample from the batch, extracting it with a saturated sodium bicarbonate solution and ethyl acetate, concentrating the organic layer, redissolving it with the HPLC mobile phase, and analyzing the sample on HPLC.

An aqueous solution of 13 wt. % Rochelle salt was then prepared by dissolving 19.5 g of potassium sodium tartrate tetrahydrate in 130.5 g of deionized water at 20°C. The aqueous Rochelle salt solution (90 ml) was added into the reaction mixture in one portion at ambient temperature, the batch stirred for about 10 min and filtered. Both layers were saved. The organic layer was washed with 60 ml of aqueous Rochelle salt solution (both layers were saved). The organic layer was washed with a mixture of 30 ml brine solution and 30 ml 5% sodium bicarbonate solution (both layers were saved). All aqueous layers were then combined and extracted with 43 g (50 ml) of toluene. The aqueous layer was discarded. The organic layers were then combined and concentrated in vacuo at temperature 55°C to near dryness. 22 g (25 ml) of toluene was added and the resultant organic layer concentrated in vacuo twice more to remove residual cyclohexanone. Subsequently, 11.8 g (15 ml) of 2-propanol was added and the mix slurried at 0-5°C for at least eight hours under a nitrogen atmosphere. Solids were then filtered. The latter operation was repeated until no solids were left in the flask. The chilled wet cake was then rinsed with chilled (5-10°C) 2-propanol (12 g, 15 ml), and filter dried. The wet cake was then rinsed with heptane (6.8 g, 10 ml) and dried. The resulting solids were vacuum dried at 50°C to a constant weight. A yield of 5.2 to 6.45 g (65.4 to 81.2%) of white solids, with HPLC purity of about 96-99.3% was obtained. The compound was stored in a dark and cool place.

Preparation of dienolsilyl ether of codeinone:

Codeinone (6.0 g) with toluene (104 g) was added to a reaction flask equipped with a mechanical stirrer, thermocouple, Dean-Stark trap with condenser attached, and a nitrogen inlet. The batch was heated to reflux and about 27.7 g (32 ml) of distillate was collected in the Dean-Stark trap. The

contents were then cooled to 20°C under a nitrogen atmosphere. A solution of dibutyl urea (DBU) (4.22 g) in toluene (3 g) was added in one portion. Subsequently, a solution of t-$BuMe_2SiCl$ (4.22 g) in toluene (5 g) was likewise added in one portion. The batch was slowly warmed to 58°C and stirred at this temperature for about 2 hours. Completion of the reaction was adjudged by withdrawing a 20 small sample from the batch, extracting it with a mixture of ethyl acetate and saturated sodium bicarbonate solution, spotting the organic layer on a TLC plate, and then eluting it with a mobile phase of 9:1 mixture of dichloromethane and methanol plus 3-4 drops of concentrated ammonium hydroxide. If the reaction was determined to be incomplete, stirring was continued at 58°C for an additional 2 hours and a TLC check performed once more. Alternatively reaction completion was accomplished by adding about 5-10% more of both DBU and t-$BuMe_2SiCl$ to the reaction mixture at the same temperature. The contents were then cooled to 20°C, and a mixture of 5% sodium bicarbonate solution (80 ml) and 60 ml of water was added in one portion. Stirring continued for about 10 min. The aqueous layer was then separated and discarded. The organic layer was washed with a mixture of 50 ml brine and 50 ml saturated ammonium chloride solution (the aqueous layers were discarded). The organic layer was concentrated to near dryness in vacuo at temperature 50°C, and the residue diluted with 33.2 g of toluene to make up a 20 wt % stock solution. Yield was approximately quantitative. The stock solution was found to be stable at ambient temperature under nitrogen atmosphere for at least 6 months.

Preparation of 14-hydroxycodeinone from denolsilyl ether of codeinone:

Peracetic acid solution (107.7 g of 9.0 wt % peracetic acid) at ambient temperature was added to a reaction flask equipped with mechanical stirrer and thermocouple, nitrogen inlet adapter and addition funnel. A 20 wt % stock solution of the dienolsilyl ether of codeinone (41.7 g) was added through the addition funnel over a period of about 5 min and the temperature of the contents maintained at 28°C. The batch was stirred at 22°C for at least 3 hours. In order to test reaction completeness, a small sample was withdrawn from the batch and quenched with saturated sodium bicarbonate solution, and extracted with ethyl acetate. The EtOAc layer was spotted onto a TLC plate and subsequently checked for the disappearance of starting dienolsilyl ether of codeinone. The TLC mobile phase was a mixture of 95:5 of dichloromethane and methanol plus 3-5 drops of concentrated ammonium hydroxide. If the reaction was adjudged incomplete, the mixture was stirred at the same temperature for an additional 2 hours then analyzed by TLC again. Alternatively completion of the reaction was pushed by the addition of 10 g of peracetic acid (9.0 wt %) and stirring for an additional 1 h (analysis was then once more performed using TLC).

Upon determination of the completion of the reaction 20.0 g of 10 wt. % of aqueous sodium hydrogen sulfate solution was added in one portion, and the resultant admixture stirred for 10 min at ambient temperature. The batch was then concentrated in vacuo at 45°C to dryness. Subsequently water (180 g), toluene (69 g), ethyl acetate (36 g) were added and vigorous stirring for about 10 min undertaken. The resulting layers were separated and the aqueous layer saved in a flask. The organic layer was washed thrice with a solution of 26 ml of 2.5% HCl. The combined aqueous layers were then filtered through a pad of wet (with water) hyflo-supercel filter aid. Subsequently, EtOAc (85 g) was added to the filtrate and concentrated

ammonium hydroxide added in a quantity to adjust the pH of the aqueous layer to about 11. The mixture was stirred for 10 min at about 60°C and the layers were separated and saved. The aqueous layer was washed with EtOAc (50 g) and then discarded. The combined organic layers were concentrated in vacuo to dryness at 50°C. To the residue was added 2-propanol (13 g), and the resultant mixture stirred at 5-10°C for at least 5 hours. The solids were filtered, the flask and solids rinsed with the chilled (5°C) filtrate followed by chilled (5-10°C) 2-propanol (10 g) and heptane (8 g). The solid was then vacuum dried at 50°C to a constant weight. A yield of between 3.50-4.96 g (55%-78%) of 14-hydroxycodeinone free base with a purity of over 96A% was obtained.

Preparation of oxycodone from 14-hydroxycodeinone by catalytic hydrogenation:

14-Hydroxycodeinone (4.98 g) and acetic acid (155 g) were added to a Parr shaker equipped with hydrogen inlet and outlet connectors. The mixture was shaken for about 5 min to completely dissolve the 14-hydroxycodeinone at ambient temperature. The system was then evacuated and the Parr shaker was filled with nitrogen. In one portion, under the nitrogen atmosphere, 10% Pd/C (50% water wet, 4.0 g) was added. The system was then evacuated, and was filled with hydrogen gas to a pressure of about 38 psi. The hydrogen inlet from the supply tank was then closed and the mixture was shaken at an initial pressure of 38 psi for about 3 hours (at ambient temperature). After 3 hours of shaking, the system was evacuated and filled with nitrogen. The contents were filtered over a hyflo-supercel filtering pad (3 g, wetted with water). The Parr bottle and wet cake were then rinsed with acetic acid (2 x 21 g). The filtrate was concentrated in vacuo to dryness at 50°C. The residue was then dissolved with deionized water (50 g), and the pH adjusted to about 11.0 to 12.0 using 20% aqueous KOH solution and concentrated ammonium hydroxide (4 g). The mixture was then extracted with ethyl acetate (4 x 135 g), and the combined organic layers concentrated in vacuo to dryness. A yield of 3.51 to 4.26 g of crude oxycodone with HPLC purity of over 85A% (70.0 to 85.0% yield) was obtained.

Preparation of oxycodone from 14-hydroxycodeinone by catalytic transfer hydrogenation method:

14-Hydroxycodeinone (4.98 g) and acetic acid (137 g) were added to a reaction flask (3-neck, 250 ml) equipped with mechanical stirrer, addition funnel, thermocouple and nitrogen-inlet adapter. The system was evacuated and the flask filled with nitrogen. Subsequently, 5% Pd/C (50% water wet, 3.0 g) in one portion was added under the nitrogen atmosphere. While the mixture was stirred for about 5 min at ambient temperature, a solution of sodium hypophosphite (6.0 g) in deionized water (25 g) was prepared. The aqueous sodium hypophosphite solution was transferred into the addition funnel, and added to the reaction mixture over a period of about 30 min at about 22°C. The mixture was then warmed to about 45°C and stirred for about 1 hour.

Upon the reaction was complete, the batch was cooled to ambient temperature under the nitrogen atmosphere, and the contents filtered over a hyflo-supercel filtering pad (3.0 g, wetted with water). The flask and wet cake were rinsed with acetic acid (20 g). The filtrate was concentrated in vacuo to

near dryness at temperature 50°C. The residue was dissolved with deionized water (50 g) and the pH adjusted to 11.0 to 12.0 with 20% aqueous KOH solution and concentrated ammonium hydroxide (about 4 g). The mixture was then extracted with ethyl acetate (4 x 135 g) and the combined organic layers concentrated to dryness in vacuo. Crude oxycodone with an HBLC purity of over 85% was obtained in a yield of 70.0 to 85.0% (3.51 to 4.26 g).

References

Chiu Fang-Ting, Lo Young S.; US Patent No. 6,469,170; October 22, 2002; Assigned to Boehringer Ingelheim Chemicals, Inc. (Petersburg, VA)

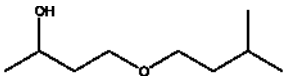
OXYDIBUTANOL

Therapeutic Function: Choleretic, Spasmolytic

Chemical Name: 4,4'-Oxybisbutan-2-ol

Common Name: Dihydroxydibutyl ether; Hydroxybutyloxide; Oxydibutanol

Structural Formula:



Chemical Abstracts Registry No.: 821-33-0

Trade Name	Manufacturer	Country	Year Introduced
Dyskineacutebyl	Saunier	-	-
Dis-Cinil	Lusofarmaco	-	-
Dihydroxydibutyl ether	Joulty	-	-

Raw Materials

Butyl magnesium bromide
β-Cyanoethyloxide
Nickel Raney
Hydrogen

Manufacturing Process

To a solution of 3 mols butylmagnesiumbromide in ether was added dropwise an one mol of β-cyanoethyloxide. The mixture was refluxed for 1 hour. Then after cooling to the mixture was added hydrochloric acid. An organic layer was dried under sodium sulfate and evaporated. An oil layer was distilled in vacuum. The oxo-3-butane oxide has a boiling point 123-125°C at 15 mm.

A mixture of 100 g of oxo-3-butane oxide, 500 ml ethanol and 15 g Nickel Reney was loaded in autoclave and heated at 45-50°C. In autoclave was introduced a hydrogene. After cooling the mixture was filtered and ethanol was distilled off. 1,1'-Dimethyl-3,3'-oxydipropanol was distilled at 160-161°C/18 mm.

References

Merck Index, Monograph number: 7094, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
FR Patent No. 1,267,084; June 5, 1961; Assigned to Joulty M.A., resident of France

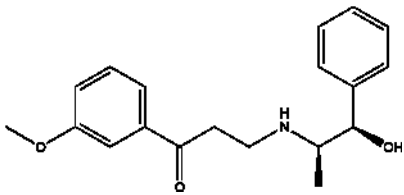
OXYFEDRINE

Therapeutic Function: Coronary vasodilator

Chemical Name: (R)-3-[(2-Hydroxy-1-methyl-2-phenylethyl)amino]-1-(3-methoxyphenyl)-1-propanone

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 15687-41-9; 16777-42-7 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Ildamen	Homburg	W. Germany	1966
Ildamen	Chugai	Japan	1970
Ildamen	Homburg	Italy	1972
Ildamen	Farmades	Italy	1973
Modacor	I.S.H.	France	-
Myofedrin	Apogepha	E. Germany	-
Timoval	Homburg	W. Germany	-

Raw Materials

m-Methoxyacetophenone
L-Norephedrine
Paraformaldehyde

Manufacturing Process

45 grams of m-methoxy acetophenone, 8 grams of paraformaldehyde and 30.2 grams of 1 norephedrine were mixed with about 135 cc of isopropanol HCl solution to provide a pH of 4 and the mixture refluxed for 4 hours. The reaction mixture was cooled and the crystals filtered off on a suction filter. 3-[1-phenyl-1-hydroxypropyl-(2)-amino]-1-(m-methoxyphenyl)-propanone-(1) HCl was obtained which after recrystallization from methanol had a MP of 190° to 193°C.

References

Merck Index 6830
Kleeman & Engel p. 673
OCDS Vol. 2 p. 40 (1980)
I.N. p. 718
Thiele, K.; US Patent 3,225,095; December 21, 1965; assigned to Deutsche Gold-und Silber-Scheideanstalt, Germany

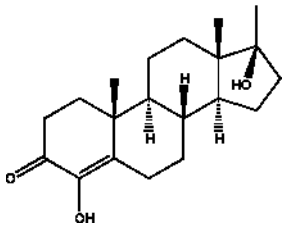
OXYMESTERONE

Therapeutic Function: Anabolic, Androgen

Chemical Name: 4,17beta-Dihydroxy-17-methylandrost-4-en-3-one

Common Name: Hydroxymethyltestosterone; Methandrostenediolone; Ossimesterone; Oximesteronum; Oxymesterone; Oxymestrone

Structural Formula:



Chemical Abstracts Registry No.: 145-12-0

Trade Name	Manufacturer	Country	Year Introduced
Anamidol	Iwaki	-	-
Oranabol	Farmitalia Carlo Erba	-	-
Balnimax	Geve	-	-

Raw Materials

Sulfuric acid	4,5-Oxido-17α-methyltestosterone
Sodium chloride	Sodium bicarbonate
Potassium hydroxide	17α-Methyltestosterone
Acetic acid	Trimethylcarbinol
Hydrogen peroxide	Osmium tetroxide
Sodium bisulfite	Acetic acid

Manufacturing Process

2 Methods of producing of 4-hydroxy-17α-methyltestosterone:

1. A solution of 1.0 g of crude 4,5-oxido-17α-methyltestosterone in 50 ml of methanol is allowed to stand at room temperature overnight with 10 ml of water and 1 ml of concentrated sulfuric acid. It is then poured into water containing sodium chloride and extracted three times with ethyl acetate. The solvent is washed with water, then with 10% sodium bicarbonate solution and again with water to neutrality. The residue remaining after evaporation of the solvent is crystallized from methanol, giving 17α-methyl-androstane-4β,5α,17β-triol-3-one with a melting point of 203°-205°C.

A solution of 0.22 g of 17α-methyl-androstane-4β,5α,17β-triol-3-one in 100 ml of methanol is allowed to stand at room temperature for 22 h, under nitrogen, with 0.30 g of potassium hydroxide in 4 ml of water and 20 ml of methanol. The solution is then neutralized with acetic acid, concentrated in vacuo, diluted with water and extracted three times with ethyl acetate. The extract is washed with water and the solvent removed by distillation. The remaining residue is chromatographed over Florisil 30-60 mesh. The fractions eluted with benzene and benzene-ether (10:1) are combined and by crystallization from ether-petroleum ether give 4-hydroxy-17α-methyltestosterone (0.120 g) melting at 168°-170°C.

2. A solution of 20.0 g of 17α-testosterone in 500 ml of trimethylcarbinol is treated by addition of 56 ml of 30% hydrogen peroxide and 1.0 g of osmium tetroxide in 80 ml of trimethylcarbinol. After the mixture has stood at room temperature for 22 h, 12 ml of hydrogen peroxide are added. The reaction mixture is allowed to stand at room temperature for an additional 20 h, then concentrated in vacuo to 1/3 of its original volume, diluted with water, and the reaction product extracted with ethyl acetate. The extract is washed with water, several times with 10% sodium bisulfite solution, then with 4% sodium bicarbonate solution and finally with water to neutrality. The residue remaining after evaporation of the solvent does not show ultraviolet absorption. 1.0 g of this crude substance, by crystallization from methanol, gives l7α-methylandrostane-4,5,17β-triol-3-one (0.400 g) melting at 192°-194°C.

A solution of 20.0 g of crude 17β-methylandrostane-4,5,17β-triol-3-one in 1 L of methanol is heated under reflux in a stream of nitrogen for 20 min; then 20.0 g of potassium hydroxide in 40 ml of water and 200 ml of methanol are added. 5 min after the addition, the solution is treated by addition of 20 ml of acetic acid and concentrated in vacuo. The residue is diluted with water containing sodium chloride and extracted three times with ethyl acetate. The extract is washed with 10% sodium bicarbonate solution and then with water to neutrality. The residue remaining after evaporation of the solvent is

dissolved in acetone; addition of petroleum ether gives 4-hydroxy-17α-methyl-testosterone (8.0 g) melting at 168°-170°C. The mother liquors chromatographed over Florisil 30-60 mesh yield an additional 5.0 g of the same substance melting at 168°-170°C.

References

Camerino B. et al; US Patent No. 3,060,201; Oct. 23, 1962; Assigned: Societa Farmaceutici Italia, Milan, Italy, a corporation of Italy

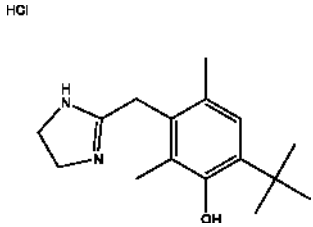
OXYMETAZOLINE HYDROCHLORIDE

Therapeutic Function: Nasal decongestant

Chemical Name: 3-[(4,5-Dihydro-1H-imidazol-2-yl)methyl]-6-(1,1-dimethylethyl)-2,4-dimethylphenol hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 2315-02-8; 1491-59-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Nasivin	Merck	W. Germany	1961
Iliadine	Merck Clevenot	France	1964
Afrin	Schering	US	1964
Nostrilla	Boehringer Ingelheim	US	1982
Alrin	Teva	Israel	-
Atomol	Allen and Hanburys	UK	-
Dristan	Whitehall	US	-
Duration	Plough	US	-
Nasivin	Bracco	Italy	-
Nasafarma	Novofarma	Spain	-
Nezeril	Draco	Sweden	-
Oxymeta	Schein	US	-
Pikorin	Medica	Finland	-
Rhinolitan	Kettelhack Riker	W. Germany	-

Trade Name	Manufacturer	Country	Year Introduced
Sinerol	Draco	Sweden	-
Utabon	Uriach	Spain	-

Raw Materials

Hydrogen chloride
Ethylene diamine
Formaldehyde
Sodium hydroxide
2,4-Dimethyl-6-t-butylphenol
4-Toluenesulfonic acid
Sodium cyanide
Hydrogen chloride

Manufacturing Process

10 grams 2,6-dimethyl-3-hydroxy-4-tertiary butylbenzylcyanide (produced by chloromethylation of 2,4-dimethyl-6-tertiary butyl-phenol with formaldehyde and HCl and conversion of the substituted benzyl chloride with NaCN; crystals, from alcohol, melting at 135° to 137°C) and 10.7 grams ethylenediamine-mono-p-toluenesulfonate are heated in an oil bath to approximately 235°C for 1½ hours, whereby ammonia is evolved. The free base is obtained from the p-toluene-sulfonic acid imidazoline salt which is difficultly soluble in water, by conversion with 50 cc of a 10% NaOH solution. Said base is recrystallized from benzene, and 7.5 grams (62% of the theoretical yield) 2-(2',6'-dimethyl-3'-hydroxy-4'-tertiary butylbenzyl)-2-imidazoline, MP 180° to 182°C, are obtained.

By dissolving the free base in an ethyl alcohol solution of hydrochloric acid and adding ether, the hydrochloride can be produced in the usual manner. Said hydrochloride melts, when recrystallized from alcoholic ether, at 300° to 303°C and is decomposed.

References

Merck Index 6834
Kleeman & Engal p. 674
PDR pp. 677, 728, 1606, 1899
OCDS Vol. 1 p. 242 (1977)
I.N. p. 719
REM p. 889
Fruhstorfer, W. and Muller-Calgan, H.; US Patent 3,147,275; September 1, 1964; assigned to E. Merck AG, Germany

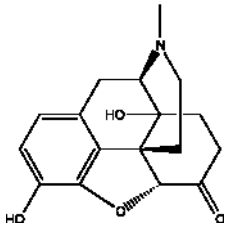
OXYMORPHONE

Therapeutic Function: Narcotic analgesic

Chemical Name: 4,5α-Epoxy-3,14-dihydroxy-17-methylmorphinan-6-one

Common Name: Dihydrohydroxymorphinone

Structural Formula:



Chemical Abstracts Registry No.: 76-41-5

Trade Name	Manufacturer	Country	Year Introduced
Numorphan	Endo	US	1959

Raw Materials

Thebaine
Hydrogen peroxide
Hydrogen bromide
Hydrogen

Manufacturing Process

Thebaine is dissolved in aqueous formic acid and treated with 30% H_2O_2; neutralization with aqueous ammonia gives 14-hydroxycodeinone. It is hydrogenated to give oxycodone. 90 ml of concentrated hydrobromic acid are heated to 90°C. 9 grams of 14-hydroxydihydrocodeinone (oxycodone) are then added under stirring and the mixture is quickly heated to 116°C and kept at this temperature under reflux condenser for 20 minutes, with continued stirring. The resulting brown solution is diluted with about 90 ml of water and chilled with ice. Aqueous 10% sodium hydroxide solution is now added to alkaline reaction and the liquid is extracted 3 times with 100 cc portions of chloroform. The layers are separated and the aqueous phase is filtered and acidified by the addition of concentrated aqueous hydrochloric acid, treated with charcoal and filtered.

The filtrate is treated with concentrated aqueous ammonia until the mixture gives a pink color on phenolphthalein paper. The liquid is extracted seven times with 100 cc portions of chloroform, the extracts are combined, dried with anhydrous sodium sulfate and evaporated. The residue is dissolved in ethanol by refluxing and the ethanol evaporated nearly to dryness. 100 cc of benzene are then added, the mixture is refluxed for ½ hour and set aside for crystallization. After cooling, the desired compound is collected by filtration, 2.3 grams of a white crystalline powder are obtained; MP 245° to 247°C. This powder consisting of 14-hydroxydihydromorphinone can be purified by recrystallization from benzene, ethylacetate or ethanol. From benzene it generally forms diamond shaped platelets, while needles are obtained from ethylacetate.

On heating, the crystals are discolored from about 200°C on, and melt at 246° to 247°C to a black liquid, which decomposes with strong volume increase if the temperature is raised further by a few degrees.

References

Merck Index 6837
Kleeman & Engel p. 675
PDR p. 859
OCDS Vol. 1 p. 290 (1977) and 2, 319 (1980)
I.N. p. 719
REM p. 1105
Lewenstein, M.J. and Weiss, U.; US Patent 2,806,033; September 10, 1957

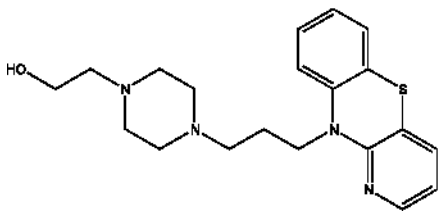
OXYPENDYL

Therapeutic Function: Antiemetic

Chemical Name: 4-[3-(10H-Pyrido[3,2-b][1,4]benzothiazin-10-yl)propyl]-1-piperazineethanol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 5585-93-3; 17297-82-4 (Dihydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Pervetral	Homburg	W. Germany	1962

Raw Materials

10-(γ-N-Piperazinopropyl)-4-azaphenthiazine
Ethylene chlorohydrin

Manufacturing Process

32 parts of 10-(γ-N-piperazinopropyl)-4-azaphenthiazine in 200 cc of butanol

with 9 parts of ethylene chlorohydrin and 14 parts of finely powdered potash are heated for 4 hours under reflux while stirring vigorously. After cooling, extraction is carried out with dilute hydrochloric acid, the substance is finally washed with water and the combined hydrochloric acid aqueous phase is washed twice with ether. The base is then liberated with concentrated sodium hydroxide solution and taken up in chloroform. The chloroform solution is dried with potash and concentrated by evaporation. 26.4 parts of (10-γ-N-B-hydroxyethylpiperazino-N^1-propyl)-4-azaphenthiazine are distilled over at 280°C to 300°C/6 mm. The dihydrochloride is obtained in isopropanol with isopropanolic hydrochloric acid. The product melts at 218°C to 220°C.

References

Merck Index 6838
Kleeman & Engel p. 676
OCDS Vol. 1 p. 430 (1977)
I.N.p. 719
Deutsche Gold-und Silber Scheideanstalt; British Patent 893,284; April 4, 1962

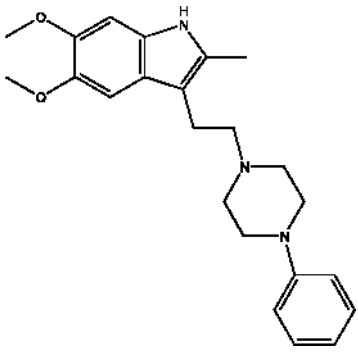
OXYPERTINE

Therapeutic Function: Antipsychotic, Neuroleptic

Chemical Name: 1H-Indole, 5,6-dimethoxy-2-methyl-3-(2-(4-phenyl-1-piperazinyl)ethyl)-

Common Name: Oxypertine; Oxipertinum

Structural Formula:



Chemical Abstracts Registry No.: 153-87-7

Trade Name	Manufacturer	Country	Year Introduced
Oxypertine capsules	Sanofi-Synthelabo	-	-

Trade Name	Manufacturer	Country	Year Introduced
Oxypertine	Bulk Drugs and Intermediates Inc.	-	-
Oxypertine	Shanghai Lansheng Corporation	-	-

Raw Materials

1-Phenylpiperazine
Acetic acid
[3-(2-Methyl-5,6-dimethoxy)indolyl] glyoxalyl chloride
Lithium aluminum hydride
Sodium hydroxide

Manufacturing Process

A cold, stirred solution of 1-phenyl-piperazine in tetrahydrofuran was treated all at once with [3-(2-methyl-5,6-dimethoxy)indolyl]glyoxalyl chloride. There was an immediate voluminous precipitate of a white crystalline solid which was removed by filtration. The filtrate was taken to dryness and the residual light brown gum was stirred and shaken with water, ethyl acetate and acetic acid. The mixture was warmed on a steam bath and the resulting solid was collected after cooling in an ice bath thus affording 1-[(3-(2-methyl-5,6-dimethoxy)indolyl)glyoxalyl]-4-phenylpiperazine as a near white solid, melting point 163°-174°C.

A solution of 1-[(3-(2-methyl-5,6-dimethoxy)indolyl)glyoxalyl]-4-phenyl piperazine in tetrahydrofuran was added over a 10 min period to a stirred suspension of lithium aluminum hydride in tetrahydrofuran. The mixture was refluxed and stirred for 6.5 h and the excess lithium aluminum hydride then destroyed by the dropwise addition of 10% sodium hydroxide solution. The mixture was filtered, the insoluble material was washed with boiling chloroform, and the filtrate dried over anhydrous sodium sulfate and concentrated to dryness. The residual light orange oil was crystallized from a benzene-hexane mixture giving 1-[(3-(2-methyl-5,6-dimethoxy)indolyl)ethyl]-4-phenyl piperazine.

References

Bethlehem S.A.; US Patent No. 3,183,313; June 8, 1965; Assigned: Sterling Drug Inc., New york, N.Y., a corporation of Delaware

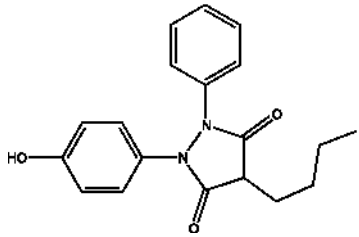
OXYPHENBUTAZONE

Therapeutic Function: Antiinflammatory

Chemical Name: 4-Butyl-1-(4-hydroxyphenyl)-2-phenyl-3,5-pyrazolidinedione

Common Name: p-Hydroxyphenylbutazone

Structural Formula:



Chemical Abstracts Registry No.: 129-20-4

Trade Name	Manufacturer	Country	Year Introduced
Tanderil	Geigy	UK	1960
Tandearil	Geigy	US	1961
Tanderil	Ciba Geigy	France	1961
Tanderil	Geigy	W. Germany	1961
Tanderil	Geigy	Italy	1962
Artroflog	Magis	Italy	-
Artzone	Continental Ethicals	S. Africa	-
Butaflogin	Chemiepharma	Italy	-
Butapirone	Brocchieri	Italy	-
Buteril	Protea	S. Africa	-
Butilene	Frencia	Italy	-
Deflogin	Valeas	Italy	-
Fibutox	Phermador	S. Africa	-
Flanaril	Osfa	Italy	-
Floghene	Chibi	Italy	-
Flogistin	Scharper	Italy	-
Flogitolo	Isnardi	Italy	-
Flogodin	Firma	Italy	-
Iltazon	Iltas	Turkey	-
Imbun	Merckle	W. Germany	-
Inflamil	Leiras	Finland	-
Ipebutona	Ipecsa	Spain	-
Iridil	Farmila	Italy	-
Isobutil	Panther-Osfa	Italy	-
Miyadril	Fako	Turkey	-
Optimal	Dojin	Japan	-
Optone	Lennon	S. Africa	-
Oxalid	U.S.V.	US	-
Oxibutol	Asla	Spain	-
Oxybutazone	I.C.N.	Canada	-
Oxybuton	Streuli	Switz.	-

Trade Name	Manufacturer	Country	Year Introduced
Phlogase	Adenylchemie	W. Germany	-
Phlogistol	Helopharm	W. Germany	-
Phlogont	Azuchemie	W. Germany	-
Phloguran	Ikapharm	Israel	-
Pirabutina	Ellea	Italy	-
Piraflogin	Jamco	Italy	-
Rapostan	Mepha	Switz.	-
Rheumapax	Erco	Denmark	-
Tantal	Sawai	Japan	-
Teneral	Eczacibasi	Turkey	-
Validil	Von Boch	Italy	-
Visobutina	I.S.F.	Italy	-

Raw Materials

Sodium
Hydrogen
n-Butylmalonic acid ethyl ester
p-Benzyloxy hydrazobenzene

Manufacturing Process

43.2 parts of n-butyl malonic acid ethyl ester are added to a solution of 4.6 parts of sodium in 92 parts by volume of absolute alcohol. 39 parts of p-benzyloxy hydrazobenzene (MP 88° to 90°C) are added. About two-thirds of the alcohol is distilled off and 92 parts by volume of absolute xylene are added. Without removing the sloping condenser, the mixture is stirred for 12 hours at a bath temperature of 140° to 145°C. It is then cooled to 0° to 5°C, 100 parts of ice are added, the xylene is removed, the aqueous solution is extracted twice with chloroform and made acid to Congo red at 0° to 5°C with 6 N hydrochloric acid.

The precipitate is taken up in chloroform, the solution obtained is washed twice with water, then with saturated salt solution, dried over Na2SO4and evaporated under vacuum (bath temperature 20°C). The residue is recrystallized from alcohol and produces 1-(p-benzyloxyphenyl)-2-phenyl-4-n-butyl-3,5-dioxo-pyrazolidine (C) as tiny white needles which melt at 132° to 133°C.

16.6 parts of (C) are suspended in 166 parts by volume of ethyl acetate and, in the presence of 16.6 parts of Raney nickel, hydrogen is allowed to act at room temperature and atmospheric pressure.

After 6 hours the calculated amount of hydrogen has been taken up. The residue obtained after filtering and evaporating is taken up in benzene and extracted twice with diluted sodium carbonate solution. The alkali extract is then made acid to Congo red with 6 N hydrochloric acid and the precipitate is taken up in ethyl acetate. The solution obtained is washed twice with salt solution, dried with sodium sulfate and evaporated. The residue is recrystallized from ether/petroleum ether. 1-(p-hydroxyphenyl)-2-phenyl-4-n-

butyl-3,5-dioxo-pyrazolidine melts at 124° to 125°C.

References

Merck Index 6840
Kleeman & Engel p. 677
PDR p. 1606
OCDS Vol. 1 p. 236 (1977)
I.N. p. 720
REM p. 1119
Hafliger, F.; US Patent 2,745,783; May 15, 1956; assigned to J.R. Geigy AG, Switzerland

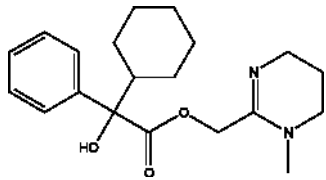
OXYPHENCYCLIMINE

Therapeutic Function: Spasmolytic

Chemical Name: α-Cyclohexyl-α-hydroxybenzeneacetic acid (1,4,5,6-tetrahydro-1-methyl-2-pyrimidinyl)methyl ester

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 125-53-1; 125-52-0 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Vio-Thene	Rowell	US	1959
Daricon	Pfizer	US	1959
Setrol	Flint	US	1961
Gastrix	Rowell	US	1973
Manir	Valpan	France	1975
Caridan	B.D.H.	UK	-
Cycmin	Toyo	Japan	-
Inomaru S	Sawai	Japan	-
Norma	Sankyo	Japan	-
Oximin	A.F.I.	Norway	-
Sedomucol	Asla	Spain	-

Trade Name	Manufacturer	Country	Year Introduced
Spazamin	G.P.	Australia	-
Ulcociclina	Confas	Italy	-
Ulcomin	Remedia	Israel	-
Vagogastrin	Benvegna	Italy	-

Raw Materials

1,3-Diaminobutane
Benzoyl formic acid
Magnesium
Ethyl chlorimidoacetate
Cyclohexyl bromide

Manufacturing Process

To a stirred solution of 8.8 grams (0.1 mol) of 1,3-diaminobutane in 150 ml of ethanol maintained at 0° to 5°C, there was added 25.8 grams (0.1 mol) of ethyl chlorimidoacetate hydrochloride during a period of 20 minutes. After the mixture had been stirred at 0° to 5°C for two hours, it was acidified at this temperature by the addition of ethanolic hydrogen chloride. The mixture was warmed to room temperature and filtered to remove 4.3 grams of solid ammonium chloride. The filtrate was concentrated to approximately 40 ml, filtered and refrigerated. The solid which separated was isolated, washed with acetone and dried. There was obtained 7.4 grams (40% of the theoretical yield) of 2-chloromethyl-4-methyl-1,4,5,6-tetrahydropyrimidine hydrochloride melting at 158° to 160°C.

In a second step, cyclohexyl bromide was reacted with magnesium, then with benzoyl formic acid to give cyclohexylphenyl glycolic acid. A solution of 1.8 grams (0.01 mol) of 2-chloromethyl-1-methyl-1,4,5,6-tetrahydropyrimidine hydrochloride in 5 ml of water was made alkaline with 5 ml of 50% NaOH and extracted with ether. The ether solution, which contained the basic chloride, was dried over calcium sulfate and added to a solution of 2.3 grams (0.01 mol) of α-cyclohexylphenylglycolic acid in 75 ml of isopropanol. The solution was distilled to remove the ether, and 0.1 gram of powdered potassium iodide added to the residual isopropanol solution which was then refluxed for 6 hours. The solid which had separated was redissolved by the addition of 20 ml of ethanol and the solution charcoaled, concentrated, and cooled. The solid which separated, 1-methyl-1,4,5,6-tetrahydro-2-pyrimidylmethyl α-cyclohexylphenyl-glycolate hydrochloride, weighed 1.4 grams and melted at 228° to 229°C with decomposition after recrystallization from ethanol.

References

Merck Index 6841
Kleeman & Engel p. 677
OCDS Vol. 2 p. 75 (1980)
I.N. p. 720
REM p.917
Chas. Pfizer & Co., Inc.; British Patent 795,758; May 28, 1958

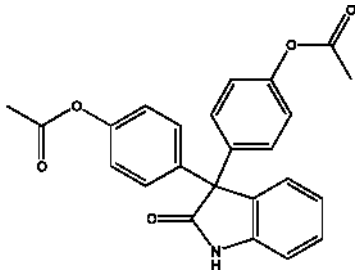
OXYPHENISATIN ACETATE

Therapeutic Function: Laxative

Chemical Name: 3,3-Bis[4-(acetyloxy)phenyl]-1,3-dihydro-2H-indol-one

Common Name: Acetphenolisatin; Endophenolphthalein; Diphesatin

Structural Formula:



Chemical Abstracts Registry No.: 115-33-3

Trade Name	Manufacturer	Country	Year Introduced
Lavema	Winthrop	US	1959
Isalax	Vale	US	1963
Acetalax	Harvey	Australia	-
Bisco-Zitron	Biscova	W. Germany	-
Bydolax	Moore	UK	-
Darmoletten	Omegin	W. Germany	-
Eulaxin	Pliva	Yugoslavia	-
Fenisan	Chemimportexport	Rumania	-
Laxatan	Divapharma	W. Germany	-
Laxanormal	Uquifa	Spain	-
Med-Laxan	Med	W. Germany	-
Nourilax	Noury Pharma	Netherlands	-
Obstilax	Zirkulin	W. Germany	-
Promassolax	Ysat Wernigerode	E. Germany	-
Prulet	Mission	US	-
Regal	Ferrosan	Denmark	-
Sanapert	Trogalen	Austria	-
Schokolax	Dallmann	W. Germany	-
Veripaque	Winthrop	UK	-

Raw Materials

Diphenolisatin
Acetic anhydride

Manufacturing Process

235 gravimetrical parts of acetic acid anhydride (90%) are poured over 106 gravimetrical parts of diphenolisatin (Berichte der Deutschen Chemischen Gesselschsft, 18, 1885, p. 2641) and the mixture is heated on the water-bath while stirring. The solid starting material temporarily dissolves almost entirely and shortly afterwards the reaction product turns into a crystalline paste. In order to complete the reaction the heating on the water-bath is continued for a short time and then the whole is left to get cold. The reaction product may, for instance, be separated in the following manner: To the cold reaction mixture is gradually added about the same volumetrical quantity of alcohol; in this manner the excess of acetic acid anhydride is destroyed and the paste becomes thinner. Then the fluid is drawn off and the product washed with alcohol. For complete cleansing another extraction is made with warm alcohol and the product crystallized, for instance, from 10 parts of acetic acid. The product represents a light, fine crystalline powder, which is difficultly soluble or even insoluble in the usual organic solvents. Its melting point lies at 242°C.

References

Merck Index 6842
Kleeman & Engel p. 678
OCDS Vol. 2 p. 350 (1980)
I.N. p. 720
Preiswerk, E.; US Patent 1,624,675; April 12, 1927; assigned to Hoffmann-LaRoche Chemical Works

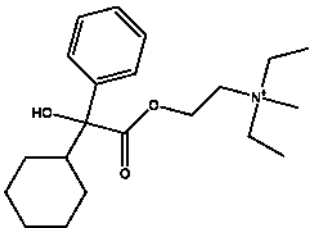
OXYPHENONIUM BROMIDE

Therapeutic Function: Anticholinergic, Spasmolytic

Chemical Name: [Ethanaminium, 2-((cyclohexylhydroxyphenylacetyl)oxy)-N,N-diethyl-N-methyl-, bromide

Common Name: Oxiphenoni bromidum; Oxyphenonium bromide

Structural Formula:



Chemical Abstracts Registry No.: 50-10-2; 14214-84-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
A-Spasm	Acme Laboratories Ltd.	-	-
Antispasmin	Pharmacia Co - Dupnitza	-	-
Oxyphenonium bromide	Yick-Vic Chemicals and Pharmaceuticals (HK) Ltd.	-	-
Oxyphenonium bromide	Pharm Products	-	-
Antrenyl	Ciba	-	-
Antrenyl	Ciba-Geigy	-	-
Antrenyl	Swiss Pharma	-	-
Calmulcer	Sons	-	-
Oxyphenon	Leciva	-	-
Spasmophen	Polfa-Pabianice	-	-
Spastrex	Propan-Generics	-	-
Antrenyl Duplex Drag (aH)	Ciba-Geigy AG Pharma Schweiz	-	-

Raw Materials

2-Diethylaminoethanol
Cycloxehylhydroxyphenylacetic acid methyl ester
Methyl bromide

Manufacturing Process

1 mol cycloxehylhydroxyphenylacetic acid methyl ester was mixed with 1 mol 2-diethylaminoethanol in presence of 1 mol sodium methylate to give cycloxehylhydroxyphenylacetic acid 2-diethylamino-ethyl ester.

5 parts by weight of it was dissolved in 50 volumes glacial acetic acid and a gaseous methyl bromide was introduced. The mixture was heated to about 50°C and crystallization of cycloxehylhydroxyphenylacetic acid diethylaminoethyl ester methyl bromide has shortly after begun. On cooling the crystals was filtered off and recrystallized from mixture of ethyl acetate ant a little ethanol to give the oxyphenonium bromide. MP: 189°-191°C.

References

Swit.R. Patent No. 259,958; Sept. 18, 1944; Assigned to Ciba

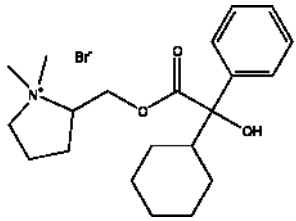
OXYPYRRONIUM BROMIDE

Therapeutic Function: Anticholinergic, Spasmolytic

Chemical Name: Pyrrolidinium, 1,1-dimethyl-2-(hydroxymethyl)-, bromide, α-phenylcyclohexaneglycolate

Common Name: Oxipyrroni bromidum; Oxypyrronium bromide

Structural Formula:



Chemical Abstracts Registry No.: 561-43-3; 116533-64-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Oxypyrronium bromide	Shanghai Lansheng Corporation	-	-

Raw Materials

Sodium	Methylphenylcyclohexylglycolate
Methanol	1-Methyl-2-hydroxymethylpyrrolidine
Methyl bromide	Hydrochloric acid
Sodium hydroxide	

Manufacturing Process

The 1-methyl-2-hydroxymethylpyrrolidine was obtained by the process of Application No 21193/56 (Serial No. 820,503).

A methanolic solution of sodium methoxide [from sodium (0.6 g) and methanol (15 ml)] was added dropwise during 3 h to a boiling solution of methyl phenylcyclohexylglycollate (33.7 g) and 1-methyl-2-hydroxymethylpyrrolidine (23.4 g) in heptane (400 ml) and the methanol that separated was removed by means of a Dean and Stark apparatus. At the end of 4 h no further separation of methanol occurred and the solvent was removed under reduced pressure. The residue was dissolved in either and the etheral solution, after washing with water (3 x 50 ml), was extracted with 5 N hydrochloric acid (3 x 100 ml). The (1-methyl-2-pyrrolidyl)methyl phenylcyclokexylglycollate hydrochloride (35.5 g 71%) crystallised out of the acid extract as colourless needles, melting point 181°-196°C. Extraction of this hydrochloride (33.0 g) with hot ethanol (150 ml) left the sparingly soluble (1-methyl-2-pyrrolidyl)methyl phenylcyclokexylglycollate hydrochloride (a-form) (7.6 g), melting point 220°-222°C.

The (1-methyl-2-pyrrolidyl)methyl phenylcyclokexylglycollate hydrochloride (a-form) (15.0 g) was dissolved in water, basified with sodium hydroxide solution and the resultant oil extracted into ether. The extracts were dried over magnesium sulfate, the ether evaporated and the residue dissolved in acetone (100 ml). Methyl bromide (7.8 g, 2 mole) was added to the acetone solution and the mixture warmed on a steam bath for 15 min. The solution was cooled and the solid filtered off, washed with a little acetone and dried to give the

(1,1-dimethyl-2-pyrrolidyl)methyl α-phenylcyclokexylglycollate bromide, melting point 185°-186°C. (86%).

References

GB Patent No. 850,260; Nov. 28, 1957; Assigned: Beecham Research Laboratories Limited, a British Company, of Brockham Park, Betchworth, Surrey

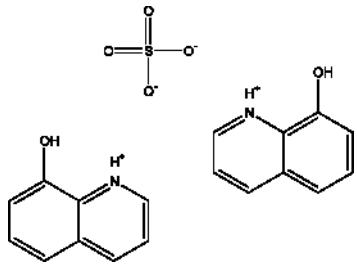
OXYQUINOL

Therapeutic Function: Antiseptic

Chemical Name: Quinolin-8-ol

Common Name: Hydroxychinolinium sulfuricum; Oxichinolini sulfas; Oxychinol; Oxyquinol; Oxyquinoline sulfate; Oxyquinolini sulfas

Structural Formula:



Chemical Abstracts Registry No.: 134-31-6; 148-24-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Chinosol	Chinosolfabrik	-	-
8-Hydroxyquinoline sulfate	GFS Chemicals	-	-
Hydroxyquinoline sulfate	Shanghai Lansheng Corporation	-	-
8-Hydroxyquinoline sulfate	AroKor Holdings Inc.	-	-
8-Hydroxyquinoline sulfate	Tianjin Mid-Chem Co., Ltd.	-	-
8-Quinolinol Sulfate	Eastman Kodak Company	-	-
Oxymeria Gargle	Nile Co.	-	-

Raw Materials

o-Nitrophenol
o-Aminophenol
Sulfuric acid

Manufacturing Process

The mixture of 1.4 kg o-nitrophenol, 2.1 kg o-aminophenol, 6 kg glycerine (d = 1.26) and 5 kg sulfuric acid (d = 1.848) was heated at reflux to temperature 130°-140°C. This temperature was kept for 1.5 hours. The obtained oxyquinoline precipitated, the liquid was removed with water-steam distillation. The residue was diluted with water and alkalized with sodium hydroxide and sodium carbonate to the strong alkaline reaction. The repeated distillation with water steam gave the oil, which hardened as the long needles by cooling. MP: 75°-76°C recrystallized from diluted ethanol.

In practice it is usually used as sulfate salt.

References

Skraup Z.H.; DR Patent No. 14,976; Feb. 16, 1881; Wien
Dictionary of Organic Compounds edited by I. Heilbron and H.M. Bunbury, v.2, p.326, 1946, London

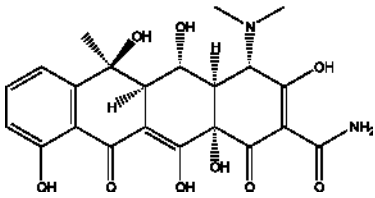
OXYTETRACYCLINE

Therapeutic Function: Antibiotic

Chemical Name: 4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 79-57-2; 2058-46-0 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Terramycin	Pfizer	US	1950
Gynamousse	Pfizer	France	1966
Oxy-Kesso-Tetra	McKesson	US	1970
Oxlopar	Parke Davis	US	1974
E.P. Mycin	Edwards	US	1983
Chrysocin	Pliva	Yugoslavia	-
Clinimycin	Glaxo	UK	-
Copharoxy	Cophar	Switz.	-
Crisamicin	Frumtost	Spain	-
Devacyclin	Deva	Turkey	-
Dura-Tetracyclin	Dura	W. Germany	-
Egocin	Krka	Yugoslavia	-
Elaciclina	I.F.L.	Spain	-
Galenomycin	Galen	UK	-
Geocycline	I.E. Kimya Evi	Turkey	-
Geomycin	Pliva	Yugoslavia	-
I.A.-Loxin	Inter-Alia Pharm.	UK	-
Imperacin	I.C.I.	UK	-
Macocyn	Mack	W. Germany	-
Oksisiklin	Uranium	Turkey	-
Ossitetra	Pierrel	Italy	-
Otesolut	Jenapharm	E. Germany	-
Oxacycline	Crookes	UK	-
Oxeten	Mochida	Japan	-
Oxymycin	Chelsea	UK	-
Proteroxyna	Proter	Italy	-
Stecsolin	Squibb	UK	-
Tetra-Tablinen	Sanorania	W. Germany	-
Tetrafen	Drifen	Turkey	-

Raw Materials

Soybean meal
Glucose

Bacterium Streptomyces rimosus

Manufacturing Process

Medium	Grams
Soybean meal	10
Cerelose	10
Distillers' solubles	0.5
Sodium chloride	5
Distilled water to	1,000 ml

The pH was adjusted to 7.0 with sodium hydroxide and calcium carbonate was added at the rate of 1 g/l.

500 ml portions of the above medium were added to Fernbach flasks which

were then sterilized at 121°C for 30 minutes. Upon cooling, the flasks were inoculated with a suspension of the growth of s. rimosus obtained from the surface of beef lactose agar slants, and the flasks were shaken for 4 days at 28°C on a rotary shaker having a displacement of 2" at an rpm of 200. At the end of this period the broth was found to contain 640 C.D.U/ml and 400 chloramphenicol units/ml. The mycelium was separated from the broth by filtration and the latter was adjusted to pH 9.0. The antibiotic was extracted from the broth with n-butanol, and when the ultraviolet absorption spectrum was observed on the butanol solution of the antibiotic, peaks in the absorption curve were found at 385 and 270 millimicrons.

References

Merck Index 6846
Kleeman & Engel p. 680
PDR pp. 887, 1413, 1533, 1606
OCDS Vol. 1 p. 212 (1977) and 2, 226 (1980)
I.N. p. 721
REM pp. 1206, 1260
Sobin, B.A., Finlay, A.C. and Kane, J.H.; US Patent 2,516,080; July 18, 1950; assigned to Chas. Pfizer & Co., Inc.

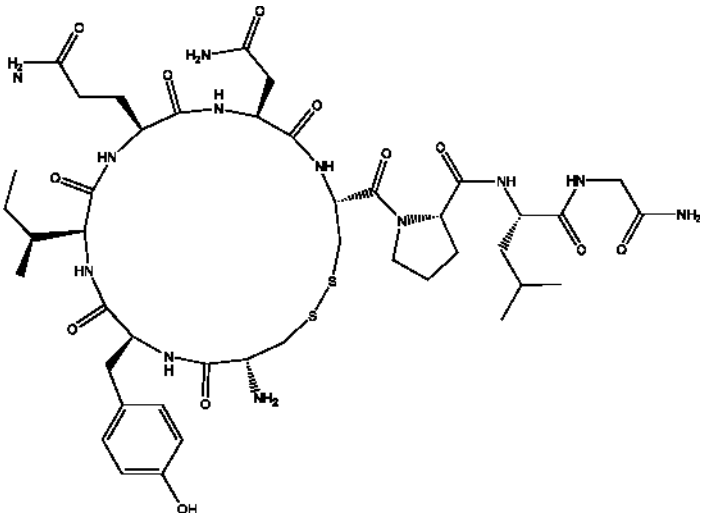
OXYTOCIN

Therapeutic Function: Oxytocic

Chemical Name: Oxytocin (a complex peptide)

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 50-56-6

Trade Name	Manufacturer	Country	Year Introduced
Syntocinon	Sandoz	US	1957
Syntocinon	Sandoz	France	1958
Uteracon	Hoechst	US	1964
Atonin-O	Teikoku Zoki	Japan	-
Endopituitrina	I.S.M.	Italy	-
Orasthin	Hoechst	W. Germany	-
Oxitocin	Chinoin	Italy	-
Oxystin	Arzneimittelwerk Dresden	E. Germany	-
Oxytal	A.L.	Norway	-
Partocon	Ferring	Sweden	-
Partolact	Medica	Finland	-
Pitocin	Sankyo	Japan	-
Pituitan	Nippon Zoki	Japan	-

Raw Materials

Hydrogen
Glycine lower alkyl ester
L-Leucine lower alkyl ester
Ammonia
Hydrogen chloride
L-Tyrosine lower alkyl ester
α-Benzyl-L-aspartic acid-α-lower alkyl ester
L-Isoleucine lower alkyl ester
S,N-Ditrityl-L-cysteine diethylamine salt
N-Trityl glutamic acid-γ-lower alkyl ester
Benzyl-L-proline hydrochloride

Manufacturing Process

As described in US Patent 2,938,891, in the process for producing oxytocin, the steps comprise:

(a) Adding dicyclohexyl carbodiimide to a solution of the α-benzyl-L-aspartic acid-β-lower alkyl ester in methylene chloride, cooling the mixture to about 0°C, adding thereto the N-trityl glutamic acid-γ-lower alkyl ester, allowing the mixture to stand at room temperature to complete condensation, acidifying the reaction mixture with acetic acid, filtering off precipitated dicyclohexyl urea, and separating the resulting (N-trityl-γ-lower alkyl-L-glutamyl)-α-benzyl-L-aspartic acid-β-lower alkyl ester.

(b) Dissolving the (N-trityl-γ-lower alkyl-L-glutamyl)-α-benzyl-1-aspartic acid-β-lower alkyl ester in ethanol, adding triethylamine and palladium black to said solution, introducing hydrogen at room temperature thereinto to split off the benzyl group, and separating the (N-trityl-γ-lower alkyl-L-glutamyl)-L-aspartic acid-β-lower alkyl ester.

(c) Adding dicyclohexyl carbodiimide to a solution of the diethylamine salt of S,N-ditrityl-L-cysteine and the hydrochloride of the lower alkyl ester of L-tyrosine in methylene chloride, allowing the mixture to stand at a temperature between room temperature and about 35°C to complete condensation, acidifying the reaction mixture with acetic acid, filtering off precipitated

dicyclohexyl urea, and separating the resulting lower alkyl ester of S,N-ditrityl-L-cysteinyl-L-tyrosine.

(d) Refluxing the aqueous alcoholic solution of said ester with an alcoholic alkali metal hydroxide solution to saponify the lower alkyl ester group, neutralizing the saponification mixture by the addition of hydrochloric acid, extracting the neutralized mixture with ether, and separating the resulting (S,N-ditrityl-L-cysteinyl)-L-tyrosine.

(e) Adding triethylamine to a solution of said S,N-ditrityl compound in chloroform, and precipitating the triethylamine salt of (S,N-ditrityl-L-cysteinyl)-L-tyrosine by the addition of petroleum ether.

(f) Adding dicyclohexyl carbodiimide to a solution of said triethylamine salt of (S,N-ditrityl-L-cysteinyl)-L-tyrosine and the hydrochloride of the lower alkyl ester of L-isoleucine in methylene chloride, allowing the mixture to stand at room temperature to complete condensation, acidifying the reaction mixture with acetic acid, filtering off precipitated dicylohexyl urea, and separating the resulting (S,N-ditrityl-L-cysteinyl)-L-tyrosyl-L-isoleucine lower alkyl ester.

(g) Refluxing the aqueous alcoholic solution of said ester with an alcoholic alkali metal hydroxide solution to saponify the lower alkyl ester group, neutralizing the saponification mixture by the addition of hydrochloric acid, extracting the neutralized mixture with ether, and separating the resulting (S,N-ditrityl-L-cysteinyl)-L-tyrosine-L-isoleucine.

(h) Adding dicyclohexyl carbodiimide to a solution of the diethylamine salt of S,N-ditrityl-L-cysteine and the hydrochloride of benzyl-L-proline in methylene chloride, allowing the mixture to stand at about room temperature to complete condensation, acidifying the reaction mixture with acetic acid, filtering off precipitated dicyclohexyl urea, and separating the resulting (S,N-ditrityl-L-cysteinyl)-L-prolinebenzyl ester.

(i) Refluxing said benzyl ester with an aqueous alcoholic alkali metal hydroxide solution to saponify the benzyl ester group, neutralizing the saponification mixture by the addition of hydrochloric acid, extracting the neutralized mixture with chloroform, and separating the resulting (S,N-ditrityl-L-cysteinyl)-L-proline.

(j) Adding diethylamine to a solution of said dipeptide compound in ether to yield the diethylamine salt of (S,N-ditrityl-L-cysteinyl)-L-proline.

(k) Adding dicyclohexyl carbodiimide to a solution of the diethylamine salt of (S,N-ditrityl-L-cysteinyl)-L-proline and the hydrochloride of the L-leucine lower alkyl ester in methylene chloride, allowing the mixture to stand at a temperature between about 25° and 30°C to complete condensation, acidifying the reaction mixture with acetic acid, filtering off precipitated dicyclohexyl urea, and separating the resulting (S,N-ditrityl-L-cysteinyl)-L-prolyl-L-leucine lower alkyl ester.

(l) Refluxing said lower alkyl ester with an aqueous alcoholic alkali metal hydroxide solution to saponify the lower alkyl ester group, neutralizing the saponification mixture by the addition of hydrochloric acid, extracting the

neutralized mixture with ether, and separating the resulting S,N-ditrityl-L-cysteinyl-L-prolyl-L-leucine.

(m) Adding dicyclohexyl carbodiimide to a solution of the diethylamine salt of S,N-ditrityl-L-cysteinyl-L-prolyl-L-leucine and the hydrochloride of the glycine lower alkyl ester in methylene chloride, allowing the mixture to stand at a temperature between about 25° and 30°C to complete condensation, acidifying the reaction mixture with acetic acid, filtering off precipitated dicyclohexyl urea, and separating the resulting (S,N-ditrityl-L-cysteinyl)-L-prolyl-L-leucyl-glycine lower alkyl ester.

(n) Adding aqueous hydrochloric acid to a mixture of said lower alkyl ester in a solvent selected from the group consisting of acetone and acetic acid, allowing the mixture to stand at a temperature of about 35°C to complete selective detritylation of the N-trityl group, and separating the resulting (S-trityl-L-cysteinyl)-L-prolyl-L-leucyl glycine lower alkyl ester.

(o) Adding dicyclohexyl carbodiimide to a solution of the diethylamine salt of the (N-trityl-γ-lower alkyl-L-glutamyl)-L-aspartic acid-β-lower alkyl ester obtained according to step (b) and the hydrochloride of the (S-trityl-L-cysteinyl)-L-prolyl-L-leucyl glycine lower alkyl ester in methylene chloride, allowing the mixture to stand at about room temperature to complete condensation, filtering off precipitated dicyclohexyl urea, and separating the resulting (N-trityl-γ-lower alkyl-L-glutamyl)-(β-lower alkyl-L-aspartyl)-(S-trityl-L-cysteinyl)-L-prolyl-L-leucyl glycine lower alkyl ester.

(p) Adding aqueous hydrochloric acid to a mixture of said lower alkyl ester in a solvent selected from the group consisting of acetone and acetic acid, allowing the mixture to stand at room temperature to complete selective detritylation of the N-trityl group, and separating the resulting hexapeptide compound (γ-lower alkyl-L-glutamyl)-(β-lower al kyl-L-aspartyl)-(S-trityl-L-cysteinyl)-L-prolyl-L-leucyl glycine lower alkyl ester.

(q) Adding dicyclohexyl carbodiimide to a solution of the diethylamine salt of (S,N-ditrityl-L-cysteinyl)-L-tyrosyl-L-isoleucine obtained according to step (g) and the hydrochloride of (γ-lower alkyl-L-glutamyl)-(β-lower alkyl-L-aspartyl)-(S-trityl-L-cysteinyl)-L-prolyl-L-leucyl glycine lower alkyl ester in methylene chloride, allowing the mixture to stand at about room temperature to complete condensation, filtering off precipitated dicyclohexyl urea, and separating the resulting (S,N-ditrityl-L-cysteinyl)-L-tyrosyl-L-isoleucyl-(γ-lower alkyl-L-glutamyl)-(β-lower alkyl-L-aspartyl)-(S-trityl-L-cysteinyl)-L-prolyl-L-leucyl glycine lower alkyl ester.

(r) Dissolving said lower alkyl ester in a lower alkanol, saturating the resulting solution at a temperature of about -15° to -20°C with ammonia gas, allowing the mixture to stand in a sealed container at room temperature to complete replacement of the lower alkyl ester group by the amide group, and separating the resulting triamide (S,N-ditrityl-L-cysteinyl)-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-(S-trityl-L-cysteinyl)-L-prolyl-L-leucyl glycine amide.

(s) Dissolving said triamide in an anhydrous solvent selected from the group consisting of chloroform, a mixture of chloroform and acetic acid, and a mixture of methylene chloride and thioglycolic acid, saturating the solution with gaseous hydrochloric acid at room temperature to complete detritylation,

and separating the resulting L-cysteinyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-L-cysteinyl-L-prolyl-L-leucyl glycine amide.

(t) Dissolving said nonapeptide triamide in water and agitating the solution in oxygen to cause conversion thereof into oxytocin.

References

Merck Index 6849
Kleeman & Engel p. 681
PDR pp. 1382, 1596, 1966, 1989
I.N. p. 722
REM pp. 949, 957
Velluz, L., Amiard, G., Bartos, J., Goffinet, B. and Heymes, R.; US Patent 2,938,891; May 31, 1960; assigned to Uclaf, France
Velluz, L., Amiard, G. and Heymes, R.; US Patent 3,076,797; February 5, 1963; assigned to Roussel-UCLAF SA, France