O

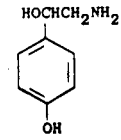
OCTOPAMINE HYDROCHLORIDE

Therapeutic Function: Hypertensive

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

Common Name: Norsympatol hydrochloride; norsynephrine hydrochloride

Structural Formula:



(base)

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
Hydrogen chloride
Aminoacetonitrile
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-aceto-nitrile was added, had dry hydrochloric acid gas introduced into it for 3 hours, while stir-ring 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 & Engel p. 655
I.N. p. 699
Asscher, M.; U.S. Patent 2,585,988; February 19, 1952

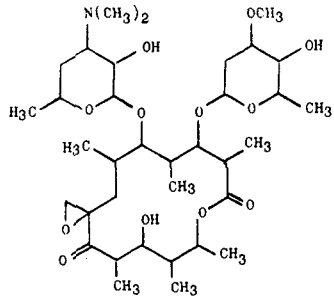
OLEANDOMYCIN

Therapeutic Function: Antibiotic

Chemical Name: Oleandomycin; see Structural Formula

Common Name: Troleandomycin

Structural Formula:



Chemical Abstracts Registry No.: 3922-90-5

Trade Name	Manufacturer	Country	Year Introduced
Matromycin	Pfizer	U.S.	1956
Oleandocyn	Pfizer	W. Germany	—
Olmicina	Morgan	Italy	—
Sigmamycin	Pfizer	Japan	—
Taocin-O	Sankyo	Japan	—
TAO	Roerig	U.S.	—
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 sus-

pension 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°C 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 & Engel p. 657
I.N. p. 701
Sobin, B.A., Routien, J.B. and Lees, T.W.; U.S. Patent 2,757,123; July 31, 1956; assigned to Chas. Pfizer & Co., Inc.
Ratajak, E.J. and Nubel, R.C.; U.S. Patent 2,842,481; July 8, 1958; assigned to Chas. Pfizer & Co., Inc.

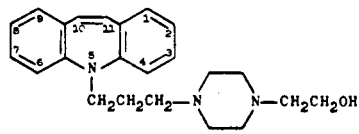
OPIPRAMOL

Therapeutic Function: Antidepressant; antipsychotic

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

Common Name: —

Structural Formula:



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

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	U.S.	—

Trade Name	Manufacturer	Country	Year Introduced
Oprimol	Taro	Israel	–
Pramolan	Polfa	Poland	–

Raw Materials

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

Manufacturing Process

A solution of 5-(3-toluene-p-sulfonyloxypropyl)dibenzazepine (9.2 g) and 1-(2-hydroxyethyl)piperazine (8.6 g) 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-hydrochloric 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 (7.95 g), the dihydrochloride of which, crystallized from ethanol, melts at about 210°C.

References

Merck Index 6727
Kleeman & Engel 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

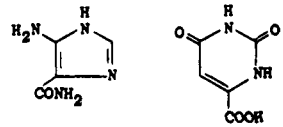
ORAZAMIDE

Therapeutic Function: Treatment of liver diseases

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.; U.S. Patent 3,271,398; September 6, 1966; assigned to Fujisawa Pharmaceutical Co., Ltd., Japan

ORGOTEIN

Therapeutic Function: Antiinflammatory

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 0.15M 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) & 13 (3) 105 (1977)
I.N. p. 705
Huber, W.; U.S. Patent 3,579,495; May 18, 1971; assigned to Diagnostic Data, Inc.
Huber, W.; U.S. Patent 3,687,927; August 29, 1972; assigned to Diagnostic Data, Inc.

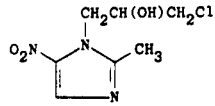
ORNIDAZOLE

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
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

5 g 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.; U.S. Patent 3,435,049; March 25, 1969; assigned to Hoffmann-LaRoche, Inc.

ORNIPRESSIN

Therapeutic Function: Vasoconstrictor

Chemical Name: 8-L-Ornithinevasopressin

Common Name: –

Structural Formula: Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Orn-GlyNH_2

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-p-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

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, 35.5 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-cysteinyl-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-carbobenzoxy-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-ornithyl-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.; U.S. Patent 3,299,036; January 17, 1967; assigned to Sandoz Ltd. (Switzerland)

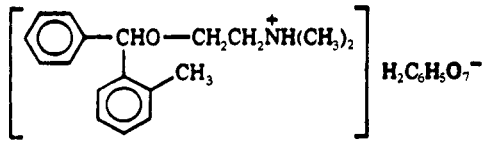
ORPHENADRINE CITRATE

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	U.S.	1959
Neocyten	Central	U.S.	1975
X-Otag	Tutag	U.S.	1976
Banflex	O'Neal, Jones	U.S.	1980
Bio-Flex	Foy	U.S.	–
Flexin	Taro	Israel	–
Mioflex	Formenti	Italy	–
Myotrol	Legere	U.S.	–
Norgesic	Riker	U.S.	–
Ro-Orphena	Robinson	U.S.	–
Tega-Flex	Ortega	U.S.	–

Raw Materials

o-Methylbenzhydryl bromide
β-Dimethylaminoethanol
Citric acid

Manufacturing Process

As described in U.S. 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) & 18 (2) 90 (1982)
I.N. p. 707
REM p. 932
Rieveschi, G. Jr.; U.S. Patent 2,567,351; September 11, 1951; assigned to Parke, Davis & Company
Harms, A.F.; U.S. Patent 2,991,225; July 4, 1961; assigned to NV Koninklijke Pharmaceutische Fabrieken, Netherlands

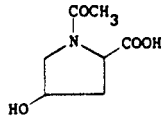
OXACEPROL

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
Jonctum	Merrell	Italy	1978
Tejuntivo	Valderrama	Spain	—

Raw Materials

L-Hydroxyproline
Acetic anhyride

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

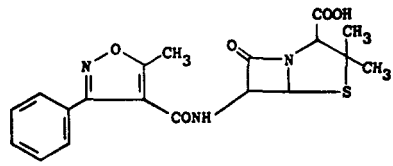
OXACILLIN SODIUM

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:



(base)

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

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

Raw Materials

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

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 (B), 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 reaction 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.; U.S. Patent 2,996,501; August 15, 1961

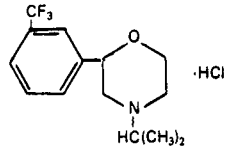
OXAFLOZANE HYDROCHLORIDE

Therapeutic Function: Antidepressant

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

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

2-Chloroethylvinyl ether
Bromine
(3-Trifluoromethyl)phenyl magnesium bromide
Isopropylamine
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)bromobenzene and 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); isopropyl amine: 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.; U.S. Patent 3,637,680; January 25, 1972; assigned to Societe Anonyme: Centre Europeen De Recherches Mauvernay

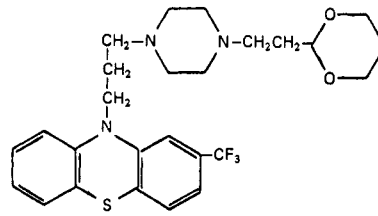
OXAFLUMAZINE DISUCCINATE

Therapeutic Function: Neuroleptic, antihistaminic, antispasmodic

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

Common Name: –

Structural Formula:



(base)

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
1-Bromo-3-chloropropane
2-Trifluoromethylphenothiazine
Sodium
Succinic acid

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

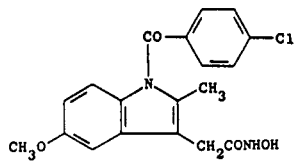
OXAMETACINE

Therapeutic Function: Antiinflammatory

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

Common Name: Indoxamic acid

Structural Formula:



Chemical Abstracts Registry No.: 27035-30-9

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 Martiis, F., Arrigoni-Martelli, E. and Tamietto, T.; U.S. Patent 3,624,103; November 30, 1971; assigned to Instituto Biologico Chemioterapico (A.B.C.) SpA (Italy)

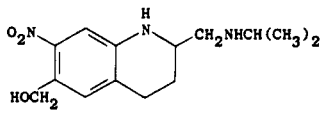
OXAMNIQUINE

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	U.S.	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.; U.S. Patent 3,821,228; June 28, 1974; assigned to Pfizer, Inc.

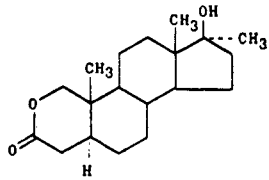
OXANDROLONE

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	U.S.	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 U.S. 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.; U.S. Patent 3,128,283; April 7, 1964; assigned to G.D. Searle & Co.
Pappo, R.; U.S. Patent 3,155,684; November 3, 1964; assigned to G.D. Searle & Co.

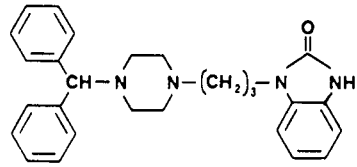
OXATOMIDE

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	U.K.	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 5.3 parts of 1-(3-chloropropyl)-2H-benzimidazol-2-one, 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-2-pentanone 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 & (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.; U.S. Patent 4,200,641; April 29, 1980; assigned to Janssen Pharmaceutica N.V.

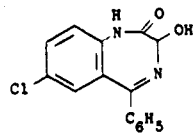
OXAZEPAM

Therapeutic Function: Minor tranquilizer

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

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 604-75-1

Trade Name	Manufacturer	Country	Year Introduced
Serax	Wyeth	U.S.	1965
Adumbran	Thomae	W. Germany	1965
Seresta	Wyeth Byla	France	1966
Praxiten	Wyeth	U.K.	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 4N 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) & 2, 402 (1980)
DOT 1 (3) 102 (1965) & 9 (6) 238 (1973)
I.N. p. 711
REM p. 1063
Bell, S.C.; U.S. Patent 3,296,249; January 3, 1967; assigned to American Home Products Corp.

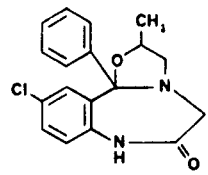
OXAZOLAM

Therapeutic Function: Minor 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) & 9 (6) 239 (1973)
I.N. p. 712
REM p. 1064
Tachikawa, R., Takagi, H., Kamioka, T., Midayera, T., Fukunaga, M. and Kawano, Y.; U.S. Patents 3,772,371; November 13, 1973; and 3,914,215; October 21, 1975; both assigned to Sankyo Co., Ltd.

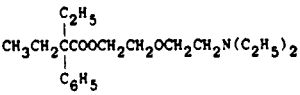
OXELADIN

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.	U.K.	—

Raw Materials

Phenylacetonitrile
Ethyl chloride
β,β'-Dichlorodiethyl ether
Sodium
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 neu-

tral 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.; U.S. Patent 2,885,404; May 5, 1959; assigned to The British Drug Houses Limited, England

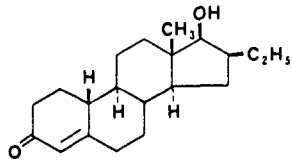
OXENDOLONE

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

16β-Ethylestra-4-ene-3,17-dione
Sodium borohydride
Ethyl orthoformate
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.; U.S. Patent 3,856,829; December 24, 1974; assigned to Takeda Chemical Industries, Ltd.

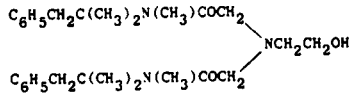
OXETHAZINE

Therapeutic Function: Topical 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)

Trade Name	Manufacturer	Country	Year Introduced
Oxaine	Wyeth	U.S.	1960
Emoren	Wassermann	Italy	—
Mucaine	Wyeth	U.K.	—
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-butylacetamide
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. 8.3%, 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.; U.S. Patent 2,780,646; February 5, 1957; assigned to American Home Products Corp.

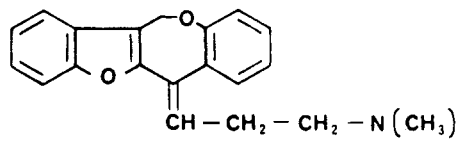
OXETORONE FUMARATE

Therapeutic Function: Antiserotonin, antihistamine

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

Common Name: –

Structural Formula:



(base)

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

γ-Dimethylaminopropyl chloride
Ethyl iodide
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[b]-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%).

(B) 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-hydroxy-benzo[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.; U.S. Patent 3,651,051; March 21, 1972; assigned to Laboratoires Labaz

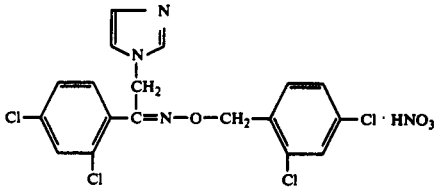
OXICONAZOLE NITRATE

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.: –

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.; U.S. Patent 4,124,767; November 7, 1978; assigned to Siegfried AG.

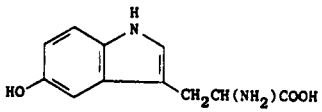
OXITRIPTAN

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 & 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)

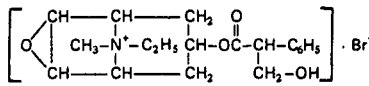
OXITROPIUM BROMIDE

Therapeutic Function: Anticholinergic bronchodilator

Chemical Name: (–)-N-Ethylnorscopolamine methobromide

Common Name: OTB

Structural Formula:



Chemical Abstracts Registry No.: –

Trade Name	Manufacturer	Country	Year Introduced
Ventilat	Boehr. Ingel.	W. Germany	1983

Raw Materials

(–)-Norscopolamine
Methyl bromide
Ethyl 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
DFU 4 (2) 117 (1979)
DOT 19 (7) 416 & (8) 444 (1983)
Zeile, K., Banholzer, R., Walther, G., Schulz, W. and Wick, H.; U.S. Patent 3,472,861; Oct. 14, 1969; assigned to Boehringer Ingelheim GmbH.

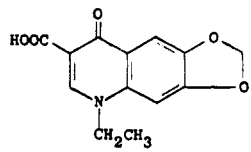
OXOLINIC ACID

Therapeutic Function: Urinary antibacterial

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	U.K.	1974
Urotrate	Substantia	France	1974
Ossian	Bioindustria	Italy	1974
Utibid	Warner Lambert	U.S.	1975
Nidantin	Sasse/Goedecke	W. Germany	1978
Decme	Poli	Italy	–
Emyrenil	Emyfar	Spain	–
Gramurin	Chinoin	Hungary	–
Oksaren	Belupo	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	–
Uropax	Lefa	Spain	–
Uroxol	Ausonia	Italy	–

Raw Materials

3,4-Methylenedioxyaniline
Diethyl ethoxymethylene malonate
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 by-product ethyl alcohol formed. The residue is recrystallized from ligroin (BP 60° to 90°C) to give diethyl[(3,4-methylenedioxyanilino)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-methylenedioxy-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) & 3, 185 (1984)
I.N. p. 34

Kaminsky, D. and Meltzer, R.I.; U.S. Patent 3,287,458; November 22, 1966; assigned to Warner-Lambert Pharmaceutical Company

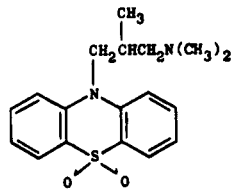
OXOMEMAZINE

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)

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
3-Dimethylamino-2-methylpropyl chloride
Sodium amide
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 (7.8 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.; U.S. Patent 2,972,612; February 21, 1961; assigned to Societe des Usines Chimiques Rhone-Poulenc (France)

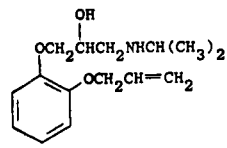
OXPRENOLOL

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)

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

Raw Materials

Pyrocatechol monoallyl ether
Epichlorohydrin
Isopropylamine

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) & 2, 109 (1980)
DOT 6 (1) 25 (1970)
I.N. p. 716
Ciba Limited, Switzerland; British Patent 1,077,603; August 2, 1967

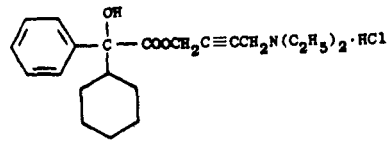
OXYBUTYNIN CHLORIDE

Therapeutic Function: Antispasmodic

Chemical Name: α-cyclohexyl-α-hydroxybenzeneacetic acid 4-(diethylamino)-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	U.S.	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 & Company; British Patent 940,540; October 30, 1963

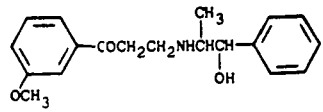
OXYFEDRINE

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)

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
Paraformaldehyde
L-Norephedrine

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.; U.S. Patent 3,225,095; December 21, 1965; assigned to Deutsche Gold- und Silber-Scheideanstalt, Germany

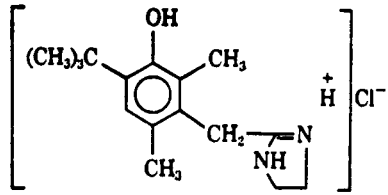
OXYMETAZOLINE HYDROCHLORIDE

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	U.S.	1964
Nostrilla	Boehr. Ingel.	U.S.	1982
Alrin	Teva	Israel	–
Atomol	Allen & Hanburys	U.K.	–
Dristan	Whitehall	U.S.	–
Duration	Plough	U.S.	–
Nasivin	Bracco	Italy	–
Nasafarma	Novofarma	Spain	–
Nezeril	Draco	Sweden	–
Oxymeta	Schein	U.S.	–
Pikorin	Medica	Finland	–
Rhinolitan	Kettelhack Riker	W. Germany	–
Sinerol	Draco	Sweden	–
Utabon	Uriach	Spain	–

Raw Materials

2,4-Dimethyl-6-t-butylphenol
Hydrogen chloride
Ethylene diamine
p-Toluene sulfonic acid
Formaldehyde
Sodium cyanide
Sodium hydroxide
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 & Engel 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.; U.S. Patent 3,147,275; September 1, 1964; assigned to E. Merck AG, Germany

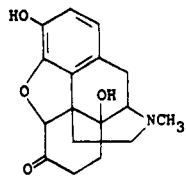
OXYMORPHONE

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	U.S.	1959

Raw Materials

Thebaine
Hydrogen bromide
Hydrogen peroxide
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) & 2, 319 (1980)
I.N. p. 719
REM p. 1105
Lewenstein, M.J. and Weiss, U.; U.S. Patent 2,806,033; September 10, 1957

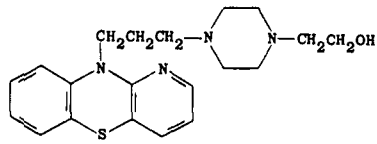
OXYPENDYL

Therapeutic Function: Antiemetic

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

Common Name: —

Structural Formula:



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

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

Raw Materials

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

Manufacturing Process

32 parts of 10-(γ-N-piperazinopropyl)-4-azaphenthiazine in 200 cc of butanol with 9 parts of ethylene chlorhydrin 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

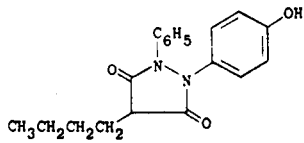
OXYPHENBUTAZONE

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	U.K.	1960
Tandearil	Geigy	U.S.	1961
Tanderil	Ciba Geigy	France	1961
Tanderil	Geigy	W. Germany	1961
Tanderil	Geigy	Italy	1962
Artroflog	Magis	Italy	–
Artzone	Cont. Ethicals	S. Africa	–
Butaflogin	Chemiepharma	Italy	–
Butapirone	Brocchieri	Italy	–
Buteril	Protea	S. Africa	–
Butilene	Francia	Italy	–
Deflogin	Valeas	Italy	–
Fibutox	Pharmador	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	–

Trade Name	Manufacturer	Country	Year Introduced
Ipebutona	Ipecsa	Spain	–
Iridil	Farmila	Italy	–
Isobutil	Panther-Osfa	Italy	–
Miyadril	Fako	Turkey	–
Optimal	Dojin	Japan	–
Optone	Lennon	S. Africa	–
Oxalid	U.S.V.	U.S.	–
Oxibutol	Asla	Spain	–
Oxybutazone	I.C.N.	Canada	–
Oxybuton	Streuli	Switz.	–
Phlogase	Adenylchemie	W. Germany	–
Phlogistol	Helopharm	W. Germany	–
Phlogont	Azochemie	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

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

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 Na_2SO_4 and 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
Häfliger, F.; U.S. Patent 2,745,783; May 15, 1956; assigned to J.R. Geigy AG, Switzerland

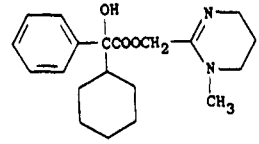
OXYPHENCYCLIMINE

Therapeutic Function: Antispasmodic

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)

Trade Name	Manufacturer	Country	Year Introduced
Vio-Thene	Rowell	U.S.	1959
Daricon	Pfizer	U.S.	1959
Setrol	Flint	U.S.	1961
Gastrix	Rowell	U.S.	1973
Manir	Valpan	France	1975
Caridan	B.D.H.	U.K.	–
Cycmin	Toyo	Japan	–
Inomaru S	Sawai	Japan	–
Norma	Sankyo	Japan	–
Oximin	A.F.I.	Norway	–
Sedomucol	Asla	Spain	–
Spazamin	G.P.	Australia	–
Ulcociclina	*Confas*	Italy	–
Ulcomin	Remedia	Israel	–
Vagogastrin	Benvegna	Italy	–

Raw Materials

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

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

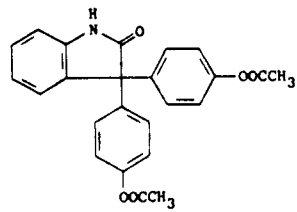
OXYPHENISATIN ACETATE

Therapeutic Function: Cathartic

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	U.S.	1959
Isalax	Vale	U.S.	1963
Acetalax	Harvey	Australia	–
Bisco-Zitron	Biscova	W. Germany	–
Bydolax	Moore	U.K.	–

Trade Name	Manufacturer	Country	Year Introduced
Darmoletten	Omegin	W. Germany	–
Eulaxin	Pliva	Yugoslavia	–
Fenisan	Chemimportexport	Rumania	–
Laxatan	Divapharma	W. Germany	–
Laxanormal	Uquifa	Spain	–
Med-Laxan	Med	W. Germany	–
Nourilax	Nourypharma	Neth.	–
Obstilax	Zirkulin	W. Germany	–
Promassolax	Ysat Wernigerode	E. Germany	–
Prulet	Mission	U.S.	–
Regal	Ferrosan	Denmark	–
Sanapert	Trogalen	Austria	–
Schokolax	Dallmann	W. Germany	–
Veripaque	Winthrop	U.K.	–

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 Gesselschaft,* 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.; U.S. Patent 1,624,675; April 12, 1927; assigned to Hoffmann-LaRoche Chemical Works

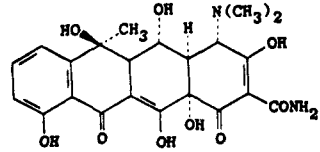
OXYTETRACYCLINE

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)

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

Raw Materials

Bacterium *Streptomyces rimosus*
Soybean meal
Cerelose (glucose)

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) & 2, 226 (1980)
I.N. p. 721
REM pp. 1206, 1260
Sobin, B.A., Finlay, A.C. and Kane, J.H.; U.S. Patent 2,516,080; July 18, 1950; assigned to Chas. Pfizer & Co., Inc.

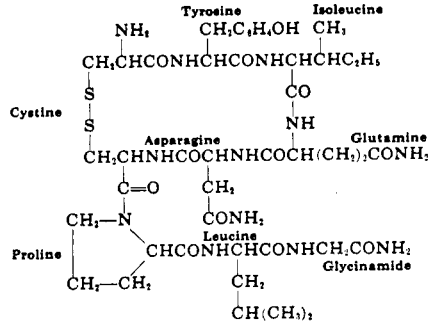
OXYTOCIN

Therapeutic Function: Oxytocic

Chemical Name: A complex peptide; see structural formula

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 50-56-6

Trade Name	Manufacturer	Country	Year Introduced
Syntocinon	Sandoz	U.S.	1957
Syntocinon	Sandoz	France	1958
Uteracon	Hoechst	U.S.	1964
Atonin-O	Teikoku Zoki	Japan	—
Endopituitrina	I.S.M.	Italy	—
Orasthin	Hoechst	W. Germany	—
Oxitocin	Chinoin	Italy	—
Oxystin	Arzneimittelwerk Dresden	E. Germany	—

Trade Name	Manufacturer	Country	Year Introduced
Oxytal	A.L.	Norway	–
Partocon	Ferring	Sweden	–
Partolact	Medica	Finland	–
Pitocin	Sankyo	Japan	–
Pituitan	Nippon Zoki	Japan	–

Raw Materials

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

Manufacturing Process

As described in U.S. 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-L-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-dityrityl-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-dityrityl-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-dityrityl-L-cysteinyl)-L-tyrosine.

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

(f) Adding dicyclohexyl carbodiimide to a solution of said triethylamine salt of (S,N-dityrityl-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-dityrityl-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-dityrityl-L-cysteinyl)-L-tyrosine-L-isoleucine.

(h) Adding dicyclohexyl carbodiimide to a solution of the diethylamine salt of S,N-dityrityl-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-dityrityl-L-cysteinyl)-L-proline benzyl 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-dityrityl-L-cysteinyl)-L-proline.

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

(k) Adding dicyclohexyl carbodiimide to a solution of the diethylamine salt of (S,N-dityrityl-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-dityrityl-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-dityrityl-L-cysteinyl-L-prolyl-L-leucine.

(m) Adding dicyclohexyl carbodiimide to a solution of the diethylamine salt of S,N-dityrityl-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-dityrityl-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 alkyl-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-dityrityl-

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.

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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.; U.S. Patent 2,938,891; May 31, 1960; assigned to Uclaf, France
Velluz, L., Amiard, G. and Heymes, R.; U.S. Patent 3,076,797; February 5, 1963; assigned to Roussel-UCLAF SA, France