N

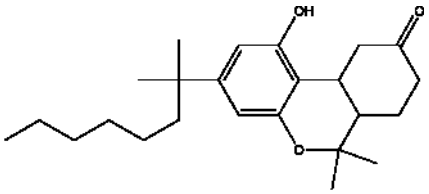
NABILONE

Therapeutic Function: Antianxiety

Chemical Name: 1-Hydroxy-3-(1',1'-dimethylheptyl)-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 51022-71-0

Trade Name	Manufacturer	Country	Year Introduced
Cesamet	Lilly	Canada	1982
Cesametic	Lilly	W. Germany	1983
Cesamet	Lilly	UK	1983

Raw Materials

dl-3-(1',1'-Dimethylheptyl)-6,6a,7,8-tetrahydro-1-hydroxy-6,6-dimethyl-9H-dibenzo[b,d]pyran-9-one
Lithium
Ammonia

Manufacturing Process

A solution of 1.5 g of dl-3-(1',1'-dimethylheptyl)-6,6a,7,8-tetrahydro-1-hydroxy-6,6-dimethyl-9H-dibenzo[b,d]pyran-9-one in 50 ml of anhydrous

tetrahydrofuran (THF) was added dropwise to a solution of lithium metal in liquid ammonia at -80°C. Excess lithium metal was added in chunks to the solution as the blue color, indicating free dissolved lithium, disappeared. After the addition was complete, ammonium chloride was added to react with any excess lithium metal still present.

The mixture was then allowed to warm to room temperature in a nitrogen atmosphere during which process the ammonia evaporated. The reaction mixture was then acidified with 1 N aqueous hydrochloric acid, and the organic constituents extracted with ethyl acetate. The ethyl acetate extracts were combined, washed with water and dried. Evaporation of the ethyl acetate under reduced pressure yielded 1.4 g of crude dl-trans-3-(1',1'-dimethylheptyl)-6,6aβ,7,8,10,10aβ-hexahydro-1-hydroxy-6,6-dimethyl-9H-dibenzo[b,d]pyran-9-one. The crude product was chromatographed over 50 g of silica gel from benzene solution and the desired product was eluted in 20 ml fractions with a benzene eluant containing 2% ethyl acetate. Fractions 200 to 240 contained 808 mg of a white crystalline solid comprising purified dl-trans-3-(1',1'-dimethylheptyl)-6,6aβ,7,8,10,10aβ-hexahydro-1-hydroxy-6,6-dimethyl-9H-dibenzo[b,d]pyran-9-one. The purified compound melted at 159°C to 160°C after recrystallization from an ethyl acetate-hexane solvent mixture.

References

Merck Index 6193
DFU 3 (3) 207 (1978)
OCDS Vol. 3, p 189 (1984)
DOT 19 (7) 415 & (8) 436 (1983)
I.N. p. 652
Archer, R.A.; US Patents 3,928,598; December 23, 1975; 3,944,673; March 16,1976; and 3,953,603; April 27, 1976; all assigned to Eli Lilly & Co.

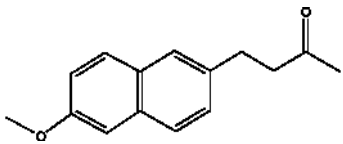
NABUMETONE

Therapeutic Function: Antiinflammatory

Chemical Name: 2-Butanone, 4-(6-methoxy-2-naphthalenyl)-

Common Name: Nabumetone

Structural Formula:



Chemical Abstracts Registry No.: 42924-53-8

Trade Name	Manufacturer	Country	Year Introduced
Artaxan	Malesci SpA Ist. Farmacobiol	Italy	-
Arthaxan	Pharm Chemical Shanghai Lansheng Corporation	China	-
Balmox	Alloga AG	Switz.	-
Dolsinal	Ferrer Internacional	Spain	-
Listran	Uriach	Spain	-
Mebutan	Bencard	-	-
Mebutan	Glaxo SmithKline Beecham	-	-
Nabuflam	Micro Labs	India	-
Nabumetone	Copley Pharmaceutical	USA	-
Nabumetone	Teva	USA	-
Nabumetone	IVAX Pharmaceuticals, Inc.	USA	-
Nabumetone	Eon Labs, Inc.	USA	-
Nabumetone	Genpharm Inc.	Canada	-
Relafen	SmithKline Beecham	-	-
Relafen	Eon Labs, Inc.	USA	-
Relifex	GlaxoSmithKline	-	-
Rodanol S	Lek	Slovenia	-

Raw Materials

Sodium methoxide
Sodium bisulfite
2-Acetyl-5-bromo-6-methoxynaphthalene
Palladium on carbon
Sodium acetate

Manufacturing Process

4-(5-Bromo-6-methoxy-2-naphthyl)-4-hydroxybut-3-en-2-one

50 grams (0.179 moles) of 2-acetyl-5-bromo-6-methoxynaphthalene and 200 ml of n-butyl acetate are placed in a flask equipped with refrigerator and stirrer and, under stirring and at the temperature of 15°C, 14.5 g (0.268 moles) of sodium methoxide are added. The temperature of the reaction mixture goes up to 25°C and is kept at this value for 30 minutes, then the mixture is warmed at 65°C for one hour, is added with 100 ml of water and is brought to pH 4 by adding a concentrated aqueous solution of hydrochloric acid. The reaction mixture is then cooled to 0°-5°C and kept at this temperature for one hour. The solid is filtered, abundantly washed with water on the filter, then washed with butyl acetate and dried in oven under vacuum obtaining 53 g of product with a yield equal to 92%.

Example 1. 4-(6-Methoxy-2-naphthyl)butan-2-one

48 grams (0.150 moles) of 4-(5-bromo-6-methoxy-2-naphthyl)-4-hydroxybut-3-en-2-one, 6.1 g of sodium acetate hydrate containing 32.4% of water, equivalent to 0.050 moles of sodium acetate, 4 g of a 50% suspension in water of 10% palladium on carbon, equivalent to 0.0019 moles of palladium, and 500 ml of methanol are put in a hydrogenator. The hydrogenator is washed with nitrogen in order to eliminate the oxygen and then hydrogen is introduced at the pressure of 2 atmospheres. The temperature of reaction is

kept at 40°C for a period of time of 6 hours, then the hydrogen is let off, the hydrogenator is washed with nitrogen and the reaction mixture is filtered to eliminate the catalyst. The solution is brought to pH 6 with a 5% aqueous solution of sodium hydroxide and concentrated under vacuum. The oily residue is dissolved into 130 ml of isopropanol and 30 ml of N,N-dimethylformamide and the solution is added with 45 ml of water and 17.6 g of sodium bisulfite obtaining a suspension that is stirred for one hour at 60°C, then is cooled to 5°C and is filtered. The obtained solid is washed with 75 ml of methanol, suspended in 200 ml of a 5% aqueous solution of sodium hydroxide and kept under stirring at room temperature for three hours. The suspension is then filtered, the solid is washed with water until neutrality and dried in oven under vacuum obtaining 18 g of product with a yield equal to 52.8%.

Example 2. 4-(6-Methoxy-2-naphthy)butan-2-one

The reaction described above is repeated with the sole changes of doubling the amount of sodium acetate hydrate containing 32.4% of water, 12.22 g equivalent to 0.100 moles of sodium acetate, and of lowering the hydrogenation time to five hours. In this way 22.5 g of product are obtained with a yield equal to 66%.

Example 3. 4-(6-Methoxy-2-naphthyl)butan-2-one

The reaction described in example 3 is repeated with the sole changes of nearly triplicating the amount of sodium acetate hydrate containing 32.4% of water, 17.60 g equivalent to 0.145 moles of sodium acetate, and of lowering the hydrogenation time to five hours. The oil obtained by evaporating the solvent at the end of the reaction is treated with 300 ml of toluene and 100 ml of water and after 15 minutes of stirring the two layers are separated. The aqueous phase is discarded while the organic phase is evaporated under vacuum at 70°C obtaining an oil that is dissolved into 100 ml of methanol. The solution is kept at 0°C for two hours and the precipitated solid is filtered, washed with 15 ml of methanol cooled to 0°C and dried in oven under vacuum. In this way 21.7 g of product are obtained. The methanolic filtrates from crystallization and washing are concentrated under vacuum to half volume so obtaining, after cooling to 0°C, the crystallization of other 4 g of product with an overall yield equal to 75.3%.

References

Cannata V. et al.; US Reissued Patent No. RE37,813; Aug. 6, 2002; Assigned to Honeywell International Inc., Morristown, NJ (US)

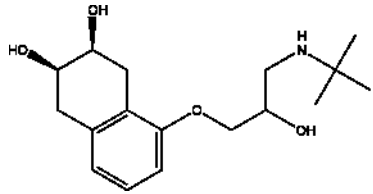
NADOLOL

Therapeutic Function: Antiarrhythmic

Chemical Name: 2,3-cis-1,2,3,4-Tetrahydro-5-[2-hydroxy-3-(tert-butylamino)propoxy]-2,3-naphthalenediol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 42200-33-9

Trade Name	Manufacturer	Country	Year Introduced
Solgol	Heyden	W. Germany	1978
Corgard	Squibb	Switz.	1978
Corgard	Squibb	UK	1979
Corgard	Squibb	US	1979
Corgard	Squibb	Italy	1980
Corgard	Squibb	France	1982
Betadol	Fako	Turkey	-
Corzide	Squibb	US	-

Raw Materials

5,8-Dihydro-1-naphthol
Sodium hydroxide
Acetic anhydride
Sodium methoxide
Silver acetate
Epichlorohydrin
Iodine
t-Butylamine

Manufacturing Process

(a) cis-5,6,7,8-Tetrahydro-1,6,7-naphthalenetriol: A solution of 29.2 g (0.2 mol) of 5,8-dihydro-1-naphthol and 40 ml of acetic anhydride in 100 ml of pyridine is prepared. After 16 hours the solvent is removed in vacuo and the residue dissolved in ether and washed with 200 ml of 5% hydrochloric acid, water, 200 ml of 10% sodium hydroxide, saturated salt solution and dried. Solvent removal gives 34.2 g (90.5%) of crude acetate which is dissolved in 900 ml of acetic acid and 36 ml of water. 53.3 g (0.32 mol) of silver acetate is added followed by 40.6 g (0.16 g-atom) of iodine. The slurry is heated with good stirring at 85°10°C for 3 hours under nitrogen, cooled and filtered. The filtrate is evaporated in vacuo and the residue dissolved in 250 ml of methanol and cooled to 0°C.

A solution of 40 g of sodium hydroxide in 200 ml of water is added under nitrogen and the mixture stirred overnight. The bulk of the methanol is removed in vacuo whereupon a solid forms. The solid is separated by filtration, dissolved in 150 ml of water and acidified with 20 ml of concentrated hydrochloric acid. Cooling gives a solid which is filtered and dried to give 16.5 g cis-5,6,7,8-tetrahydro-1,6,7-naphthalenetriol, melting point

184.5°C to 187°C. Three recrystallizations from absolute ethanol give the analytical sample, melting point 188°C to 188.5°C.

(b) 2,3-cis-1,2,3,4-Tetrahydro-5-[2,3-(epoxy)-propoxy]-2,3-naphthalenediol: A solution of 1.20 g (0.03 mol) of sodium methoxide and 5.4 g (0.03 mol) of cis-5,6,7,8-tetrahydro-1,6,7-naphthalenetriol in 200 ml of methanol is prepared under nitrogen. The residue obtained upon solvent removal is stirred overnight with 200 ml of dimethylsulfoxide and 4.65 g (0.05 mol) of epichlorohydrin under nitrogen. The bulk of the solvent is removed at 50°C at 0.1 mm and the residue dissolved in 100 ml of water. Extraction with chloroform (10 x 200 ml) gives a solid which is recrystallized from 150 ml of hexane-ethyl acetate to give epoxy diol of the above title.

(c)2,3-cis-1,2,3,4-Tetrahydro-5-[2-hydroxy-3-(tert-butylamino)propoxy]-2,3-naphthalenediol: A mixture of 2,3-cis-1,2,3,4-tetrahydro-5-[2,3-(epoxy)propoxy]-2,3-naphthalenediol (melting point 104°C to 107°C, one spot on TLC-alumina, 5% methanol in chloroform, iodine visualization) and 22 ml of tert-butylamine is heated at 85°C to 95°C for 15 hours in a Parr bomb and the excess amine removed in vacuo. The solid obtained by trituration of the residue with ether is filtered and recrystallized from benzene to give 3.4 g, melting point 124°C to 136°C.

References

Merck Index 6195
DFU 1 (9) 434 (1976)
Kleeman & Engel p. 614
PDR pp. 1739, 1741
OCDS Vol. 2 p. 110 (1980)
DOT 15 (9) 411 (1979)
I.N. p. 652
REM p. 905
Hauck, F.P., Cimarusti, C.M. and Narayanan, V.L.; US Patent 3,935,267; January 27, 1976; assigned to E.R. Squibb & Sons, Inc.

NAFARELIN ACETATE

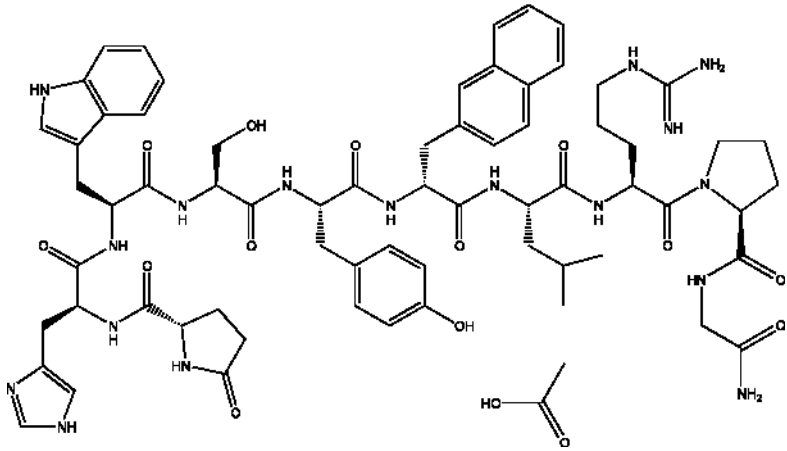
Therapeutic Function: Gonadotropic

Chemical Name: 6-(3-(2-Naphthalenyl)-D-alanine)luteinizing hormone-releasing factor (pig), monoacetate (salt)

Common Name: Nafarelin acetate

Chemical Abstracts Registry No.: 76932-60-0; 76932-56-4 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Nafarelin Acetate	Bachem AG	-	-
Nasanyl	Yamanouchi Pharmaceutical Co., Ltd.	Japan	-
Synarel	Searle	France	-
Synarel	Pfizer Canada Inc.	Canada	-
Synarel Nasal Spray	Syntex	USA	-
Synrelina	Pharmacia AG	-	-
Synrelina	Pfizer AG	Switz.	-

Raw Materials

Boc-Gly-OH
Boc-Pro-OH
Boc-Leu-OH
Boc-Trp-OH
Pyroglutamic acid
Boc-His(Tosyl)-OH
Cobalt(III) fluoride
Boc-3-(2-naphthyl)-D-alanine
Boc-Arg(Tosyl)-OH
1-Hydroxybenzotriazole
Boc-Ser(Benzyl)-OH
Hydrofluoric acid
N,N'-Dicyclohexylcarbodiimide
N-Boc, O-2-bromobenzoyloxycarbonyl-L-tyrosine
Benzhydrylamino-polystyrene-divinylbenzene resin

Manufacturing Process

In the reaction vessel of a Beckman 990 Peptide Synthesizer was placed 0.8 g (0.8 mmol) of benzhydrylamino-polystyrene-divinylbenzene resin (Lab Systems, Inc.) as described by Rivaille, supra. Amino acids were added sequentially to this resin by means of the usual methods of Boc-strategy of peptide synthesis on above copolymer.

The resin was coupled sequentially with a 2.5 molar excess of each protected

amino acid and DCC. Thus, the resin was treated during successive coupling cycles with 0.433 g Boc-Gly-OH, 0.432 g Boc-Pro-OH, 0.857 g Boc-Arg(Tosyl)-OH, 0.462 g Boc-Leu-OH, 0,504 g Boc-3-(2-naphthyl)-D-alanine and 0.272 g 1-hydroxybenzotriazole, 0.724 g N-Boc, O-2-bromobenzoyloxycarbonyl-L-tyrosine, 0.59 g Boc-Ser(Benzyl)-OH, 0.608 g Boc-Trp-OH, 0.654 g Boc-His(Tosyl)-OH and 0.524 g pyroglutamic acid. A coupling cycle for one amino acid and completeness of the reaction is checked by the ninhydrin method of E. Kaiser, et al., Anal. Biochem., 34, 595 (1970).

The resin was removed from the reaction vessel, washed with CH_2Cl_2, and dried in vacuo to yield 2.0 g of protected polypeptide resin.

The polypeptide product was simultaneously removed from the resin and completely deprotected by treatment with anhydrous liquid HF. A mixture of 2.0 g of protected polypeptide resin and 2 mL of anisole (scavenger) in a Kel-F reaction vessel was treated with 20 mL of redistilled (from CoF_3) anhydrous liquid HF at 0°C for 30 minutes. The HF was evaporated under vacuum and the residue of (pyro)-Glu-His-Trp-Ser-Tyr-3-(2-naphthyl)-D-alanyl-Leu-Arg-Pro-Gly-NH_2,as its HF salt, was washed with ether. The residue was then extracted with glacial acetic acid. The acetic acid extract was lyophilized to yield 0.8 g of crude material. The crude polypeptide was loaded on a 4x40 cm. Amberlite XAD-4 column (polystyrene-4% divinylbenzene copolymer) and eluted with a concave gradient from water (0.5 L) to ethanol (1 L). The tubes containing fractions from effluent volume 690 mL to 1,470 mL were pooled and stripped to dryness to yield 490 mg of partially purified polypeptide.

A 150 mg sample of the partially purified product was subjected to partition chromatography on a 3 times 50 cm. column of Sephadex G-25 using the solvent system 1-butanol/toluene/acetic acid/water containing 1.5% pyridine in the ratios 10:15:12:18. The pure fractions were pooled on the basis of thin layer chromatography (silica gel; BuOH/H_2O/HOAc/EtOAc; 1:1:1:1) and HPLC (5 micron, reverse phase, octadecylsilyl packing; 40% 0.03 M NH_4OAc/60% acetonitrile). The desired product came off the column in fractions from effluent volume 1,000 mL to 1,400 mL (Rf 0.1). The pure fractions were pooled, stripped to dryness, taken up in H_2O, and lyophilized to yield 57 mg of pure pyro-glutamyl-histidyl-tryptophylseryl-tyrosyl-3-(2-naphthyl)-D-alanyl-leucyl-arginylprolyl-glycinamide, as its acetic acid addition salt, $[\alpha]_D^{25}$-27.4° (c 0.9, HOAc), m.p. 185°-193°C (dec.).

References

Nestor et al.; US Patent No. 4,234,571; Nov. 18, 1980; Assinged to Syntex (U. S. A.) Inc., Polo Alto, Calif.

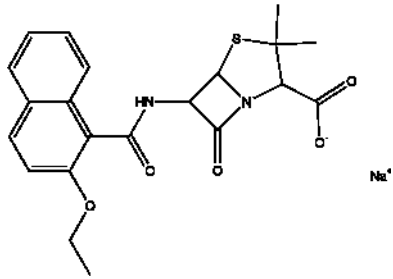
NAFCILLIN SODIUM

Therapeutic Function: Antibacterial

Chemical Name: 6-(2-Ethoxy-1-naphthamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid sodium salt

Common Name: 6-(2-Ethoxy-1-naphthamido)penicillin sodium salt

Structural Formula:



Chemical Abstracts Registry No.: 985-16-0; 147-52-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Unipen	Wyeth	US	1964
Nafcil	Bristol	US	1976
Nallpen	Beecham	US	1983
Naftopen	Gist Brocades	-	-

Raw Materials

6-Aminopenicillanic acid
2-Ethoxy-1-naphthoyl chloride
Sodium bicarbonate

Manufacturing Process

A stirred suspension of 12.6 grams 6-aminopenicillanic acid in 130 ml dry alcohol-free chloroform was treated with 16 ml triethylamine and then with 13.8 grams of a solution of 2-ethoxy-1-naphthoyl chloride in 95 ml chloroform. After being washed successively with 58 ml each of 1 N and then 0.1 N hydrochloric acid the chloroform solution was extracted with N aqueous sodium bicarbonate (58 ml + 6 ml). The combined bicarbonate extracts were washed with 20 ml ether and then evaporated at low temperature and pressure to give the crude sodium salt of 2-ethoxy-1-naphthylpenicillin [also called sodium 6-(2-ethoxy-1-naphthamido)penicillinate] as a yellow powder (20.3 grams). This was dissolved in 20 ml water at 30°C and diluted with 180 ml n-butanol, also at 30°C, with stirring. Slow cooling to 0°C gave colorless needles of the product.

References

Merck Index 6199
Kleeman & Engel p. 615
PDR pp. 700, 1991
OCDS Vol. 1 p. 412 (1977)

I.N. p. 653
REM p. 1196
Doyle, F.P. and Nayler, J.H.C.; US Patent 3,157,639; November 17, 1964; assigned to Beecham Group Limited, England

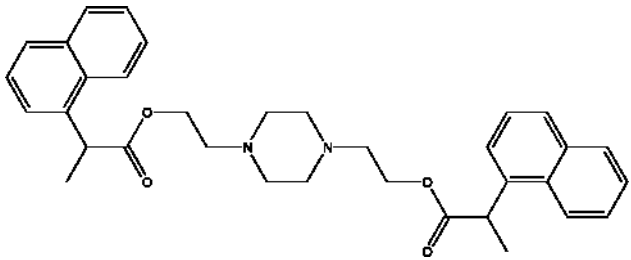
NAFIVERINE

Therapeutic Function: Spasmolytic

Chemical Name: α-Methyl-1-naphthaleneacetic acid 1,4-piperazinediyldi-2,1-ethanediyl ester

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 5061-22-3

Trade Name	Manufacturer	Country	Year Introduced
Naftidan	De Angeli	Italy	1969

Raw Materials

α-Methyl-1-naphthylacetic acid
Thionyl chloride
N,N'-Di-(β-hydroxyethyl)piperazine

Manufacturing Process

15 grams of α-methyl-1-naphthylacetic acid were refluxed with 50 ml of thionyl chloride during 3 hours. The excess thionyl chloride was removed under reduced pressure and the product was also isolated by distillation under reduced pressure. Yield: 15.6 grams (96%). The α-methyl-1-naphthyl acetyl chloride boils at 120° to 124°C. 1.76 grams of N,N'-di-(β-hydroxyethyl)-piperazine, 1.9 grams of sodium bicarbonate and 4.45 grams of α-methyl-1-naphthyl acetyl chloride in 30 ml of anhydrous acetonitrile were refluxed with stirring during 5 hours. After cooling the mixture was filtered and the

acetonitrile evaporated off under reduced pressure. 5.2 grams of crude ester were obtained. The hydrochloride, melting at 220° to 221°C, may be prepared by dissolving the ester in absolute ethanol and treating the solution with anhydrous gaseous hydrogen chloride.

References

Merck Index 6200
I.N. p. 653
Pala, G.; British Patent 1,016,968; Jan. 12, 1966; assigned to Instituto de Angeli, SpA, Italy

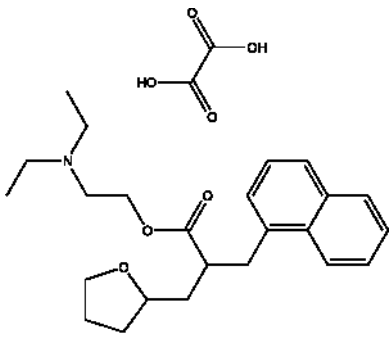
NAFRONYL OXALATE

Therapeutic Function: Vasodilator

Chemical Name: Tetrahydro-α-(1-naphthalenylmethyl)-2-furanpropanoic acid 2-(diethylamino)ethyl ester acid oxalate

Common Name: Naftidofuryl

Structural Formula:



Chemical Abstracts Registry No.: 3200-06-4; 31329-57-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Dusodril	Roland	W. Germany	1968
Praxilene	Oberval	France	1968
Prazilene	Lipha	UK	1972
Praxilene	Formenti	Italy	1973
Praxilene	Biochimica	Switz.	1980
Citoxid	Disprovent	Argentina	-

Raw Materials

Oxalic acid
β-Chloroethyl-N-diethylamine
β-(1-Naphthyl)-β'-tetrahydrofurfurylisobutyric acid

Manufacturing Process

30 grams (0.106 mol) of β-(1-naphthyl)-β'-tetrahydrofuryl isobutyric acid are heated under reflux for 8 1/2 hours in 230 cc of isopropanol with 14 grams (0.103 mol) of β-chloroethyl-N-diethylamine. After evaporation of the isopropanol in vacuo, the syrupy residue is treated with a solution of K_2CO_3. Extraction with ether is carried out after drying over Na_2SO_4.

Distillation of the extract yields 28.5 grams of a very viscous yellow liquid with a $BP_{0.95\text{-}1.09 millibar}$ = 198° to 202°C. The yield is 70.5% (theoretical quantity = 40.5 grams).1.3 grams (0.0103 mol) of dihydrated oxalic acid are dissolved while being made tepid in 8 cc of acetone. The cooled solution has added thereto 4 grams (0.0104 mol) of N-diethylaminoethyl-β-(1-naphthyl)-β'-tetrahydrofuryl isobutyrate, obtained according to the process described above and dissolved in 10 cc of acetone. The solution is brought to boiling point for 15 minutes. After cooling to ambient temperature, it is placed in a refrigerator. Crystallization occurs after 2 hours, the crystals which have formed are separated by centrifuging, and after washing in hexane and drying in vacuo 3.5 grams of white crystals are obtained. After being recrystallized three times, in alcohol and then in a mixture of alcohol and ethyl acetate, the product is analytically pure and has a MP = 110° to 111°C (heating stage).

References

Merck Index 6201
Kleeman & Engel p. 615
OCDS Vol .2 p. 213 (1980)
DOT 5 (1) 19 (1969)
I.N. p. 654
Szarvasi, E. and Bayssat, M.; US Patent 3,334,096; August 1, 1967; assigned to Lipha, Lyonnaise Industrielle Pharmaceutique, France

NAFTIFINE

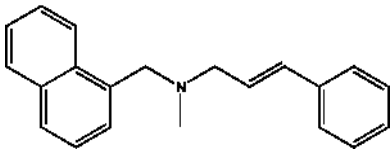
Therapeutic Function: Antifungal

Chemical Name: 1-Naphthalenemethanamine, N-methyl-N-(3-phenyl-2-propenyl)-, (E)-

Common Name: Naftifine; Naftifugin

Chemical Abstracts Registry No.: 65472-88-0

Structural Formula:



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

Raw Materials

Methyl-(1-naphthylmethyl)amine hydrochloride
Sodium carbonate
Dimethylformamide
Cinnamyl chloride

Manufacturing Process

To a mixture of 1.42 g of methyl-(1-naphthylmethyl)amine hydrochloride, 2.89 g of sodium carbonate and 10 ml of dimethylformamide is added, at room temperature, 1.25 g of cinnamyl chloride, dropwise. After 18 hours stirring, at room temperature, the mixture is filtered and the filtrate is evaporated in vacuo. The residue is dissolved in toluene and, after drying over sodium sulphate, evaporated to obtain the trans-N-(cinnamylmethyl)-N-methyl-(1-naphthylmethyl)amine compound, boiling point 162-167°C/0.015 Torr.

The free base may be converted, with isopropanolic hydrogen chloride solution, into the hydrochloride form, melting point 177°C (from propanol).

References

Berney Daniel; US Patent No. 4,282,251; August 4, 1981; Assigned to Sandoz Ltd. (Basel, CH)

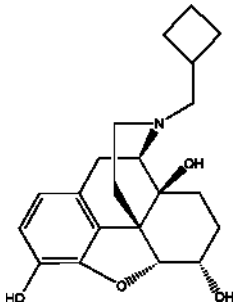
NALBUPHINE

Therapeutic Function: Analgesic

Chemical Name: N-Cyclobutylmethyl-14-hydroxydihydronormorphinone

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 20594-83-6; 23277-43-2 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Nubain	Du Pont	US	1979
Nubain	Du Pont	UK	1983

Raw Materials

14-Hydroxydihydronormorphinone
Cyclobutane carboxylic acid chloride
Lithium aluminum hydride

Manufacturing Process

To a slurry of 110.5 g of 14-hydroxydihydronormorphinone in 2.5 liters of methylene chloride and 280 ml of triethylamine was added a solution of 106 g of cyclobutanecarboxylic acid chloride in 500 ml of methylene chloride. The temperature of the reaction mixture was maintained at 20°C to 25°C during the addition. After 5 minutes the reaction mixture was brought to reflux and heated for 5 hours.

It was then cooled, washed with water, dried over sodium sulfate and evaporated to dryness. The residue was crystallized from benzene and pentane to give 138.5 g of the dicyclobutanecarbonyl derivative, melting point about 112°C (dec.).

The dicyclobutanecarbonyl derivative (136.7 g) was dissolved in 200 ml of tetrahydrofuran and added dropwise to a suspension of 34.2 g of lithium aluminum hydride in 1 liters of tetrahydrofuran. The temperature of the mixture rose to reflux during the addition. Reflux was maintained for 2 hours after the addition was completed. After cooling, 110 ml of ethyl acetate was added dropwise, followed by 30 ml of water, followed by a solution of 53 g of ammonium chloride in 125 ml of water. The resulting mixture was filtered and the inorganic precipitate was washed with methanol. Evaporation of the combined filtrates gave 66 g of N-cyclobutylmethyl-14-

hydroxydihydronormorphinone, melting point 229°C to 231°C.

References

Merck Index 6203
DFU 2 (9) 613 (1977)
Kleeman & Engel p. 616
PDR p. 858
OCDS Vol. 2 p. 319 (1980)
DOT 16 (2) 51 (1980)
I.N. p. 654
REM p. 1109
Blumberg, H., Pachter, I.J. and Matossian, Z.; US Patent 3,332,950; July 25, 1967; assigned to Endo Laboratories, Inc.

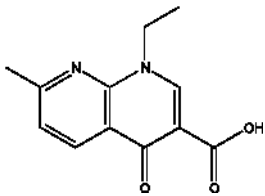
NALIDIXIC ACID

Therapeutic Function: Antibacterial

Chemical Name: 1-Ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid

Common Name:-

Structural Formula:



Chemical Abstracts Registry No.: 389-08-2

Trade Name	Manufacturer	Country	Year Introduced
Neggram	Winthrop	US	1964
Nalidixique	Winthrop	France	1974
Jicsron	Towa Yakuhin	Japan	1981
Baktogram	Farmakos	Yugoslavia	-
Betaxina	Amelix	Italy	-
Chemiurin	Cifa	Italy	-
Cybis	Breon	US	-
Dixiben	Benvegna	Italy	-
Dixurol	I.T.I.	Italy	-
Enexina	S.I.T.	Italy	-
Entolon	Sawai	Japan	-

Trade Name	Manufacturer	Country	Year Introduced
Eucistin	San Carlo	Italy	-
Faril	Saita	Italy	-
Innoxalon	Sanko	Japan	-
Kusnarin	Kodama	Japan	-
Nali	Iltas	Turkey	-
Nalcidin	Schoum	Italy	-
Nalidicron	San-A	Japan	-
Nalidixico	Level	Spain	-
Nalidixin	Spofa	Czechoslovakia	-
Nalidixol	Hermes	Spain	-
Naligen	Sam	Italy	-
Naligram	Isis	Yugoslavia	-
Nalissina	Armour	Italy	-
Nalitucsan	Hishiyama	Japan	-
Nalix	Sigurta	Italy	-
Nalixan	Neofarma	Finland	-
Nalurin	Von Boch	Italy	-
Narigix	Taiyo	Japan	-
Naxuril	Esterfarm	Italy	-
Negabatt	Dessy	Italy	-
Nicelate	Toyo Jozo	Japan	-
Nogermin	Madaus	Spain	-
Notricel	Hortel	Spain	-
Pielos	S.T.I.P.	Italy	-
Poleon	Sumitomo	Japan	-
Renogram	Belupo Ltd.	Yugoslavia	-
Restelon	Maruishi	Japan	-
Sicmylon	Niichiko	Japan	-
Specifin	Bergamon	Italy	-
Unaserus	Isei	Japan	-
Uralgin	Ceccarelli	Italy	-
Uretrene	Mitim	Italy	-
Uriben	R.P. Drugs	UK	-
Uriclar	Crosara	Italy	-
Uri-Flor	A.G.I.P.S.	Italy	-
Urigram	Trima	Israel	-
Urisco	I.C.I.	Italy	-
Uristeril	Ripari-Gero	Italy	-
Urodixin	Italchimici	Italy	-
Urogram	Firma	Italy	-
Urolex	Sirt-B.B.P.	Italy	-
Urolgin N	Takata	Japan	-
Uromina	Ausonia	Italy	-
Uroneg	Ibirn	Italy	-
Valuren	Intersint	Italy	-
Wintomylon	Daiichi	Japan	-
Wintron	Tobishi	Japan	-

Raw Materials

2-Amino-6-methylpyridine
Ethoxymethylene malonic acid diethyl ester
Sodium hydroxide
Ethyl iodide

Manufacturing Process

A warm solution containing 41 grams of 4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylic acid and 39 grams of potassium hydroxide in 1 liter of ethanol and 200 cc of water was treated with 50 cc of ethyl iodide and the resulting mixture was refluxed gently overnight, acidified with hydrochloric acid and cooled. The resulting precipitate was collected and recrystallized twice from acetonitrile to yield 26 grams (56% yield) of 1-ethyl-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid, MP 229° to 230°C.

The starting material is prepared by reacting 2-amino-6-methylpyridine with ethoxymethylene-malonic acid diethyl ester and then reacting that product with sodium hydroxide.

References

Merck Index 6205
Kleeman & Engel p. 616
PDR p. 1922
OCDS Vol. 1 p. 429 (1977) & 2,370,469 (1980)
DOT 1 (1) 16 (1965)
I.N. p. 33
REM p. 1216
Lesher, G.Y. and Gruett, M.D.; US Patent 3,149,104; September 15, 1964; assigned to Sterling Drug Inc.

NALMEFENE

Therapeutic Function: Antagonist to narcotics

Chemical Name: Morphinan-3,14-diol, 17-(cyclopropylmethyl)-4,5-epoxy-6-methylene-, (5alpha)-

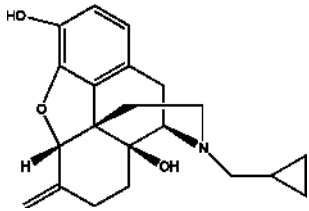
Common Name: Nalmefene; Nalmetrene

Chemical Abstracts Registry No.: 55096-26-9

Raw Materials

Potassium t-butoxide
Methyltriphenylphosphonium bromide
Naltrexone

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Nalmefene	Mallinckrodt Inc.	-	-
Nalmefene	Somaxon Pharmaceuticals	-	-
Arthene	Ohmeda	-	-
Cervene	Baker Norton	-	-
Incystene	SSPharma	-	-
Incystene	Ivax Corporation	-	-
Revex	Baxter Healthcare Corp Anesthesia And Critical Care	-	-
Revex	Ohmeda	-	-

Manufacturing Process

A dry, 2-liter, 3-neck, round bottom flask fitted with two stoppers and a magnetic stirring bar was charged with potassium t-butoxide (61.1 g, 0.545 mol) and methyltriphenylphosphonium bromide (194.4 g, 0.544 mol). Freshly distilled tetrahydrofuran (450 ml) was introduced at 20°C. The resultant thick, bright yellow dispersion was stirred at 20°C for 0.5 h and further dry tetrahydrofuran (100 ml) was added. A solution of dry naltrexone (30 g, 0.088 mol) in dry tetrahydrofuran (200 ml) was then added dropwise over 40 min. Then the reaction mixture was stirred for a further 1.25 h, then cooled to 10°C, and quenched with 20% aqueous ammonium chloride solution (75 ml) followed by water (100 ml). The organic layer was separated and the aqueous layer extracted with four 100 ml portions of chloroform. Solvent was evaporated from the tetrahydrofuran layer and the combined chloroform extracts, the residues combined and brought to pH 2 by addition of 2 N hydrochloric acid. The resultant precipitate was filtered, washed with chloroform and suspended in a mixture of chloroform (500 ml) and water (250 ml). Ammonium hydroxide was added to attain a pH of 8 and the aqueous layer separated. The organic layer was dried over anhydrous sodium sulfate, filtered, and the solvent removed in vacuo. The resultant solid was dissolved in ethyl acetate (1400 ml), the solution filtered through a silica pad and the solvent evaporated. The product was recrystallized from chloroform and washed with hexane to yield pure 6-desoxy-6-methylenenaltrexone (also called nalmefene) as a white solid. Yield: 27.0 g, 88%.

References

Merck Index, Monograph number: 6447, Twelfth edition, 1996, Editor: S. Budavari

Merck and Co., Inc.; Meltzer P.C., Coe J. W.; US Patent No. 4,535,157; August 13, 1985; Assigned: Key Pharmaceuticals, Inc. (Miami, FL)

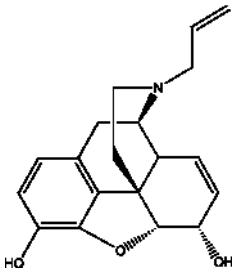
NALORPHINE

Therapeutic Function: Narcotic antagonist

Chemical Name: 7,8-Didehydro-4,5-epoxy-17-(2-propenyl)morphinan-3,6-diol

Common Name: N-Allylnormorphine

Structural Formula:



Chemical Abstracts Registry No.: 62-67-9; 57-29-4 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Nalline	MSD	US	1952
Lethidrone	Wellcome	W. Germany	-
Nalorphine	Clin-Comar-Byla	France	-
Norfin	Lusofarmaco	Italy	-

Raw Materials

Normorphine
Allyl bromide
Sodium bicarbonate

Manufacturing Process

6 grams of normorphine, 2.7 grams of allyl bromide, 2.65 grams of sodium bicarbonate, and 75 cc of methanol were mixed together, and the resulting mixture was heated under reflux with stirring for a period of about 5 1/2 hours. The reaction mixture was evaporated to dryness in vacuo, the residual material was extracted with 60 cc of boiling chloroform, 0.5 gram of activated charcoal was added, and the resulting mixture was filtered through a layer of diatomaceous silica. The filter cake was washed with four 10 cc portions of

boiling chloroform, and the chloroform filtrate and washings were combined and evaporated to dryness in vacuo. The residual material was triturated with 25 cc of anhydrous ether until crystalline, the ethereal mixture was cooled, maintained at a temperature of 3°C overnight, filtered, and the crystalline mixture was washed with three 10 cc portions of ice-cold ether. The resulting crystalline product was dried to give 6.0 grams of N-allylnormorphine, yield approximately 87% of theory, according to US Patent 2,891,954.

References

Merck Index 6206
Kleeman & Engel p. 617
OCDS Vol. 1 p. 288 (1977) & 2,318 (1980)
I.N. p. 655
REM p. 1106
Weijlard, J. and Erickson, A.E.; US Patent 2,364,833; December 12, 1944; assigned to Merck & Co., Inc.
Weijlard, J.; US Patent 2,891,954; June 23, 1959; assigned to Merck and Co., Inc.

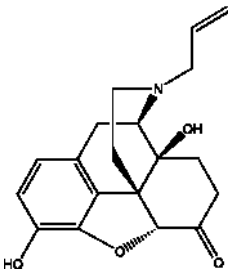
NALOXONE

Therapeutic Function: Narcotic antagonist

Chemical Name: 17-Allyl-4,5α-epoxy-3,14-dihydroxy-morphinan-6-one

Common Name: N-Allylnoroxymorphone; N-Allyl-1,4-hydroxydihydronormorphinone

Structural Formula:



Chemical Abstracts Registry No.: 465-65-6; 357-08-4 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Narcan	Du Pont	US	1971
Narcan	Du Pont	UK	1975
Narcanti	Winthrop	W. Germany	1978

Trade Name	Manufacturer	Country	Year Introduced
Narcan	Winthrop	France	1980
Narcan	Crinos	Italy	1980
Nalone	Endo	US	-
Talwin	Winthrop-Breon	US	-

Raw Materials

Oxymorphone
Allyl bromide
Hydrogen chloride
Cyanogen bromide
Acetic anhydride

Manufacturing Process

10 grams of 14-hydroxydihydromorphinone (oxymorphone) was converted into its diacetate by warming it on the steam bath with 80 cc of acetic anhydride for about 2 hours. The acetic anhydride was removed on the water bath under a vacuum of about 30 mm absolute pressure. The melting point of the residue was 220°C. The residue was taken up in 100 cc of chloroform. An equal amount by weight of cyanogen bromide was added and the mixture was refluxed at about 60°C for about 5 hours. After refluxing, the mixture was washed with 100 cc of a 5% aqueous hydrochloric acid solution, dried over sodium sulfate and the chloroform removed by evaporation under a vacuum of about 30 mm. The residue had a melting point of 240°C.

The residue was then heated at about 90°C for 16 hours on a steam bath with 300 cc of 20% aqueous hydrochloric acid solution, and treated with a small amount, e.g., 1 gram of charcoal. The hydrochloric acid was then removed under a vacuum of 15 mm, the residue dissolved in 30 cc of water and precipitated by the addition of 2.4 cc of concentrated aqueous ammonia. The precipitate was filtered off and dried. It consists of 14-hydroxydihydronormorphinone. It is soluble in ethanol.

The 14-hydroxydihydronormorphinone was suspended in 200 cc of pure ethyl alcohol, half its weight of sodium bicarbonate and half its weight of allyl bromide added and the resulting mixture was refluxed at about 75°C for 48 hours. The solution was cooled, e.g., to 10°C and filtered and the alcohol removed under a vacuum of 30 mm. The residue was dissolved in chloroform and filtered. The chloroform was removed under a vacuum of 30 mm and the residue was crystallized from ethylacetate. The crystallized product, N-allyl-1,4-hydroxydihydronormorphinone, has a melting point of 184°C, is soluble in chloroform and insoluble in petroleum ether. The yield amounts to 20% based on the weight of the reacted 14-hydroxydihydromorphinone.

References

Merck Index 6208
Kleeman & Engel p. 618
PDR pp. 858, 1932
OCDS Vol. 1 p. 289 (1977) & 2,318,323 (1980)
DOT 8 (8) 295 (1972); I.N. p. 655
REM p. 1106
Lewenstein, M.J. and Fishman, J.; US Patent 3,254,088; May 31,1966

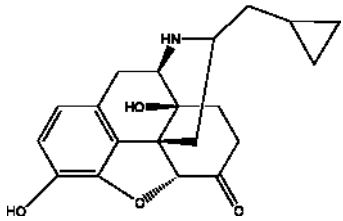
NALTREXONE

Therapeutic Function: Narcotic analgesic

Chemical Name: Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-α-oxy-3,14-dihydoxy-

Common Name: Naltrexone

Structural Formula:



Chemical Abstracts Registry No.: 16590-41-3

Trade Name	Manufacturer	Country	Year Introduced
Antaxone	Zambon Group	Italy	-
Nalorex	DuPont Pharmaceuticals	-	-
Naltima	Intas Pharm.	-	-
Naltrexone	DuPont Merck	-	-
Nodict	Synergy (Sun)	India	-
ReVia	DuPont Pharmaceuticals	-	-

Raw Materials

Codeine
Acetic anhydride
Oxalyl chloride
Formic acid
Palladium on carbon
4-Dimethylaminopyridine
1-Chloroethyl chloroformate
(Chloromethyl)cyclopropane
3-Chloroperbenzoic acid
Boron tribromide

Manufacturing Process

Codeine is a component of gum opium and can also be produced by methylation of morphine using known prior art techniques.

A solution of codeine (30 g, 100.2 mmol), acetic anhydride (18.4 g, 180.2 mmol), triethylamine (18.25 g, 180.2 mmol) and 4-dimethylaminopyridine (0.5 g) in dry ethyl acetate (620 ml) was stirred at rt. under nitrogen for 12 hr, added saturated aqueous sodium bicarbonate solution until no acetic anhydride detected. The organic portion was separated, washed with water (3

times 120 ml), dried over anhydrous sodium sulfate, and evaporated in vacuo to dryness to give 6-acetylcodeine as white solids (34.0 g, 99% yield).

Preparation of 6-acetylnorcodeine hydrochloride.

A solution of 6-acetylcodeine (10.0 g, 29.3 mmol), 1-chloroethyl chloroformate (5.51 g, 37.8 mmol), and proton sponge (1.0 g) in methylene chloride (80 ml) was heated at reflux for 80 min. The reaction mixture was evaporated in vacuo to dryness. The residue was chromatographed on silica gel with ethyl acetate to give 6-acetyl-17-(1-chloroethoxycarbonyl)norcodeine as an oil (12.13 g), which was dissolved in methanol with a few drops of conc. HCl. The solution was heated at reflux for 1 hr and evaporated in vacuo to almost dryness. The residue was added hexane and filtered to give 6-acetylnorcodeine hydrochloride (10.7 g, 100% yield).

Preparation of norcodeine hydrochloride.

A solution of 6-acetylcodeine (10.0 g, 29.3 mmol), 1-chloroethyl chloroformate (5.56 g, 38.1 mmol), and proton sponge (1.0 g) in methylene chloride (50 ml) was heated at reflux for 50 min. The reaction mixture was evaporated in vacuo to about 30 ml. Methanol (25 ml) and concentrated HCl (2 ml) were added. The solution was heated at reflux for 40 min. and evaporated in vacuo to almost dryness. The residue was added hexane and filtered to give norcodeine hydrochloride (8.8 g, 93% yield).

Preparation of 17-cyclopropylmethylnorcodeine.

A mixture of norcodeine hydrochloride (11.48 g, 27.8 mmol), (chloromethyl)cyclopropane (5.14 g, 55.6 mmol), sodium carbonate (14.73 g, 139.0 mmol), and potassium iodide (4.61 g, 27.8 mmol) in ethanol (250 ml) was heated at reflux for 20 hr, cooled, and evaporated in vacuo to dryness. The residue was basified with NH_4OH, and extracted with methylene chloride. The extract was washed with water and evaporated in vacuo to dryness. The residue (11.7 g) was chromatographed on silica gel with a eluting solvent system of methanol/ethyl acetate (10/90) to give 17-cyclopropylmethylnorcodeine (10.68 g, 91% yield).

Preparation of 17-cyclopropylmethylnorcodeinone.

To a solution of DMSO (14.50 g, 185.6 mmol) in methylene chloride (80 ml) at -78°C, was added a solution of oxalyl chloride (11.78 g, 92.8 mmol) in methylene chloride (20 ml) in 20 min. After stirring at -78°C for 20 min., a solution of 17-cyclopropylmethylnorcodeine (9.0 g, 26.5 mmol) in methylene chloride (40 ml) was added dropwise in 50 min. The reaction mixture was stirred at -74° to -76°C for 3 hr, added triethylamine (9.39 g, 92.8 mmol), allowed to warm up to rt., added methylene chloride (200 ml), washed with water (10 times 50 ml), and evaporated in vacuo to dryness. The residue was mixed with hexane and filtered to give 17-cyclopropylmethylnorcodeinone (8.85 g, 99% yield).

Preparation of 17-cyclopropylmethylnorcodeinone dienol acetate.

A mixture of 17-cyclopropylmethylnorcodeinone (3.55 g, 10.5 mmol), acetic

anhydride (20 ml, 210.4 mmol), sodium acetate (1.3 g, 15.8 mmol), and toluene (6 ml) was heated at 71°-73°C for 14 hr. The reaction mixture was cooled, added methylene chloride (250 ml), water (50 ml), and sodium bicarbonate (73.5 g), stirred for 4 hr, and filtered. The organic portion of the filtrate was separated, washed with water (30 ml), dried over anhydrous sodium sulfate, and evaporated in vacuo to dryness. The residue (3.94 g) was chromatographed on silica gel with 100% ethyl acetate to give 17-cyclopropylmethylnorcodeinone dienol acetate (2.87 g, 72% yield).

Preparation of 17-cyclopropylmethyl-14-hydroxynorcodeinone. A solution of 17-cyclopropylmethylnorcodeinone (0.20 g, 0.59 mmol), formic acid (90%, 0.304 g), water (0.504 g), EtOAc (0.27 g), and hydrogen peroxide (30%, 0.17 g) was heated at 42°-43°C for 15 hr, added water (20 ml), basified with Na_2CO_3 (1.02g), and extracted with EtOAc (80 ml and 2 times 20 ml). The combined extract was washed with water, dried over anhydrous sodium sulfate, and evaporated in vacuo to dryness to give 17-cyclopropylmethyl-14-hydroxynorcodeinone (0.10 g, 56% yield). The Rf value in TLC and the IR spectrum of the product were comparable to those obtained from an authentic sample.

Preparation of 17-cyclopropylmethyl-14-hydroxynorcodeinone.

A solution of 17-cyclopropylmethylnorcodeinone dienol acetate (1.00 g, 2.63 mmol), formic acid (8 ml, 90%), and hydrogen peroxide (0.37 g, 30%, 3.26 mmol) was heated at 44°-45°C for 6 hr, added water (20 ml) and ethyl acetate (80 ml), basified with sodium bicarbonate. The organic portion was separated, washed with water (15 ml), dried over anhydrous sodium sulfate and evaporated in vacuo to dryness, the residue (0.9 g) was chromatographed on silica gel with methanol/methylene chloride (2.5/97.5) to give 17-cyclopropylmethyl-14-hydroxynorcodeinone (0.72 g, 78% yield).

Preparation of 17-cyclopropylmethyl-14-hydroxynorcodeinone.

A solution of 17-cyclopropylmethylnorcodeinone dienol acetate (0.5 g, 1.31 mmol), 3-chloroperbenzoic acid (0.36 g, 2.10 mmol) and oxalic acid (0.27 g, 2.90 mmol) in acetic acid (7 ml) was stirred at rt. overnight, added cold water (35 ml), basified with sodium carbonate, and extracted with methylene chloride (100 ml). The extract was washed with water (2 times 30 ml), dried over anhydrous sodium sulfate, and evaporated in vacuo to dryness. The residue (0.41 g) was chromatographed on silica gel to give 17-cyclopropylmethyl-14-hydroxynorcodeinone (0.34 g, 74% yield). The Rf value in TLC and the IR spectrum of the product were comparable to those obtained from an authentic sample.

Preparation of 3-methylnaltrexone.

A mixture of 17-cyclopropylmethyl-14-hydroxynorcodeinone (0.30 g, 0.85 mmol) and Pd/C (5%, 0.45 g) in ethanol (35 ml) was hydrogenated in a Parr hydrogenator at rt. under 28 psi of hydrogen gas. The mixture was filtered. The filtrate was evaporated in vacuo to dryness to give 3-methylnaltrexone (0.30 g, 99% yield).

Preparation of naltrexone from 3-methylnaltrexone.

A solution of 3-methylnaltrexone (0.48 g, 1.35 mmol) in methylene chloride (30 ml) was cooled with an ice-water bath, and then added a solution of boron tribromide (5.4 ml, 1 M solution in methylene chloride, 5.4 mmol). The reaction mixture was stirred at rt. for 15 hr, basified with NH_4OH, and extracted with methylene chloride (60 ml). The extract was washed with water (2 times 15 ml), dried over anhydrous sodium sulfate, and evaporated in vacuo to dryness to give naltrexone (0.45 g, 98% yield).

References

Huang B.-S. et al.; US Patent No. 6,013,796; Assigned to Penick Corporation, Newark, N.J.

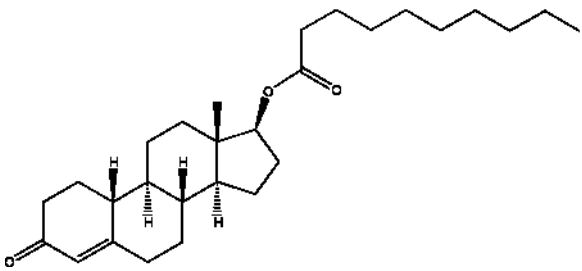
NANDROLONE DECANOATE

Therapeutic Function: Anabolic

Chemical Name: 17β-[(1-Oxodecyl)oxy]estr-4-en-3-one

Common Name: 19-Nortestosterone decanoate; Norandrostenolone decanoate

Structural Formula:



Chemical Abstracts Registry No.: 360-70-3; 434-22

Trade Name	Manufacturer	Country	Year Introduced
Deca-Durabolin	Organon	US	1962
Deca-Hybolin	Hyrex	US	1979
Deca-Noralone	Taro	Israel	-
Fortabolin	Deva	Turkey	-
Iebolan	I.E. Kimya Evi	Turkey	-
Kabolin	Legere	US	-
Methybol	Mepha	Switz.	-

Trade Name	Manufacturer	Country	Year Introduced
Nordecon	Ibsa	Switz.	-
Sterobolin	Neofarma	Finland	-
Turinabol-Depot	Jenapharm	E. Germany	-

Raw Materials

19-Nortestosterone
Decanoic acid chloride

Manufacturing Process

1 gram of 19-nortestosterone is dissolved in 3 ml of dry pyridine, after which the resulting solution is cooled to -20°C. A solution of 1.0 gram of decanoic acid chloride in 3 ml of dry benzene is added to the cooled solution. The mixture is maintained at -15°C for 16 hours and then poured into ice water. The aqueous liquid is extracted with benzene, the benzene solution is washed with respectively 1 N sodium hydroxide solution, 2 N hydrochloric acid and with water until neutral reaction.

Then the solution is dried on sodium sulfate, filtered, and evaporated to dryness. The residue, 1.63 grams is dissolved in hexane, this solution is filtered over 30 grams of neutral aluminum oxide, and evaporated to dryness. On paper chromatographic investigation it turned out that the obtained 19-nortestosterone 17-decanoate which at room temperature is an oil consists of a single compound, according to US Patent 2,998,423.

References

Merck Index 6212
Kleeman & Engel p. 620
PDR pp. 1033, 1286
OCDS Vol. 1 p. 171 (1977)
I.N. p. 655
REM p. 999
Donia, R.A. and Ott, A.C.; US Patent 2,798,879; July 9, 1957; assigned to The Upjohn Company
De Wit, E.D. and Overbeek, G.A.; US Patent 2,998,423; August 29, 1961; assigned to Organon Inc.

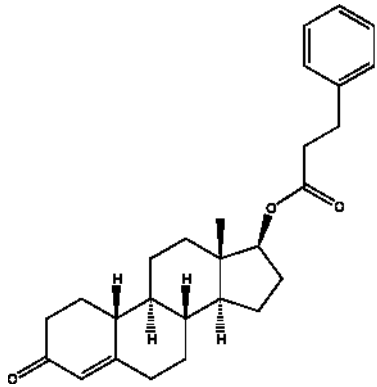
NANDROLONE PHENPROPIONATE

Therapeutic Function: Anabolic

Chemical Name: 17β-Hydroxyestr-4-en-3-one 3-phenylpropionate

Common Name: 19-Nortestosterone β-phenylpropionate

Structural Formula:



Chemical Abstracts Registry No.: 62-90-8; 434-22-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Durabolin	Organon	US	1959
Nandrolin	Tutag	US	1979
Activin	Aristegui	Spain	-
Anticatabolin	Falorni	Italy	-
Hepa-Obaton	Noury Pharma	W. Germany	-
Hybolin Improved	Hyrex	US	-
Norabol	Pharmacia	Sweden	-
Noralone	Taro	Israel	-
Norandrol	Panther-Osfa	Italy	-
Norandros	Castillon	Spain	-
Norbalin	Bieffe	Italy	-
Noromon	Ibsa	Switz.	-
Norstenol	Ravizza	Italy	-
Sintabolin	A.F.I.	Italy	-
Strabolene	Isola-Ibi	Italy	-
Superanbolon	Spofa	Czechoslovakia	-
Superbolin	Labif	Italy	-
Turinabol	Jenapharm	E. Germany	-

Raw Materials

19-Nortestosterone
β-Phenylpropionyl chloride

Manufacturing Process

An ice-cold solution of 1.5 grams of 19-nortestosterone and 1.5 ml of dry

pyridine in 10 ml of dry benzene is prepared and a solution of 1.5 ml of β-phenylpropionyl chloride in 5 ml of dry benzene is added dropwise over a period of about 2 minutes with stirring. The resulting mixture is allowed to stand overnight under an atmosphere of nitrogen and then washed successively with cold 5% aqueous hydrochloric acid solution, cold 2.5% aqueous sodium hydroxide solution, and water. After drying over anhydrous sodium sulfate, the solvent is evaporated to give an almost colorless oil. Recrystallization from methanol gives white crystals of 19-nortestosterone 17-β-phenylpropionate, MP 91° to 92.5°C.

References

Merck Index 6214
Kleeman & Engel p. 621
PDR p. 1286
OCDS Vol. 1 p. 171 (1977)
I.N. p. 656
REM p. 999
Donia, R.A. and Ott, A.C.; US Patent 2,868,809; January 13, 1959; assigned to The Upjohn Company

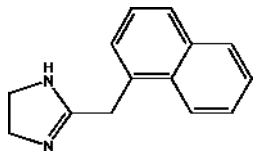
NAPHAZOLINE

Therapeutic Function: Nasal decongestant

Chemical Name: 4,5-Dihydro-2-(1-naphthalenylmethyl)-1H-imidazole

Common Name: 2-(1-Naphthylmethyl)imidazoline

Structural Formula:



Chemical Abstracts Registry No.: 835-31-4

Trade Name	Manufacturer	Country	Year Introduced
Privine	Ciba	US	1942
Albalon	Allergan	US	1970
Naphcon Forte	Alcon	US	1975
Clera	Person Covey	US	1978
Vasoclear	Smith, Miller and Patch	US	1979
Opcon	Muro	US	1981
Nafazair	Pharmafair	US	1983

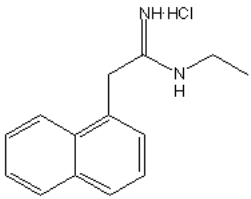
Trade Name	Manufacturer	Country	Year Introduced
Actinophtyl	Gregoire	France	-
Bactio-Rhin	Byk Liprandi	Argentina	-
Biogan	Recip	Sweden	-
Coldan	Sigmapharm	Austria	-
Degest-2	Barnes Hind	US	-
Gotinal	Promeco	Argentina	-
Imidazyl	Tubi Lux Pharma	Italy	-
Imidin	Ysat Wernigerode	E. Germany	-
Imizol	Farmigea	Italy	-
Murine	Abbott	UK	-
Naftazolina	Bruschettini	Italy	-
Naline	Ibsa	Switz.	-
Nasal Yer	Yer	Spain	-
Nomaze	Fisons	UK	-
Ocunasal	Sam-On	Israel	-
Pivanol	Tek	Turkey	-
Privin	Ciba	W. Germany	-
Proculin	Ankerwerk	E. Germany	-
Ran	Corvi	Italy	-
Rhinex S	Ysat Wernigerode	E. Germany	-
Rhinon	Petrasch	Austria	-
Rimidol	Leo	Sweden	-
Rinofug	Chimimport Export	Rumania	-
Vasoconstrictor	Pensa	Spain	-
Vistalbalon	Pharm-Allergan	W. Germany	-

Raw Materials

Naphthyl-(1)-acetonitrile
Ethanol
Methanol
Ethylene diamine

Manufacturing Process

2.7 parts of naphthyl-(1)-acetiminoethylether hydrochloride of the formula



(produced from naphthyl-(1)-acetonitrile and methanol) are dissolved in 12 parts of absolute alcohol. 1 part of ethylenediamine is then added and the

whole is heated to gentle boiling while passing nitrogen through it and simultaneously stirring until ammonia escapes no longer. The alcohol is then distilled and the residue mixed with 40 parts of benzene and 1.8 parts of caustic potash. Stirring is continued for some time whereby the imidazoline base is dissolved in benzene. The benzene residue is recrystallized several times from toluene.

References

Merck Index 6218
Kleeman & Engel p. 622
PDR pp. 728, 809, 1549
OCDS Vol. 1 p. 241 (1977)
I.N. p. 657
REM p. 888
Sonn, A.; US Patent 2,161,938; June 13, 1939; assigned to the Society of Chemical Industry in Basle, Switzerland

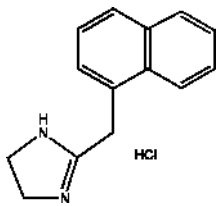
NAPHAZOLINE HYDROCHLORIDE

Therapeutic Function: Vasoconstrictor, Nasal decongestant

Chemical Name: 2-Imidazoline, 2-(1-naphthylmethyl)-, monohydrochloride

Common Name: Nafazolin(a) hydrochloride; Naftazolina hydrochloride; Naphazoline hydrochloride; Naphtazoline hydrochloride; Naphthizin(um) hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 550-99-2

Trade Name	Manufacturer	Country	Year Introduced
Albalon	Allergan	Australia	-
Clear Eyes	Farnam Companies, Inc.	USA	-
Naphazoline Hydrochloride	Allergan	-	-
Niazol	Dahuachem	China	-
Rhinantin	Dahuachem	China	-

Trade Name	Manufacturer	Country	Year Introduced
Rinofug	Sc Meduman Sa	Rumania	-
Sanorin	Galena	Czech Republic	-
Vasoclear	CIBA Vision	-	-
Vasocon	Novartis	USA	-

Raw Materials

Naphtyl-(1)-acetiminoethylether
Ethylenediamine

Manufacturing Process

2.7 parts of naphtyl-(1)-acetiminoethylether (produced from naphthyl-1-acetonitrile) were dissolved in 12 parts of absolute alcohol. 1 part of ethylenediamine is then added and the mixture was heated to gentle boiling while passing it through nitrogen and simultaneously stirring until ammonia escaped no longer. The alcohol was is then distilled and the residue mixed with 40 parts of benzene and 1.8 parts of caustic potash. Stirring was continued for some time whereby the imidazoline base was dissolved in benzene. The benzene residue, is recrystallized several times from toluene. The 2-[naphthyl-1-methyl]-imidazoline represented the coloriless crystalls of melting point 252°-253°C. Its hydrochloride is easily soluble in water.

References

Sonn A., US Patent No. 2,161,938; June 13, 1939

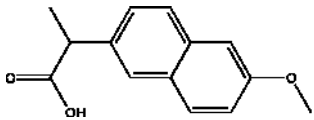
NAPROXEN

Therapeutic Function: Antiinflammatory

Chemical Name: (+)-6-Methoxy-α-methyl-2-naphthaleneacetic acid

Common Name: d-2-(6-Methoxy-2-naphthyl)propionic acid

Structural Formula:



Chemical Abstracts Registry No.: 22204-53-1

Trade Name	Manufacturer	Country	Year Introduced
Naprosyn	Syntex	UK	1973
Naprosyne	Cassenne	France	1975

Trade Name	Manufacturer	Country	Year Introduced
Proxen	Gruenenthal	W. Germany	1975
Naprosyn	Recordati	Italy	1975
Naprosyn	Syntex	Switz.	1975
Naprosyn	Syntex	US	1976
Naixan	Tanabe	Japan	1978
Congex	Nemi	Argentina	-
Floginax	Farmochimica	Italy	-
Gibixen	Gibipharma	Italy	-
Laser	Tosi-Novara	Italy	-
Madaprox	Madariaga	Spain	-
Naprium	Radiumpharma	Italy	-
Naprius	Magis	Italy	-
Naprux	Andromaco	Argentina	-
Naxyn	Teva	Israel	-
Novonaprox	Novopharm	Canada	-
Numide	Hosbon	Spain	-
Prexan	Lafare	Italy	-
Veradol	Schering	W. Germany	-
Xenar	Alfar Farma Clutici	Italy	-

Raw Materials

Sodium hydroxide
Magnesium
Cadmium chloride
2-Bromo-6-methoxynaphthalene
Ethyl-2-bromopropionate

Manufacturing Process

According to US Patent 3,658,858, a solution of 24 grams of 2-bromo-6-methoxynaphthalene in 300 ml of tetrahydrofuran is slowly added to 2.5 grams of magnesium turnings and 100 ml of tetrahydrofuran at reflux temperature. After the addition is complete, 20 grams of cadium chloride is added, and the resultant mixture is refluxed for 10 minutes to yield a solution of di-(6-methoxy-2-naphthyl)cadmium (which can be separated by conventional chromatography, although separation is unnecessary).

A solution of 18 grams of ethyl 2-bromopropionate in 20 ml of tetrahydrofuran is then added to the cooled reaction mixture. After 24 hours at 20°C, the product is hydrolyzed by adding 200 ml of 5 weight percent methanolic sodium hydroxide followed by heating to reflux for 1 hour. The reaction mixture is then diluted with excess 1 N sulfuric acid and extracted with ether. The ether phase is separated, evaporated to dryness and the residue is recrystallized from acetone-hexane to yield 2-(6-methoxy-2-naphthyl)propionic acid.

References

Merck Index 6269
Kleeman & Engel p. 623
PDR p. 1801

OCDS Vol. 1 p. 86 (1977)
DOT 9 (9) 384 (1973) & 10 (3) 95 (1974)
I.N. p. 658
REM p. 1119
Alvarez, F.S.; US Patent 3,637,767; January 25, 1972; assigned to Syntex Corp., Panama Harrison, I.T.; US Patent 3,658,858; April 25, 1972; assigned to Syntex Corp., Panama Alvarez, F.S.; US Patent 3,663,584; May 16, 1972; assigned to Syntex Corp., Panama

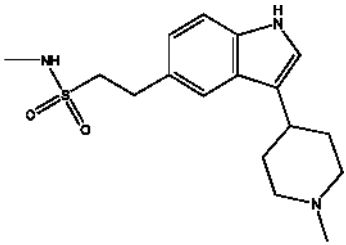
NARATRIPTAN

Therapeutic Function: Serotonin antagonist, Migraine therapy

Chemical Name: 1H-Indole-5-ethanesulfonamide, N-methyl-3-(1-methyl-4-piperidinyl)-

Common Name: Naratriptan

Structural Formula:



Chemical Abstracts Registry No.: 121679-13-8

Trade Name	Manufacturer	Country	Year Introduced
Amerge	Glaxo Wellcome	UK	-
GR 85548 X	GlaxoSmithKline	USA	-
Naratriptan	GlaxoSmithKline	USA	-

Raw Materials

N-Methyl-4-piperidone
Oxalic acid
Palladium on carbon
4-Hydrazino-N-methyl-benzenethanesulphonamide
N-Methyl-1H-indole-5-ethanesulphonamide
1-Methyl-4-piperidineacetaldehyde

Manufacturing Process

N-Methyl-3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indole-5-ethanesulphonamide oxalate

A solution of N-methyl-1H-indole-5-ethanesulphonamide (1.0 g) in methanol (50 ml) containing potassium hydroxide (5.6 g) and N-methyl-4-piperidone (1.0 ml) was heated at reflux for 24 h, cooled, and the resulting solid filtered off (1.0 g). A sample of the solid (0.2 g) was dissolved in a hot methanolic solution of oxalic acid (0.06 g), the solution cooled, and the salt precipitated by adding ethyl acetate (20 ml) and dry ether (50 ml). The salt was filtered off, and dried in vacuo to give the title compound as a solid (0.12 g), m.p. 87°-90°C (shrinks).

Analysis Found: C,52.2; H,5.6; N,9.5. $C_{17}H_{23}N_3O_2S \cdot C_2H_2O_4 \cdot 0.6H_2O$ requires C,52.5; H,6.0; N,9.7%.

N-Methyl-3-(1-methyl-4 -piperidinyl)-1H-indole-5-ethansulphonamide

N-Methyl-3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indole-5-ethanesulphonamide oxalate (as the free base) (0.36 g, 0.001 mol) in absolute alcohol (70 ml) and anhydrous dimethylformamide (5 ml) was hydrogenated, in the presence of 5% palladium on activated carbon (0.36 g) at ambient temperature and atmospheric pressure. After 20 h, hydrogen absorption (25 cm^3, theoretical = 24 cm^3) ceased. The catalyst was filtered off and the solvent removed in vacuo to given an opaque gum which solidified as a soft white solid (0.3 g). Purification by flash chromatography (Sorbsil C60 silica gel, CH_2Cl_2/EtOH/0.88 ammonia; 50:80:1) gave a colorless oil (0.21 g) that was triturated with ether to give the title compound (0.17 g) m.p. 156°-158°C. TLC SiO_2(CH_2Cl_2/EtOH/0.88 ammonia; 50:8:1) Rf 0.4.

N-Methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulphonamide may be prepared the another way.

A solution of 4-hydrazino-N-methyl-benzenethanesulphonamide (0.5 g) and 1-methyl-4-piperidineacetaldehyde (0.35 g) in a mixture of water (10 ml) of 2 N hydrochloric acid (1.0 ml, 2.00 mmol) was stirred for 2 days at room temperature. A further quantity of the aldehyde (0.35 g) was added and stirring continued for a further 30 min. The solution was then basified with 8% sodium bicarbonate to pH 8 and extracted with chloroform (3 times 50 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo to give the crude hydrazone as an oil (1.0 g). A solution of the hydrazone (1.0 g) in chloroform (20 ml) containing polyphosphate ester (10 g) was heated at reflux for 8 min. The solution was poured onto ice (200 g), stirred for 2 h treated with 2 M sodium carbonate (20 ml) and extracted with chloroform (3 times 50 ml). The combined organic extracts were dried (Na_2SO_4), evaporated in vacuo and the residue purified by flash chromatography (silica 9385, 100 g) eluting with CH_2Cl_2/EtOH/NH_3(75:8:1) to give impure material as a yellow oil. Further flash chromatography (silica 9385, 100 g) eluting with CH_2Cl_2/EtOH/NH_3 (100:8:1) gave the product as an oil (0.05 g). This was crystallised from ethyl acetate to give the title compound solid m.p. 156°-157°C. TLC SiO_2(CH_2Cl_2/EtOH/NH_3(50:8:1)) Rf 0.6.

References

Oxford A.W. et al.; US Patent No. 4,997,841; Mar. 5, 1991; Assigned to Glaxo Group Limited, England

EPA No. 0,303,507 A2, 12.08.88

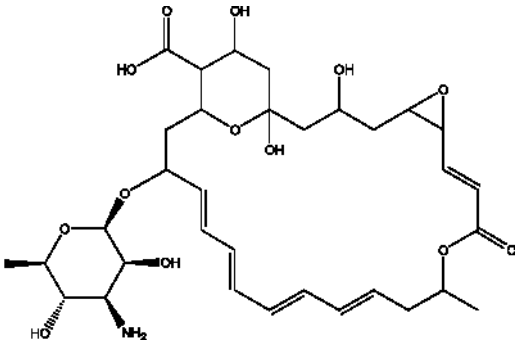
NATAMYCIN

Therapeutic Function: Antibacterial (ophthalmic)

Chemical Name: Natamycin

Common Name: Pimaricin

Structural Formula:



Chemical Abstracts Registry No.: 7681-93-8

Trade Name	Manufacturer	Country	Year Introduced
Pimafucine	Beytout	France	1964
Pimafucin	Brocades	UK	1965
Pimafucort	Brocades	Italy	1966
Pimafucin	Basotherm	W. Germany	1967
Natacyn	Alcon	US	1979
Myprozine	Lederle	US	-

Raw Materials

Bacterium Streptomyces gilvosporeus
Starch
Corn steep liquor

Manufacturing Process

The Fermentation Process: The process by which this antifungal substance is produced is an aerobic fermentation of an aqueous nutrient medium

inoculated with a pimaricin-producing strain of Streptomyces gilvosporeus. The nutrient medium contains an assimilable source of carbon such as starch, molasses, or glycerol, an assimilable source of nitrogen such as corn steep liquor and inorganic cations such as potassium, sodium or calcium, and anions such as sulfate, phosphate or chloride. Trace elements such as boron, molybdenum or copper are supplied as needed in the form of impurities by the other constituents of the medium.

In more detail the nutrient medium used may contain sources of carbon such as starch, hydrolyzed starch, sugars such as lactose, maltose, dextrose, sucrose, or sugar sources such as molasses; alcohols, such as glycerol and mannitol; organic acids, such as citric acid and acetic acid; and various natural products which may contain other nutrient materials in addition to carbonaceous substances.

Nitrogen sources include proteins, such as casein, zein, lactalbumin; protein hydrolyzates such proteoses, peptones, peptides, and commercially available materials, such as N-Z Amine which is understood to be a casein hydrolyzate; also corn steep liquor, soybean meal, gluten, cottonseed meal, fish meal, meat extracts, stick liquor, liver cake, yeast extracts and distillers' solubles; amino acids, urea, ammonium and nitrate salts. Such inorganic elements as sodium, potassium, calcium and magnesium; and chlorides, sulfates, phosphates and combinations of these anions and cations in the form of mineral salts may be advantageously used in the fermentation.

The so-called trace elements, such as boron, cobalt, iron, copper, zinc, manganese, chromium, molybdenum and still others may also be used to advantage. Generally, these trace elements occur in sufficient quantities in the carbonaceous and nitrogenous constituents of the medium, particularly if derived from natural sources, or in the tap water, and the addition of further quantities of these trace elements may consequently be unnecessary.

The fermentation liquor is aerated in the customary manner by forcing sterile air through the fermenting mixture usually at the rate of about 1 volume of air per volume of fermentation medium per minute. To minimize contamination with foreign microorganisms, the fermentation vessels should be closed and a pressure of 2 to 15 pounds above atmospheric pressure maintained in the vessel. In addition to the agitation provided by aeration, mechanical agitation is generally desirable. Antifoaming agents, such as 1% octadecanol in lard oil, may be added from time to time as required to prevent excessive foaming. Fermentation is conducted at a temperature preferably on the order of 26°C to 30°C but may be as low as 17°C or as high as 42°C.

The time required for maximum production of the antifungal substance will vary considerably depending upon other conditions of the fermentation. Generally, about 48 hours is required before appreciable quantities of the antifungal substance are detected in the medium. The production of the antifungal substance increases with time, and the fermentation may run as long as 120 hours. The hydrogen ion conditions normally vary from about pH 6 to pH 8.0, although deviations from these values are permissible, according to British Patent 846,933. The reader is referred to the patents cited for detals of pimaricin purification.

References

Merck Index 6278
Kleeman & Engel p. 624
DOT 14 (6) 255 (1978)
I.N. p. 659
REM p. 1230
Koninkijke Nederlandsche Gist- & Spiritusfabriek N.V., Netherlands; British Patent 844,289; August 10, 1960
American Cyanamid Company; British Patent 846,933; September 7, 1960

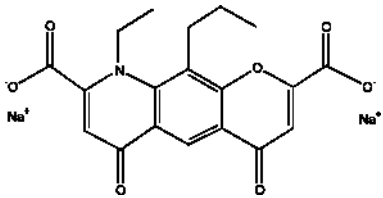
NEDOCROMIL DISODIUM

Therapeutic Function: Antiallergic, Anti-asthmatic

Chemical Name: 4H-Pyrano(3,2-g)quinoline-2,8-dicarboxylic acid, 9-ethyl-6,9-dihydro-4,6-dioxo-10-propyl-, disodium salt

Common Name: Nedocromil sodium

Structural Formula:



Chemical Abstracts Registry No.: 69049-74-7; 69049-73-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Alocril	Allergan	USA	-
Cetimil	Lab. Lesvi	-	-
Irtan	Rhone-Poulenc Rorer	France	-
Halamid	Viatris	Germany	-
Halamid	ASTA Medica AWD	-	-
Kovilen	Mediolanum Farmaceutici S.p.A.	Italy	-
Nedocromil Disodium	Rhone-Poulenc Rorer	France	-
Tilade	Rhone-Poulenc Rorer	France	-
Tilade Mint.	Fisons	UK	-
Tilavist	Fisons	UK	-
Tilavist	Aventis Pharma AB	Sweden	-

Raw Materials

Allyl bromide
4-Acetamido-2-hydroxyacetophenone
Sodium ethoxide
Dimethyl acetylene dicarboxylate
Polyphosphoric acid

Manufacturing Process

4,6-Dioxo-10-propyl-4H,6H-pyrano[3,2-]quinoline-2,8-dicarbxylic acid disodium salt was prepared in 8 steps

1. 4-Acetamido-2-allylacetophenone

4-Acetamido-2-hydroxyacetophenone (19.3 g), allyl bromide (12.1 ml) and hydrous potassium carbonate (21.5 g) were stirred in dry dimethylformamide (250 ml) at room temperature for 24 hours. The reaction mixture was poured into water and the product was extracted with ethyl acetate. The organic solution was then washed well with water dried over magnesium sulphate and evaporated to dryness. The sub-title product was obtained as buff coloured solid (20.5 g). The structure of the product was confirmed by NMR and mass spectroscopy.

2. 4-Acetamido-3-allyl-2-hydroxyacetophenone

The above allyl ether (18.4 g) was heated at 200-210°C for 4 hours. 17.1 g of the thermally rearranged sub- title product was obtained as a brown solid. Again the structure was confirmed by NMR and mass spectroscopy.

3. 4-Acetamido-2-hydroxy-3-propyl acetophenone

The product of step 2 (17 g) was dissolved in glacial acetic acid and hydrogenated in the presence of Adams catalyst until hydrogen uptake had ceased. The catalyst was filtered off through a keiselguhr filter and the filtrate was evaporated to leave 13.0 g of almost colorless solid. The mass and NMR spectra confirmed the structure of product.

4. Ethyl-7-acetamido-4-oxo-8-propyl-4H-l-benzopyran-2-carboxylate

A mixture of diethyl oxalate (19.3 g; 17.9 ml) and the above product of step 3 (12.4 g) in dry ethanol (100 ml) was added to a stirred solution of sodium ethoxide in ethanol (prepared by dissolving sodium (6.1 g) in dry ethanol (200 ml)). The reaction mixture was refluxed for 3 hours and then poured into dilute hydrochloric acid and chloroform. The chloroform layer was separated, washed with water and dried. The solvent was evaporated to leave a brown solid which was dissolved in ethanol (300 ml) containing concentrated hydrochloric acid (3 ml) and the whole was refluxed for 1 hour. The reaction mixture was poured into water and the product was extracted into ethyl acetate which was washed with water and dried. The solvent was evaporated to leave 10 g of a sticky solid which had mass and NMR spectra consistent with the expected product.

5. Ethyl 7-amino-4-oxo-8-propyl-4H-1-benzopyran-2-carboxylate

A solution of the amide of step 4 (10 g) in ethanol (300 ml), containing concentrated hydrochloric acid (5 ml), was refluxed for 8 hours. The reaction mixture was diluted with water and extracted into ethyl acetate. The extract was washed with water, dried and the solvent was evaporated to leave a dark brown semi-solid. This was chromatographed on a silica gel column, using ether as eluant to give 4.8 g of the required product whose structure was confirmed by mass and NMR spectral evidence; mp 84-87°C.

6.8-Ethoxycarbonyl-2-methoxycarbonyl-4,6-dioxo-10-propyl-4H,6H-pyrano[3.2-g]quinoline

The amino benzopyran of step 5 (2.0 g) and dimethyl acetylene dicarboxylate (1.24 g; 1.01 ml) were refluxed in ethanol (30 ml) for 26 hours. The reaction mixture was cooled to 0°C and the insoluble yellow-brown solid was collected by filtration and washed with a little ethanol and dried to give 2.0 g of a product which was a mixture of maleic and fumaric esters obtained by Michael addition of the amine to the acetylene. This mixture of esters (2.0 g) was treated with polyphosphoric acid (30 ml) and heated on the steam bath with stirring for 20 minutes. The reaction mixture was then poured onto ice and stirred with ethyl acetate. The organic layer was separated, washed with water and dried. The solvent was evaporated to leave 1.6 g of a yellow orange solid. Recrystallisation of this solid from ethyl acetate gave the required product as fluffy orange needles, mp 187°-188°C.

7. 4,6-Dioxo-10-propyl-4H,6H-pyrano[3.2-g]quinoline-2,8-dicarboxylic acid

The above bis ester (2.5 g) was refluxed with sodium bicarbonate (1.64 g) in ethanol (100 ml) and water (50 ml) for 1.5 hours. The whole was poured into water and acidified to precipitate a gelatinous solid. This was collected by filtration, refluxed with ethanol and the product was separated by centrifugation (1.4 g), mp 303°-304°C dec. The structure of the product was confirmed by mass and NMR evidence.

8. Disodium 4,6-dioxo-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylate

The bis acid from step 6 (1.35 g) and sodium bicarbonate (0.661 g) in water (150 ml) were warmed and stirred until a clear solution was obtained. This solution was filtered and the filtrate was freeze dried to give 1.43 g of the required disodium salt.

References

Cairns H., Cox D.; G.B. Patent 2,022,078, 1979-12-12

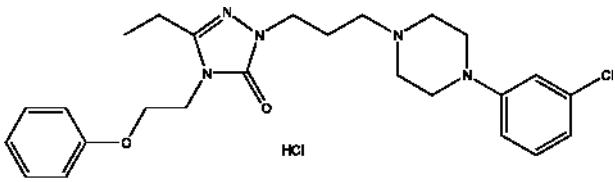
NEFAZODONE HYDROCHLORIDE

Therapeutic Function: Antidepressant

Chemical Name: 3H-1,2,4-Triazol-3-one, 2,4-dihydro-2-(3-(4-(3-chlorophenyl)-1-piperazinyl)propyl)-5-ethyl-4-(2-phenoxyethyl)-, monohydrochloride

Common Name: Nefazodone hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 82752-99-6; 83366-66-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Dutonin	Bristol-Myers Squibb	USA	-
Menfazona	Laboratorios Menarini, S. A.	Italy	-
Nefadar	Squibb-von Heyden	Germany	-
Nefazodone Hydrochloride	Bristol-Myers Squibb	USA	-
Reseril	Mead Johnson	USA	-
Rulivan	Europharma	-	-
Serzone	Bristol-Myers Squibb	Australia	-

Raw Materials

Hydrazine	1-(3-Chlorophenyl)-piperazine
Thionyl chloride	1-Bromo-3-chloropropane
Sodium azide	Phenoxypropionic acid
Sodium nitrite	Triethyl orthopropionate

Manufacturing Process

1. 1-(3-Chloropropyl)-4-(3-chlorophenyl)piperazine hydrochloride

A 25% NaOH solution (320 ml, 2.0 mol) is added dropwise to a stirred solution of 1-(3-chlorophenyl)-piperazine hydrochloride (196.5 g, 1.0 mol) and 1-bromo-3-chloropropane (99.0 ml, 1.0 mol) in acetone (200 ml) while maintaining temperature of 0°-10°C. After the addition is completed, the mixture is allowed to warm to room temperature and is stirred for 18 hours. The upper organic phase is then separated and concentrated under reduced pressure. The residual oil is taken up in 250 ml acetone and filtered. The filtrate is concentrated under reduced pressure and the oily residue is dissolved in 1 L of 15% boiling HCl solution. A viscous oil is separated from the cooled mixture and poured into 1 L of ice-H_2O with vigorous stirring,

forming white precipitates. Recrystallization of the solid from boiling water gave 171.8 g (55.6% yield) of 1-(3-chloropropyl)-4-(3-chlorophenyl) piperazine hydrochloride; m.p 199.5°-200.5°C.

2. 1-(3-Chlorophenyl)-4-(hydrazinopropyl)piperazine

1-(3-Chloropropyl)-4-(3-chlorophenyl)piperazine hydrochloride (20.0 g, 0.065 mol) is suspended in isopropanol (65 ml) and anhydrous hydrazine (31.7 g, 0.988 mol) is added. The reaction mixture is heated at 70°-80°C for 2.5 hours and cooled to room temperature. The upper layer is separated and concentrated under reduced pressure. The residue is dissolved in isopropanol (50 ml) and the upper layer is separated, dried (Na_2SO_4), and concentrated to yield 16.5 g (94.5% yield) of 1-(3-chlorophenyl)-4-(3-hydrazinopropyl) piperazine (85% pure) as a viscous oil. The product is used directly without further purification or stored at room temperature in toluene or isopropanol solution by adding 1% MgO.

The hydrazine is dissolved in isopropanol and 1% magnesium oxide is added. The mixture is stirred for 30 min and filtered. The filtrate is cooled with ice-bath and one equivalent of anhydrous HCl in isopropanol is added under vigorous stirring. The precipitates are collected by filtration and dried at 60°C under reduced pressure to afford white powder; mp 147°-150°C.

3. Phenoxypropionic acid (249.0 g, 1.50 mol) is dissolved in four equivalents of thionyl chloride (438.0 ml, 6.0 mol) and heated to reflux until the HCl evolution has ceased. The solution is then cooled to room temperature and concentrated under reduced pressure to give 281.0 g (100% yield) of phenoxypropionyl chloride as a brown oil which solidifies on cooling.

4. Phenoxypropionyl chloride (9.23 g, 0.05 mol) is dissolved in 100 ml acetone and cooled with an ice bath as sodium azide (3.6 g, 0.055 mol) in 10 ml water is added dropwise. After addition is completed, the reaction mixture is warmed to room temperature and stirred for 30 minutes. The solution is decanted and concentrated. The residue is dissolved in 100 ml ether and washed with saturated sodium bicarbonate and brine. The organic phase is separated, dried ($MgSO_4$) and concentrated to give 6.52 g (68.0% yield) of phenoxypropionyl azide as a yellow oil which solidifies on cooling

5. Ethyl phenoxypropionate

Phenoxypropionic acid (6.64 g, 0.04 mol) is mixed with excess ethanol (10 ml) and concentrated sulfuric acid (0.5 ml) is added. The reaction mixture is refluxed for 3 hours, cooled to room temperature and concentrated. The residue is washed with 1 N NaOH and brine, dried (Na_2SO_4), and concentrated to yield 7.32 g (94.3% yield) of the ester which can be used directly for the subsequent reaction without further purification.

6. Phenoxypropionyl hydrazide

Ethyl phenoxypropionate (161 g, 0.83 mol) is cooled with an ice bath and anhydrous hydrazine (32 ml, 1 mol) is added dropwise. After the addition is completed, the solution is warmed to room temperature and stirred for 4 hours. The solution is then cooled with an ice bath under vigorous stirring.

After the white precipitate formed the mixture is kept in refrigerator for 14 hours. The solid is collected by filtration, washed with cold 10% ethanol/hexane and dried in reduced pressure at 50°C for 12 hours to give 134.7 g (90%) of phenoxypropionyl hydrazide as white powder. Mp 66°-70°C.

The hydrochloride salt of phenoxypropionyl hydrazide is prepared by dissolving the hydrazide in dichloromethane, cooling with an ice bath and bubbling through anhydrous HCl gas until pH 3. The solid is collected by filtration, washed with cold dichloromethane and air-dried to give the hydrochloride salt as fine white powder, mp 172°-174°C.

7. Phenoxyethyl isocyanate

Method A: Phenoxypropionyl azide (15.2 g, 0.08 mol) is dissolved in 50 ml toluene and heated with an external oil bath. At 75°-80°C (internal temperature) vigorous N2evolution is observed and the reaction is very exothermic. The solution is refluxed for further 30 min after the gas evolution has finished. The solution is concentrated and the residue is distilled in vacuo to give 7.8 g (60% yield) of phenoxyethyl isocyanate as a colorless oil (94°-96°C, 1 mm Hg).

Method B: Phenoxypropionyl hydrazide (125.9 g, 0.7 mol) is suspended in 650 ml ice-water and concentrated hydrochloric acid (123 ml, 1.47 mol) was added. The mixture is stirred for 20 min and toluene (350 ml) is added. A solution of sodium nitrite (53.1 g, 0.77 mol) in 200 ml water is added over a period 15 min. The internal temperature is kept below 15°C and if necessary, ice is directly added to the reaction mixture. After the addition is completed the mixture is stirred for a further 1 hour and filtered through Celite. The solid is washed with 30 ml toluene and the filtrate is separated. The aqueous layer is extracted with 200 ml toluene and the combined toluene solutions are dried over $MgSO_4$. The dried toluene solution is filtered and added dropwise to a preheated flask at 95°-100°C. Nitrogen evolution occurs as the solution is dropped in. After the addition is complete, the reaction mixture is heated to gentle reflux until nitrogen evolution has ceased. The reaction mixture is cooled to room temperature and can be used directly in subsequent reactions. 1 ml of the reaction mixture is withdrawn and evaporated to dryness, and the weight of the residue is measured. This provides an estimate of the concentration of isocyanate per ml of reaction mixture.

8.2-3-(4-[3-Chlorophenyl]-1-piperazinyl)propyl]-4-(2-phenoxyethyl)-semicarbazide)

A solution of phenoxyethyl isocyanate (89 g, 0.55 mol) in toluene (450 ml) is generated in situ (see step 7) and cooled to -20°C. To the solution is added a solution of 1-(3-chlorophenyl)-4-(3-hydrazinopropyl)piperazine (131.2 g, 0.49 mol) in 100 ml toluene at the speed that the internal temperature is below -10°C. After the addition is completed the mixture is stirred for 30 min at -20°C and for 1.5 hours at 0°C and quenched with 150 ml 1 N NaOH solution. The mixture is stirred at 0°C for 10 min and filtered through celite. The filtrate is saturated with NaCl and separated. The aqueous layer is extracted with 100 ml toluene and the combined toluene solution was dried over Na_2SO_4, filtered and concentrated to give a viscous oil. A small amount sample was purified by column chromatography (5% MeOH/CH_2Cl_2) to give a colorless oil. The crude

product is dissolved in isopropanol, cooled with ice bath, and two equivalents of HCl/isopropanol are added. The precipitates are collected by filtration and further purified by recrystallization from ethanol to give 170.6 g (69%) of hydrochloride salt as white crystal. Mp 172°-176°C.

9.2-[3-4-(3-Chlorophenyl)-1-piperazinyl]-propyl]-5-ethyl-4-(2-phenoxyethyl)-2H-1,2,4-triazol-3(4H)-one monohydrochloride (Nefazodone monohydrochloride)

2-[3-(4-[3-Chlorophenyl-1-piperazinyl)propyl]-4-(2-phenoxyethyl)-semicarbazidedihydrochloride (23.3 g, 46 mmol) is suspended in 50 ml toluene and refluxing with Dean-Stark apparatus to remove water. The mixture is then cooled to room temperature and triethyl orthopropionate (50 ml, about 5 eq) is added. The suspension is refluxed again with Dean-Stark apparatus. As toluene is distilled the suspension becomes a clear solution which is refluxed for 48 hours. Distillation under reduced pressure removes unreacted trietyl orthopropionate and the resulting residue is dissolved in 50 ml isopropanol, treated with HCl to pH 4, stirred at 0°C for 1 hour and standed in refrigerator for 12 hours. The solid is collected with filtration and recrystallized from ethanol to give 10.5 g (45%) of nefazodone monohydrochloride as white powder (95% pure by HPLC). Further purification is achieved by fractional recrystallization to give the product with 99.5% purity. mp 183°-185°C.

References

Lei B. et al.; US Patent No. 5,900,485; May 4, 1999; Assigned to Apotex, Inc., Weston, Canada
Murthy K.S.K. et al.; US Patent No. 6,596,866 B2; Jul. 22, 2003; Assigned to Brantford Chemicals Inc., Banntford

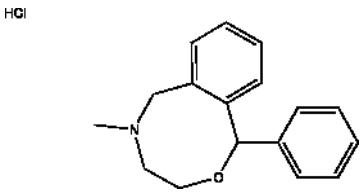
NEFOPAM HYDROCHLORIDE

Therapeutic Function: Muscle relaxant, Antidepressant

Chemical Name: 3,4,5,6-Tetrahydro-5-methyl-1-phenyl-1H-2,5-benzoxazocine hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 13669-70-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Ajan	Kettelhack Riker	W. Germany	1976
Acupan	Carnegie	UK	1978
Acupan	Riker	France	1981
Lenipan	Chiesi	Italy	1981
Oxadol	I.S.I.	Italy	1982
Acupan	Boehringer Mannheim	Italy	1983

Raw Materials

2-Benzoylbenzoic acid
2-Methylaminoethanol
4-Toluenesulfonic acid
Thionyl chloride
Lithium aluminum hydride
Hydrogen chloride

Manufacturing Process

The starting material is prepared by reacting 2-benzoylbenzoic acid with thionyl chloride and then with 2-methylaminoethanol. 20.0 grams (0.07 mol) of N-(2-hydroxyethyl)-N-methyl-o-benzoylbenzamide is suspended in 100 ml tetrahydrofuran and then slowly added in small portions to a solution of 5.5 grams (0.14 mol) of lithium aluminum hydride in 150 ml tetrahydrofuran with cooling and stirring. The mixture is then refluxed for 18 hours, cooled and then to it is successively added 5.5 ml water, 5.5 ml of 3.75 N sodium hydroxide and 16 ml water. After removal of precipitated salts by filtration, the solution remaining is concentrated under reduced pressure and the residue dried to yield 19.5 grams of crude product. Yield after conversion to the hydrochloride salt and recrystallization is 17.0 grams (89%), MP 128° to 133°C.

5-methyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f] -2,5-oxazocine is prepared as follows. 3.0 grams (0.011 mol) of 2-([N-(2-hydroxyethyl)-N-methyl]amino)methylbenzhydrol, prepared as described above, 3.0 grams p-toluenesulfonic acid and 15 ml benzene are heated together with stirring until all the benzene is distilled off. The residual oil is heated to 105°C and held at this temperature for 1 hour, then cooled and dissolved in 30 ml water. This aqueous solution is then basified to pH 10.0 with 12 N sodium hydroxide, extracted with ether, and the extracts washed with water, dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. The 2.26 grams (81%) oil remaining is converted to the hydrochloride salt, MP 238° to 242°C.

References

Merck Index 6287
Kleeman & Engel p. 626
OCDS Vol. 2 p. 447 (1980)
DOT 12 (7) 275 (1976)

I.N. p. 661
Baltes, B.J.; US Patent 3,487,153; December 30, 1969; assigned to Rexall Drug and Chemical Company

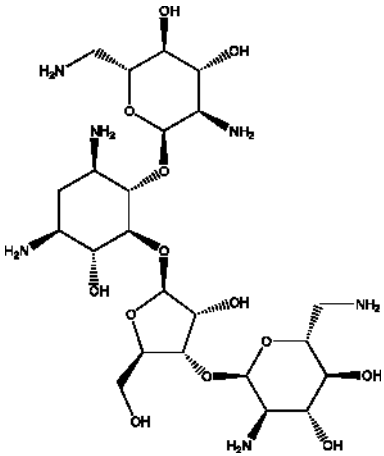
NEOMYCIN

Therapeutic Function: Antibacterial

Chemical Name: O-2,6-Diamino-2,6-dideoxy-α-D-glucopyranosyl-(1->3)-O-β-D-ribofuranosyl(1->5)-O-[2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl-(1->4)]-2-deoxy-D-streptamine

Common Name: Framycetin

Structural Formula:



Chemical Abstracts Registry No.: 1404-04-2; 4146-30-9 (Sulfate salt)

Trade Name	Manufacturer	Country	Year Introduced
Myciguent	Upjohn	US	1951
Otobiotic	Schering	US	1954
Mycifradin	Upjohn	US	1957
Neobiotic	Pfizer	US	1958
Apokalin	A.L.	Norway	-
Biofradin	Uriach	Spain	-
Bykomycin	Byk Gulden	W. Germany	-
Cortisporin	Burroughs-Wellcome	US	-
Dexmy	Takeda	Japan	-

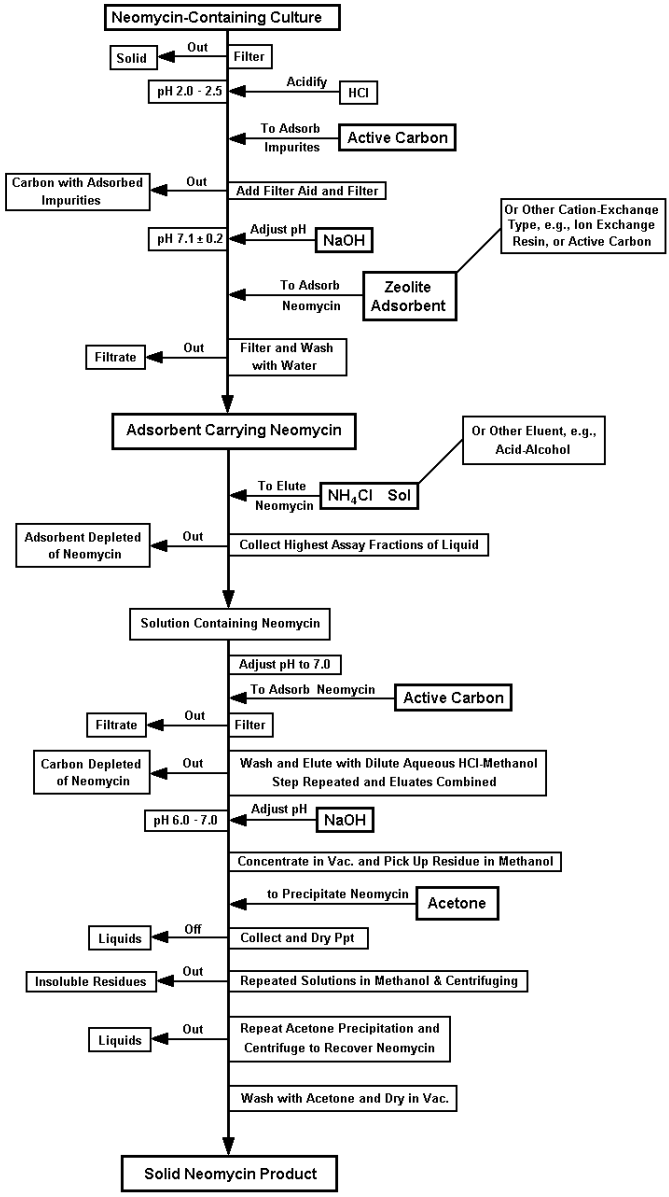
Trade Name	Manufacturer	Country	Year Introduced
Endomixin	Lusofarmaco	Italy	-
Fradio	Nippon Kayaku, Co.	Japan	-
Fradyl	Christiaens	Belgium	-
Ivax	Boots	UK	-
Larmicin	Larma	Spain	-
Myacyne	Werner Schnur	W. Germany	-
Mytrex	Savage	US	-
Neobretin	Norbrook	UK	-
Neodecadron	MSD	US	-
Neointestin	Hosbon	Spain	-
Neolate	Therafarm	UK	-
Neomicina Roger	Roger	Spain	-
Neomin	Glaxo	UK	-
Neo-Polycin	Merrell Dow	US	-
Neopt	Sigma	Australia	-
Neosporin	Burroughs-Wellcome	US	-
Neosulf	Protea	Australia	-
Neo-Synalar	Syntex	US	-
Octicair	Pharmafair	US	-
Otocort	Lemmon	US	-
Siquent	Sigma	Australia	-
Tampovagan	Norgine	UK	-
Topisporin	Pharmafair	US	-
Tri-Thalmic	Schein	US	-

Raw Materials

Bacterium Streptomyces fradiae
Nutrient medium

Manufacturing Process

Neomycin has been produced by growing the organism, Strepromyces No. 3535, in a suitable nutrient medium under appropriate stationary or submerged aerobic (viz shaken) conditions, and then isolating and purifying the substance, e.g., by procedure of the sort described in the figure including various steps of adsorption, recovery by elution, separation from impurities, and precipitation.



Neomycin is usually used as the sulfate.

References

Merck Index 6300

Kleeman & Engel 626
PDR pp.673, 738, 756, 888, 993, 1034, 1206, 1232, 1429, 1569, 1604, 1800
I.N. p. 663
REM p. 1181
Waksman, S.A. and Lechevalier, H.A.; US Patent 2,799,620; July 16, 1957; assigned to Rutgers Research and Educational Foundation
Jackson, W.G.; US Patent 2,848,365; August 19, 1958; assigned to The Upjohn Company
Miller, T.W.; US Patent 3,005,815; October 24, 1961; assigned to Merck & Co., Inc.
Moses, W.; US Patent 3,022,228; February 20, 1962; assigned to S.B. Penick & Company
Haak, W.J.; US Patent 3,108,996; October 29, 1963; assigned to The Upjohn Company

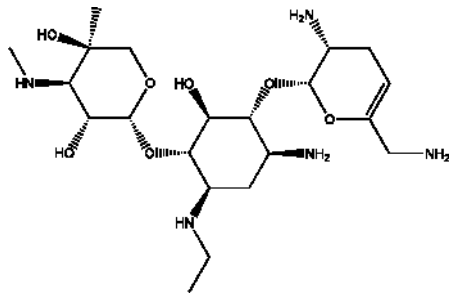
NETILMICIN

Therapeutic Function: Antibiotic

Chemical Name: 1-N-Ethylsisomicin

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 56391-56-1

Trade Name	Manufacturer	Country	Year Introduced
Netromycine	Schering	Switz.	1980
Certomycin	Byk-Essex	W. Germany	1980
Netillin	Kirby-Warrick	UK	1981
Netromicine	Unicet	France	1981
Nettacin	Essex	Italy	1982
Netromycin	Schering	US	1983

Raw Materials

Sisomicin
Acetaldehyde
Sulfuric acid
Sodium cyanoborohydride

Manufacturing Process

To a solution of 5 g of sisomicin in 250 ml of water add 1 N sulfuric acid until the pH of the solution is adjusted to about 5. To the solution of sisomicin sulfuric acid addition salt thereby formed, add 2 ml of acetaldehyde, stir for 10 minutes, then add 0.85 g of sodium cyanoborohydride. Continue stirring at room temperature for 15 minutes, then concentrate solution in vacuo to a volume of about 100 ml, treat the solution with a basic ion exchange resin [e.g., Amberlite IRA 401S (OH^-)], then lyophilize to a residue comprising 1-N-ethylsisomicin.

Purify by chromatographing on 200 g of silica gel, eluting with lower phase of a chloroformmethanol-7% aqueous ammonium hydroxide (2:1:1) system. Combine the eluates as determined by thin layer chromatography and concentrate the combined eluates of the major component in vacuo to a residue comprising 1-N-ethylsisomicin (yield 1.25 g). Further purify by again chromatographing on 100 g of silica gel eluting with a chloroform-methanol-3.5% ammonium hydroxide (1:2:1) system. Pass the combined, like eluates (as determined by thin layer chromatography) through a column of basic ion exchange resin and lyophilize the eluate to obtain 1-N-ethylsisomicin (yield 0.54 g).

There is also a fermentation route to netilmicin as noted by Kleeman & Engel.

References

Merck Index 6322
DFU 3 (7) 527 (1978)
Kleeman & Engel p. 627
PDR p. 1635
DOT 17 (8) 324 (1981)
I.N. p. 666
REM p. 1183
Wright, J.J., Daniels, P.J.L., Mallams, A.K. and Nagabhushan, T.L.; US Patent 4,002,742; January 11, 1977; assigned to Schering Corp.

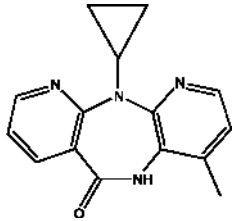
NEVIRAPINE

Therapeutic Function: Antiviral

Chemical Name: 5H-Dipyrido(3,2-b:2',3'-e)(1,4)diazepin-6-one, 5,11-dihydro-11-cyclopropyl-4-methyl-

Common Name: Nevirapine

Structural Formula:



Chemical Abstracts Registry No.: 129618-40-2

Trade Name	Manufacturer	Country	Year Introduced
Neve	Le Sante	India	-
Nevimune	Cipla Limited	India	-
Nevirapine	Boehringer Ingelheim Pharma	USA	-
NVP	Roxane Laboratories	USA	-
Viramune	Boehringer Ingelheim Pharma	Germany	-
Viramune	Cipla Limited	India	-
Viramune	Roxane Laboratories	USA	-
Viramine	Boehringer Ingelheim Pharma	USA	-

Raw Materials

Calcium oxide
Sodium hydride
Cyclopropylamine
Diethylene glycoldimethyl ether
2-Chloro-N-(2-chloro-4-methyl-3-pyridyl)-3-pyridine carboxamide

Manufacturing Process

There are 3 ways for preparing of nevirapine.

117.5 kg of 2-chloro-N-(2-chloro-4-methyl-3-pyridyl)-3-pyridine carboxamide, 23.3 kg of calcium oxide and 59.4 kg of cyclopropylamine (molar ratio: 1:1:2.5) are heated to between 135° and 145°C in 235 L of diglyme (diethylene glycoldimethylether) in a 500 L VA autoclave over a period of 6 to 8 hours. The reaction mixture is then cooled to a temperature of 20°-30°C and filtered. The filter cake is washed with 58.8 L of diglyme. The filtrates are combined and initially 200 L of solvent is distilled off. The residue is then diluted with a further 117.5 L of diglyme. The resultant diluted solution is added over a period of 20 to 40 minutes to a suspension of 45.0 kg of 60% sodium hydride in 352.5 L of diglyme, heated to 130°C. The storage vessel and conduits are rinsed with a further 55.8 L of diglyme, and the mixture is stirred at a temperature of between 130° and 140°C for a further 30 to 60 minutes. The majority of the diglyme is then distilled off. Finally, the

remaining residue is carefully mixed with 470 L of water. After cooling to a temperature of about 25°C, 235.0 L of cyclohexane and 57.11 of glacial acetic acid are added to the reaction mixture. The mixture is then stirred for about 1 hour at temperature of 10° to 25°C. The resultant suspension is centrifuged and the centrifuged material is then washed with 235.0 L of methyl-tert-butylether and subsequently with 353.5 L of water and finally with 235 L of ethanol. In this way, after drying, 92.5 kg (83.5% of theory) of 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one (nevirapine) is isolated.

117.5 kg of 2-chloro-N-(2-chloro-4-methyl-3-pyridyl)-3-pyridine carboxamide, 46.7 kg of calcium oxide and 47.5 kg of cyclopropylamine (molar ratio: 1:2:2) are heated to 135° to 145°C in 235 L of diglyme (diethylene glycol dimethylether) in a 500 L VA autoclave over a period of 6 to 8 hours. The reaction mixture is then cooled to a temperature of 20° to 30°C and filtered. The filter cake is washed with 58.8 L of diglyme. The filtrates are combined and about 188 L of solvent is distilled off. The residue is then diluted with a further 117.5 L of diglyme. Over a period of 20 to 40 minutes, the resultant diluted solution is added to a suspension of 45.0 kg of 60% sodium hydride in 352.5 L of diglyme, heated to 130°C. The storage vessel and conduits are rinsed with a further 55.8 L of diglyme and the mixture is stirred at a temperature of 130° to 140°C for a further 30 to 60 minutes. The majority of the diglyme is then distilled off. Finally, the remaining residue is carefully mixed with 470.0 L of water. The reaction mixture is cooled to a temperature of about 25°C and 235.0 L of cyclohexane and 57.1 L of glacial acetic acid are added. The mixture is then stirred for about 1 hour at a temperature of 10o to 25°C. The resultant suspension is centrifuged and the centrifuged material is washed with 235.0 L of methyl tert-butylether, followed by 353.5 L of water and finally with 235 L of ethanol. In this way, after drying, 90.6 kg (81.7% of theory) of 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido-[3,2-b:2',3'-e][1,4]diazepin-6-one (nevirapine) is isolated.

287.2 kg of 2-chloro-N-(2-chloro-4-methyl-3-pyridyl)-3-pyridine carboxamide, 57.0 kg of calcium oxide and 87.1 kg of cyclopropylamine (molar ratio: 1:1:1.5) are heated in 574 L of diglyme (diethylene glycol-dimethylether) to 135°-145°C for about 30 minutes in a 1200 L VA stirring apparatus. This produces a pressure of 1.2-1.5 bar and about 50% of the starting material is reacted. To this mixture, over about 30 minutes at 135°-145°C, a further 58.1 kg of cyclopropylamine is added producing a pressure of 3.0-3.5 bar, and another 25% of the starting material is reacted. The mixture is then kept at 135°-145°C for a period of 5 to 6 hours. The reaction mixture is then cooled to a temperature of 20° to 30°C and filtered. The filter cake is washed with 144 L of diglyme. The filtrates are combined and 400 L of solvent is distilled off. The residue is then diluted with a further 287 L of diglyme. Over 20-40 minutes, the resultant diluted solution is added to a suspension of 110 kg of 60% sodium hydride in 862 L of diglyme, heated to 130°C. The storage vessel and conduits are rinsed with a further 144 L of diglyme and the mixture is stirred at a temperature of 130° to 140°C for another 30 to 60 minutes. The majority of the diglyme is then distilled off. Finally, the remaining residue is carefully mixed with 1150 L of water. After the reaction mixture has been cooled to a temperature of about 25°C, 575 L of cyclohexane and 147 L of glacial acetic acid are added. The mixture is then stirred for about 1 hour at a temperature of 10°-25°C. The resultant suspension is centrifuged and the centrifuged material is then washed with 575 L of methyl-tert-butylether, followed by 862 L of water and finally with 575 L of ethanol. In this way, after

drying, 225 kg (83.0% of theory) of 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b :2',3'-e][1,4]diazepin-6-one (nevirapine) is obtained.

References

Schneider H. et al.; US Patent No. 5,559,760; Oct. 29, 1996; Assigned to Boehringer Ingelheim KG, Ingelheim am Rhein, Germany

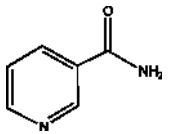
NIACINAMIDE

Therapeutic Function: Enzyme cofactor vitamin

Chemical Name: 3-Pyridinecarboxylic acid amide

Common Name: Aminicotin; Niacinamide; Nicosylamide; Nicotilamid(e); Nicotinamide; Nicotinsaureamid; Nikotinsaureamid; Vitamin B_3; Vitamin PP; Vitaminum pellagrapraeventivum; Witamina PP

Structural Formula:



Chemical Abstracts Registry No.: 98-92-0

Trade Name	Manufacturer	Country	Year Introduced
Niacinamide	Twinlab	-	-
Niazcol	Locatelli	-	-
Nicotinamide	Endur-Amide TM, Innovite Inc.	USA	-
Vitamin B_3	Twinlab	-	-
Vitamin B_3	Biocare	-	-

Raw Materials

Gaseous ammonia Nicotinic aci
Anhydrous ethyl acetate

Manufacturing Process

Gaseous ammonia was passed into nicotinic acid at a temperature between 200-235°C until the conversion to nicotinamide was 85%. The reaction mixture was colored light brown. The reaction mass was cooled and grounds to a fine powder. Fifty grams of this crude nicotinamide were boiled with 500 ml of anhydrous ethyl acetate until a dark solution was. obtained. A little solid

remained in suspension. Gaseous ammonia was passed in below the surface of the ethyl acetate at a temperature between 60-70°C. After a short time ammonium nicotinate started to precipitate out of solution as a brown solid. Sufficient gaseous ammonia, was passed into the ethyl acetate solution to insure complete precipitation of the nicotinic acids as ammonium nicotinate. The solution was filtered at about 60-70°C. The filter cake consisted of ammonium nicotinate, which, upon drying, weighed 12.4 grams. The filtrate was stirred arid boiled for 20 minutes with one-half gram of activated carbon and two grams of activated adsorbent clay. The mixture was filtered hot. The filtrate was boiled twenty minutes with one-half gram of activated carbon and two grams of activated adsorbent clay and then filtered hot. The carbon and clay treatment was repeated once more. The final filtrate was cooled slowly with stirring to room temperature to precipitate white crystalline nieocinamide which, upon drying, weighed 26.7 grams and had a melting point of 129.5°C, and was over 99 percent pure. The mother liquor from the above filtration was boiled down to one-third of its volume and cooled to room temperature. A second crop of nicotinamide of three grams was obtained.

References

Truchan E. et al.; US Patent No. 2,993,051; July 18, 1961; Assigned to Cowles Chemical Company, Cleveland, Ohio, a corporation of Ohio

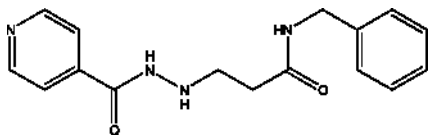
NIALAMIDE

Therapeutic Function: Antidepressant

Chemical Name: 4-Pyridinecarboxylic acid 2-[3-oxo-3-[(phenylmethyl)-amino]propyl]hydrazide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 51-12-7

Trade Name	Manufacturer	Country	Year Introduced
Niamid	Pfizer	US	1959
Niamide	Pfizer	France	1960
Niamid	Taito Pfizer	Japan	-
Nuredal	EGYT	Hungary	-
Surgex	Firma	Italy	-

Raw Materials

Isoniazid
Methyl acrylate
Benzylamine

Manufacturing Process

Methyl acrylate, 28.0 g (0.4 mol) was added dropwise during one hour to a solution containing 54.8 g (0.4 mol) of isonicotinic acid hydrazide (isoniazid) and 10 ml of glacial acetic acid in 400 ml of tertiary butyl alcohol. The resulting solution then was heated for 18 hours on a steam bath. Concentration of the reaction mixture to 100 ml yielded 13.0 g of unreacted isonicotinic acid hydrazide. The filtrate was concentrated to a thick syrup which was triturated with anhydrous ether and recrystallized from isopropyl alcohol; MP 87°C to 88.5°C. Elemental analysis of the product gave 1-isonicotinyl-2-(β-carbomethoxyethyl)hydrazine.

A slurry of 7.5 g (0.034 mol) of 1-isonicotinyl-2-(carbomethoxyethyl)-hydrazine and 5 ml of benzylamine is heated with stirring at 130°C for three hours. The cooled mass is then recrystallized from ethyl acetate to yield white needles melting at 151.1°C to 152.1°C.

References

Merck Index 6330
Kleeman & Engel p. 628
OCDS Vol. 1 p. 254 (1977)
I.N. p. 667
Bloom, B.M. and Carnahan, R.E.; US Patent 2,894,972; July 14, 1959; assigned to Chas. Pfizer and Co., Inc.

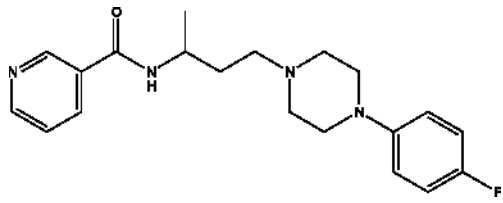
NIAPRAZINE

Therapeutic Function: Antihistaminic

Chemical Name: 1-(4-Fluorophenyl)-4-[3-(3-pyridoyl)amino]butyl-piperazine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 27367-90-4

Trade Name	Manufacturer	Country	Year Introduced
Nopron	Carrion	France	1976
Norpron	Riom	Italy	-

Raw Materials

Trioxymethylene
1-(4-Fluorophenyl)piperazine dihydrochloride
Acetone
Hydroxylamine hydrochloride
Nicotinic acid chloride
Lithium aluminum hydride

Manufacturing Process

1st Stage: 10 ml of concentrated (10 N) hydrochloric acid and 240 ml of acetone were added to a solution of 217.5 g (1 mol) of 1-(4-fluorophenyl)piperazine dihydrochloride in 400 ml of 96% ethanol. 50 g of powdered trioxymethylene were then added and the mixture was then slowly heated to reflux, which was maintained for 1 hour. A further 60 g of trioxymethylene were then added and heating to reflux was continued for a further 6 hours.

The mixture was then cooled, the precipitate formed was filtered off, washed with acetone and recrystallized from 96% ethanol.

The base was liberated from its salt by taking up the product in an aqueous solution of sodium bicarbonate. The precipitate of the base thus obtained was recrystallized from petroleum ether to give 160 g of the desired product; melting point 46°C; yield 64%.

2nd Stage: 45.5 g (0.65 mol) of hydroxylamine hydrochloride were added to a solution of 128 g (0.5 mol) of the amino-ketone obtained in the preceding stage in 100 ml of ethanol and 40 ml of water. The mixture was allowed to react for 15 minutes at room temperature and was then heated to reflux for ½ hour. A part of the solvent was then distilled off and the product was then allowed to crystallize on cooling. After recrystallization from 96% ethanol, 117 g of the desired product were obtained; melting point 170°C; yield 77%.

3rd Stage: 93 g (0.35 mol) of the oxime obtained in the preceding stage, in the form of the base, were added in portions to a suspension of 17 g (0.45 mol) of lithium aluminum hydride in 400 ml of anhydrous ether. The mixture was then heated to reflux for 15 hours.

10 ml of ethyl acetate and then 50 ml of dilute caustic soda were added slowly with the usual precautions to the mixture. The organic phase was separated, dried over anhydrous Na_2SO_4, the solvent was distilled off and the residue obtained was distilled under reduced pressure to give 51 g of a thick oil; boiling point (2 mm Hg), 142°C to 143°C; yield 58%.

4th Stage: 10 ml of triethylamine were added in a solution of 25.2 g (0.1 mol) of the amine obtained in the preceding stage in 100 ml of anhydrous chloroform and the mixture was cooled to 2°C to 3°C. While maintaining this temperature, 17 g (0.12 mol) of nicotinic acid chloride were added with vigorous agitation.

After evaporation of the solvent, the residue was washed with water, the product taking the form of a mass. After recrystallization from ethyl acetate, a constant melting point of 131°C was obtained.

References

Merck Index 6331
Kleeman & Engel p. 628
DOT 13 (1) 29 (1977)
I.N. p. 667
Mauvernay, R.Y., Busch, N., Simond, J. and Moleyre, J.; US Patent 3,712,893; January 23, 1973; assigned to SA Centre Europeen De Recherches Mauvernay, CERM

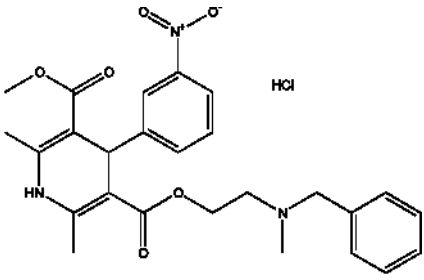
NICARDIPINE

Therapeutic Function: Vasodilator

Chemical Name: 2,6-Dimethyl-4-(3-nitrophenyl)-3-methoxycarbonyl-1,4-dihydropyridine-5-carboxylic acid-2(N-benzyl-N-methylamino)ethyl ester hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 55985-32-5

Trade Name	Manufacturer	Country	Year Introduced
Nicodel	Mitsui	Japan	1981
Perdipin	Yamanouchi	Japan	1981

Raw Materials

Acetoacetic acid N-benzyl-N-methylaminoethyl ester
β-Aminocrotonic acid methyl ester
m-Nitrobenzaldehyde

Manufacturing Process

A mixture of 4.98 g of acetoacetic acid N-benzyl-N-methylaminoethyl ester, 2.3 g of β-aminocrotonic acid methyl ester, and 3 g of m-nitrobenzaldehyde was stirred for 6 hours at 100°C in an oil bath. The reaction mixture was subjected to a silica gel column chromatography (diameter 4 cm and height 25 cm) and then eluted with a 20:1 mixture of chloroform and acetone. The effluent containing the subject product was concentrated and checked by thin layer chromatography. The powdery product thus obtained was dissolved in acetone and after adjusting the solution with an ethanol solution saturated with hydrogen chloride to pH 1-2, the solution was concentrated to provide 2 g of 2,6-dimethyl-4-(3'-nitrophenyl)1,4-dihydropyridine-3,5-dicarboxylic acid 3-methylester-5-β-(N-benzyl-N-methylamino)ethyl ester hydrochloride. The product thus obtained was then crystallized from an acetone mixture, melting point 136°C to 140°C (decomposed).

References

Merck Index 6334
DFU 2 (6) 409 (1977) (as Yc-93) & 4 (12) 911 (1979)
OCDS Vol. 3 p. 150 (1984)
DOT 18 (7) 325 (1982)
I.N. p. 668
Murakami, M., Takahashi, K., Iwanami, M., Fujimoto, M., Shibanuma, T., Kawai, R. and Takenaka, T.; US Patent 3,985,758; October 12, 1976; assigned to Yamanouchi Pharmaceutical Co., Ltd.

NICERGOLINE

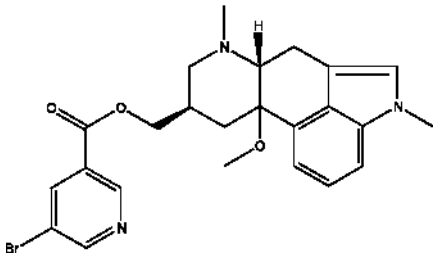
Therapeutic Function: Vasodilator

Chemical Name: 10-Methoxy-1,6-dimethylergoline-8β-methanol 5-bromonicotinate (ester)

Common Name: Nicotergoline; 1-Methyllumilysergol-8-(5-bromonicotinate)-10-methyl ether

Chemical Abstracts Registry No.: 27848-84-6

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Sermion	Farmitalia	Italy	1974
Sermion	Specia	France	1975
Nicergolyn	Farnex	Italy	-
Nicotergoline	Carlo Erba	Italy	-
Varson	Almirall	Spain	-
Vasospan	Exa	Argentina	-

Raw Materials

1-Methyl-lumilysergic acid
5-Bromonicotinyl chloride
Hydrogen chloride
Lithium aluminum hydride
Methanol

Manufacturing Process

Preparation of 1-Methyl Lumilysergic Acid 8-Methyl Ester-10-Methyl Ether: Into a suspension of 10 grams of 1-methyl-lumilysergic acid in 600 cc of absolute methanol a stream of anhydrous hydrogen chloride is bubbled for 1.5 hours with strong cooling. The stream of hydrogen chloride is stopped and the mixture is allowed to stand for 30 minutes at 0°C, and is evaporated in vacuo to dryness. The residue is taken up with ice-cooled water made alkaline with concentrated ammonia and extracted with chloroform. The combined chloroform extracts are washed first with a 5% aqueous solution of sodium bicarbonate, then with water, and are thereafter dried over anhydrous sodium sulfate and finally evaporated in vacuo to dryness.

Preparation of 1-Methyl Lumilysergol-10-Methyl Ether: To a boiling suspension of 2 grams of lithium aluminum hydride in 50 cc of anhydrous tetrahydrofuran, a solution of 1 gram of 1-methyl lumilysergic acid-8-methyl ester-10-methyl ether in 20 cc of anhydrous tetrahydrofuran is added dropwise and the resulting solution is refluxed for a further 2 hours. After cooling the resulting solution, aqueous tetrahydrofuran is added to destroy the excess reducing agent and the solution is filtered. Tetrahydrofuran is distilled off and the residue is recrystallized from acetone petroleum ether.

Preparation of Nicergoline: To a solution of 1-methyl lumilysergol-10-methyl ether in pyridine, 5-bromonicotinyl chloride is used as an acylating agent at

room temperature. The mixture is stirred for 1 hour. Water and methanol are added and the resulting mixture is stirred for 1 hour, extracted with chloroform, and washed in sequence with 1% aqueous caustic soda, 5% aqueous sodium bicarbonate solution, and water. The resulting solution is dried over anhydrous sodium sulfate and the solvent is distilled off. By recrystallization of the residue from acetone petroleum ether, nicergoline is obtained, melting at 136° to 138°C.

References

Merck Index 6335
Kleeman & Engel p. 629
OCDS Vol. 2 p. 478 (1980)
DOT 10 (12) 342 (1974)
I.N. p. 668
Bernardi, L., Bosisio, G. and Goffredo, O.; US Patent 3,228,943; January 11, 1966; assigned to Societa Farmaceutici Italia, Italy

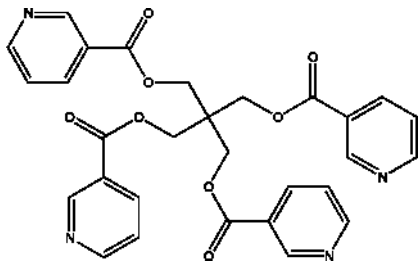
NICERITROL

Therapeutic Function: Antihyperlipidemic

Chemical Name: 3-Pyridinecarboxylic acid 2,2-bis[[(3-pyridinylcarbonyl) oxy]methyl]-1,3-propanediyl ester

Common Name: Pentaerythritol tetranicotinate

Structural Formula:



Chemical Abstracts Registry No.: 5868-05-3

Trade Name	Manufacturer	Country	Year Introduced
Cardiolipol	Gremy-Longuet	France	1972
Perycit	Sanwa	Japan	1979
Perycit	Tosi	Italy	1980
Perycit	Astra	Sweden	-

Raw Materials

Nicotinic acid chloride
Pentaerythritol
Pyridine

Manufacturing Process

160 grams of nicotinic acid chloride is charged into and made to react with 35 grams of pentaerythritol dissolved in 600 grams of dried, stabilized chloroform and 100 grams of carefully dried pyridine. Pyridine hydrochloride, pyridine and the excess of nicotinic acid chloride are removed through repeated extraction with water at a pH of approximately 3. Pentaerythritol nicotinate remains in the chloroform phase and is extracted by forming the hydrochloric acid salt of the ester using 1,000 ml of aqueous HCl at a pH of 1. The strongly acid extract is thereafter extracted several times with toluene. The acid extract is allowed to stand at room temperature for several hours in the presence of active carbon and the substance known as Versenate, i.e., the disodium salt of ethylene diamine tetraacetic acid; it is then filtered and pentaerythritol nicotinate is precipitated as a white, amorphous substance using 25% w/v aqueous ammonia, while stirring. Recrystallization of the product from ethyl alcohol gives flaky crystals, according to British Patent 1,022,880.

References

Merck Index 6336
Kleeman & Engel p. 630
I.N. p. 668
AB Bofors, Sweden; British Patent 1,022,880; March 16, 1966
AB Bofors, Sweden; British Patent 1,053,689; January 4, 1967

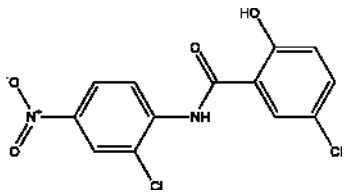
NICLOSAMIDE

Therapeutic Function: Anthelmintic

Chemical Name: 2',5-Dichloro-4'-nitrosalicylanilide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 50-65-7

Trade Name	Manufacturer	Country	Year Introduced
Yomesan	Bayer	W. Germany	1960
Yomesan	Bayer	UK	1961
Yomesan	Bayer	Italy	1962
Tredemine	Roger Bellon	France	1964
Niclocide	Miles	US	1982
Anti-Tenia	Uranium	Turkey	-
Atenase	I.C.N.-Usafarma	Brazil	-
Radeverm	Arzneimittelwerk Dresden	E. Germany	-
Teniarene	A.M.S.A.	Italy	-
Tenisid	Liba	Turkey	-

Raw Materials

5-Chlorosalicylic acid
2-Chloro-4-nitroaniline
Phosphorus trichloride

Manufacturing Process

17.2 g of 5-chlorosalicylic acid and 20.8 g of 2-chloro-4-nitroaniline are dissolved in 250 ml of xylene. While boiling, there are introduced slowly 5 g of PCl_3.Heating is continued for 3 further hours. The mixture is then allowed to cool down and the crystals which separate are filtered off with suction. The crude product may be recrystallized from ethanol, melting at 233°C.

References

Merck Index 6356
Kleeman & Engel p. 630
PDR p. 1260
OCDS Vol. 2 p. 94 (1980)
I.N. p. 669
REM p. 1236
Schraufstatter, E. and Gonnert, R.; US Patent 3,147,300; September 1, 1964; assigned to Farbenfabriken Bayer A.G.

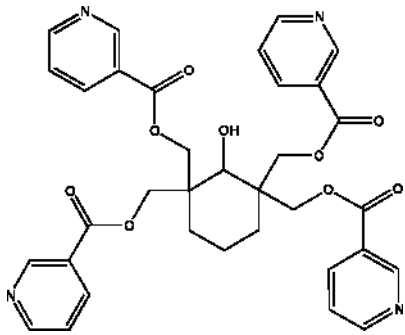
NICOMOL

Therapeutic Function: Anticholesteremic

Chemical Name: Cyclohexanol-2,2,6,6-tetrakis(hydroxymethyl) tetranicotinate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 27959-26-8

Trade Name	Manufacturer	Country	Year Introduced
Cholexamine	Kyorin	Japan	1971
Acenol	Kissei Pharmaceutical Co., Ltd.	Japan	1981
Nicolanta	Sawai	Japan	-

Raw Materials

2,2,6,6-Tetramethylolcyclohexanol
Nicotinic acid chloride

Manufacturing Process

To a mixture of 60 cc of benzene, 40 cc of pyridine and 17 g of hydrochloric acid salt of nicotinic acid chloride, was added 4.5 g of 2,2,6,6-tetramethylolcyclohexanol, and the whole mixture was refuxed at 75°C to 80°C for 2.5 hours. After the mixture was cooled water was added. Precipitate formed was separated by filtration, washed thoroughly with water and dried. Recrystallization from dilute acetic acid gave 14 g of the final compound, melting point 177°C to 180°C.

References

Merck Index 6360
DOT 7 (5) 173 (1971)
I.N. p. 670
Irikura, T., Sato, S., Abe, Y. and Kasuga, K.; US Patent 3,299,077; January 17, 1967; assigned to Kyorin Seiyaku KK

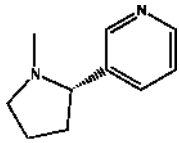
NICOTINE

Therapeutic Function: Ganglion depressant, Smoking deterrent

Chemical Name: Pyridine, 3-(1-methyl-2-pyrrolidinyl)-, (S)-

Common Name: Nicotine; Nikotin

Structural Formula:



Chemical Abstracts Registry No.: 54-11-5

Trade Name	Manufacturer	Country	Year Introduced
Nicotinell TTS	Novartis	-	-
Habitrol	Ciba-Geigy	-	-
Habitrol	Novartis	-	-
Nicabate	HMR	-	-
Nicoderm CQ	SKB	-	-
Paro	Esro	-	-
Toban	Pharmacia	-	-
Nicorette	GlaxoSmithKline	-	-

Raw Materials

Extract from Nicotiana tabacum
Calcium hydroxide
Calcium sulfate

Manufacturing Process

The water extract from Nicotiana tabacum was prepared by distillation of nicotine contained liquor from tobacco leaves, as described in D.R. Patent No. 319,846; September 12, 1913.

5 kg this water extract or the same quantity of tobacco powder in water was mixed with 1.5 kg of grinded calcium hydroxide and 1.5 kg calcium sulfate. The mixture stood for 24 hours. The obtained mixture looked like a dry powder. It was extracted with ether. The ether was distilled and the residue contented 98% of clear nicotine - liquid with odor of pyridine; BP: 246C/735 mm; d_4^{20} =1.0097; $[\alpha]_d^{20}$=- 166.5.

References

Hovler H.F.; DR Patent No. 320,897; Dec. 25, 1913
Dictionary of Organic Compounds edited by I. Hielbron and H.M. Bunbury, v.3, p. 60, 1946; London

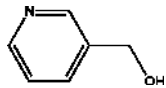
NICOTINYL ALCOHOL

Therapeutic Function: Vasodilator

Chemical Name: 3-Pyridinemethanol

Common Name: 3-Pyridylcarbinol

Structural Formula:



Chemical Abstracts Registry No.: 100-55-0

Trade Name	Manufacturer	Country	Year Introduced
Roniacol	Roche	US	1949
Danaden	Cascan	W. Germany	-
Peritard	Ikapharm	Israel	-
Ronicol	Roche	UK	-
Thilocombin	Thilo	W. Germany	-

Raw Materials

3-Cyanopyridine
Ethanol
Hydrogen
Nitrosyl chloride

Manufacturing Process

The catalyst is prepared by suspending 5 kg of catalyst grade charcoal in 200 liters of water, in a pressure vessel, and adding thereto 25 liters of 4% (as Pd metal) aqueous palladous chloride. Air is displaced from the vessel and then hydrogen is passed into the aqueous mixture at a pressure of 3 to 5 psi, while stirring, until no further absorption is noted and the chloride is completely reduced to metal.

To the aqueous suspension of the palladized charcoal catalyst thus obtained are added 20.8 kg of 3-cyano-pyridine (96% purity); and then are added 70

liters of a hydrochloric acid solution prepared by diluting 30 liters of 36% HCl with 40 liters of water. This represents approximately 1.75 mols of HCl for each mol of 3-cyano-pyridine. The suspension is maintained at 10° to 15°C and stirred continuously while introducing a current of hydrogen at a pressure of 3 to 5 psi. When absorption of hydrogen ceases and the 3-cyanopyridine is completely reduced, the reaction mixture is filtered to remove the catalyst. The filter cake is washed with 40 liters of water in two equal portions, and the wash water is added to the filtrate.

The combined liquors, which comprise an aqueous hydrochloric acid solution of 3-aminomethyl-pyridine hydrochloride, are then heated to a temperature of 60° to 65°C, and ethyl nitrite gas is passed into the heated solution. The ethyl nitrite is generated by placing 20 liters of 90% ethyl alcohol in a suitable vessel, diluting with 200 liters of water, and, while stirring, adding to the dilute alcohol 18.3 kg of nitrosyl chloride at the rate of 2.25 kg per hour. (The process using methyl nitrite is carried out by substituting a stoichiometrically equivalent quantity of methyl alcohol for the ethyl alcohol.)

When all the ethyl nitrite has been added, the reaction mixture is refluxed for approximately one hour, then concentrated to dryness under reduced pressure (25 to 30 mm Hg) and at a maximum temperature of 70°C. The crystalline residue is dissolved in 35 liters of water and adjusted to a pH of 8 to 9 by addition (with cooling and stirring) of 11 to 12 kg of caustic soda. The sodium chloride formed is filtered off, and the filter cake is washed with 20 liters of normal butyl alcohol. This wash liquid is used for the first extraction of the product from the aqueous filtrate. The filtrate is then further extracted with four successive 20-liter portions of n-butyl alcohol.

All the extracts are combined and concentrated in vacuo (100°C/20 mm) to remove the n-butyl alcohol. The residue is submitted to fractionation under reduced pressure. The forerun (up to 112°C/2 to 3 mm) consists of a small amount of n-butyl alcohol and some 3-pyridylcarbinol. The main fraction, boiling at 112° to 114°C/2 to 3 mm, consists of 3-pyridylcarbinol.

References

Merck Index 6369
Kleeman & Engel p. 633
I.N. p. 672
REM p. 852
Ruzicka, L. and Prelog, V.; US Patent 2,509,171; May 23, 1950; assigned to Ciba Limited, Switzerland
Cohen, A.; US Patent 2,520,037; August 22, 1950; assigned to Hoffmann-La Roche Inc.
Schlapfer, R.; US Patent 2,547,048; April 3, 1951; assigned to Hoffmann-La Roche Inc.
Chase, G.O.; US Patent 2,615,896; October 28, 1952; assigned to Hoffmann-La Roche Inc.

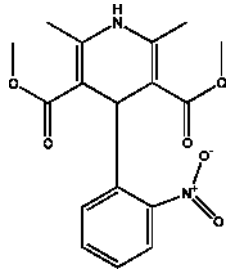
NIFEDIPINE

Therapeutic Function: Coronary vasodilator

Chemical Name: 1,4-Dihydro-2,6-dimethyl-4-(2'-nitrophenyl)-3,5-pyridinedicarboxylic acid dimethyl ester

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 21829-25-4

Trade Name	Manufacturer	Country	Year Introduced
Adalat	Bayer	W. Germany	1975
Adalat	Bayer	Italy	1976
Adalat	Bayer	Japan	1976
Adalat	Bayer	UK	1977
Adalate	Bayer	France	1979
Procardia	Pfizer	US	1982
Alfadat	Alfa	Italy	-
Anifed	Zoja	Italy	-
Atanal	Sawai	Japan	-
Citilat	C.T.	Italy	-
Coral	Tosi	Italy	-
Corinfar	Arzneimittelwerk Dresden	E. Germany	-
Nifedicor	Schiapparelli	Italy	-
Nifedin	Gentili	Italy	-
Nifelat	Sidus	Argentina	-
Oxcord	Biosintetica	Brazil	-

Raw Materials

2-Nitrobenzaldehyde
Acetoacetic acid methyl ester
Ammonia

Manufacturing Process

45 grams 2-nitrobenzaldehyde, 80 cc acetoacetic acid methyl ester, 75 cc methanol and 32 cc ammonia are heated under reflux for several hours, filtered off, cooled and, after suction-filtration, 75 grams of yellow crystals of MP 172° to 174°C are obtained, according to US Patent 3,485,847.

References

Merck Index 6374
DFU 6 (7) 427 (1981)
Kleemen & Engel p. 633
PDR p. 1423
OCDS Vol. 2 p. 283 (1980)
DOT 8 (11) 438 (1972); 11 (4) 154 (1975) & 19 (3) 171 (1983)
I.N. p. 673
REM p. 862
Bossert, F. and Vater, W.; US Patent 3,485,847; December 23, 1969; assigned to Farbenfabriken Bayer AG, Germany
Bossert, F. and Vater, W.; US Patent 3,488,359; January 6, 1970; assigned to Farbenfabriken Bayer AG, Germany
Bossert, F. and Vater, W.; US Patent 3,511,837; May 12, 1970; assigned to Farbenfabriken Bayer AG, Germany

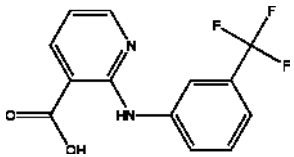
NIFLUMIC ACID

Therapeutic Function: Antiinflammatory

Chemical Name: 2-[[3-(Trifluoromethyl)phenyl]amino]-3-pyridinecarboxylic acid

Common Name: 2-[3-(Trifluoromethyl)anilino]nicotinic acid

Structural Formula:



Chemical Abstracts Registry No.: 4394-00-7

Trade Name	Manufacturer	Country	Year Introduced
Nifluril	U.P.S.A.	France	1968
Actol	Von Heyden	W. Germany	1971
Flaminon	Squibb	Italy	1979

Trade Name	Manufacturer	Country	Year Introduced
Forenol	Roemmers	Argentina	-
Landruma	Landerlan	Spain	-
Nifluran	Eczacibasi	Turkey	-
Niflux	Labofarma	Brazil	-

Raw Materials

Nicotinic acid
m-Trifluoromethylaniline
Potassium iodide

Manufacturing Process

Niflumic acid is prepared as follows: Nicotinic acid, m-trifluoromethylaniline, and potassium iodide are intimately mixed and heated on an oil bath at 140°C. The mixture melts to give a dark red liquid. The temperature of the oil bath is allowed to fall to 100°C and is maintained at this temperature for an hour and a half. The mixture puffs up and forms a yellow crystalline mass. After cooling to ordinary temperature, this mass is ground up in a mortar and extracted several times with small volumes of ether to remove excess m-trifluoromethylaniline. The residue is then washed twice with 10 ml of distilled water to remove m-trifluoromethylaniline hydrochloride and potassium iodide, and finally twice with 10 ml of 95% alcohol to remove colored resinous contaminants. After drying at 100°C, 2-(m-trifluoromethylanilino)nicotinic acid is obtained as pale yellow needles (from 70% ethanol) melting at 204°C (Kofler block).

References

Merck Index 6377
Kleeman & Engel p. 634
OCDS Vol. 1 p. 256 (1977)
DOT 4 (2) 82 (1968)
I.N. p. 34
Hoffmann, C. and Faure, A.; US Patent 3,415,834; December 10, 1968; assigned to Societe anonyme dite: Laboratoires UPSA, France

NIFURATEL

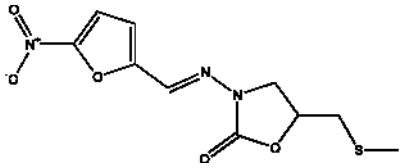
Therapeutic Function: Vaginal antiinfective

Chemical Name: 5-[(Methylthio)methyl]-3-[[(5-nitro-2-furanyl)methylene] amino]-2-oxazolidinone

Common Name: Methylmercadone

Chemical Abstracts Registry No.: 4936-47-4

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Macmiror	Poli	Italy	1965
Inimur	Woelm	W. Germany	1969
Omnes	Fumouze	France	1971
Magmilor	Calmic	UK	-
Polmiror	Poli	Italy	-
Tydantil	Poli	Italy	-

Raw Materials

Methyl mercaptan
5-Nitro-2-furaldehyde
Diethyl carbonate
Hydrazine hydrate
Epichlorohydrin

Manufacturing Process

In an initial step of reactions, methyl mercaptan is reacted with epichlorohydrin to give 1chloro-3-methylthio-2-propanol. That is reacted with hydrazine hydrate to give 3-methylmercapto-2-hydroxypropyl hydrazine.

11.8 grams of diethyl carbonate (0.1 mols) and a solution of sodium methoxide prepared from 0.12 gram of sodium in 4 cc of anhydrous methanol, were added to 13.2 grams of 3-methylmercapto-2-hydroxypropyl hydrazine. After the reaction vessel had been fitted with a Liebig condenser, the reaction mixture was heated by means of an oil bath which was gradually heated up to 110°C, to remove first methyl alcohol and then ethyl alcohol formed during the reaction. After about two-thirds of the theoretical amount of ethyl alcohol had been distilled off, the heating was discontinued and the reaction mixture was diluted with 50 cc of ethyl alcohol and poured into a 5-nitro-2-furfuraldehyde solution prepared by boiling for 30 minutes 0.1 mol of nitrofurfuraldehyde diacetate in 100 ml of ethyl alcohol and 50 ml of 1:10 sulfuric acid.

A yellow crystalline precipitate was immediately formed, which, after crystallization from acetic acid, melted at 182°C and consisted of N-(5-nitro-2-furfurylidene)-3-amino-5-methyl-mercaptomethyl-2-oxazolidinone.

References

Merck Index 6380
Kleeman & Engel p. 635

I.N. p. 674
Polichimica Sap, SpA, Italy; British Patent 969,126; September 9, 1964

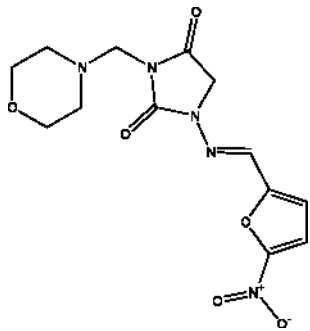
NIFURFOLINE

Therapeutic Function: Antibacterial

Chemical Name: 3-(4-Morpholinylmethyl)-1-[[(5-nitro-2-furanyl)-methylene] amino]-2,4-imidazolidinedione

Common Name:-

Structural Formula:



Chemical Abstracts Registry No.: 3363-58-4

Trade Name	Manufacturer	Country	Year Introduced
Furobactil	Carrion	France	1974
Urbac	Merck Clevenot	France	-

Raw Materials

Nitrofurantoin
Formaldehyde
Morpholine

Manufacturing Process

20 g of nitrofurantoin are placed in 100 cc of dimethylformamide and the solution is heated to 75°C to 80°C. This temperature is maintained and 100 cc of 40% formaldehyde are added, followed by 10 g of freshly distilled morpholine. The heating is continued for one hour, the mixture cooled and filtered and the precipitate obtained is washed with 95% alcohol. 20 g of the desired product are obtained as yellow crystals which melt at 206°C.

References

Merck Index 6381
I.N. p. 674
Laboratorios del Dr. Esteve S.A.; British Patent 1,245,095; September 2, 1971

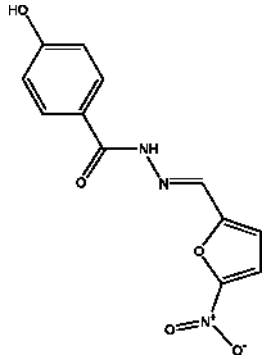
NIFUROXAZIDE

Therapeutic Function: Antiseptic

Chemical Name: 4-Hydroxybenzoic acid [(5-nitro-2-furanyl)methylene]-hydrazide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 965-52-6

Trade Name	Manufacturer	Country	Year Introduced
Ercefuryl	Carriere	France	1964
Pentofuryl	Karlspharma	W. Germany	1978
Antinal	Roques	France	-
Dicoferin	Andrade	Portugal	-
Enterokod	Genekod	France	-
Mucifural	Robert and Carriere	France	-

Raw Materials

4-Hydroxybenzhydrazide
5-Nitrofurfural

Manufacturing Process

13 g (0.1 mol) of 4-hydroxybenzhydrazide were dissolved in a boiling mixture of 100 ml of water and an equal volume of dimethylformamide. 15.5 g (0.11 mol) of 5-nitrofurfural dissolved in 31 ml of dimethylformamide were added to this hot solution, and the mixture was stirred and brought to the boiling point.

The mixture was then allowed to stand for fifteen hours. The precipitate was separated, washed twice with 100 ml of water, and recrystallized by dissolving it in 250 ml of hot pyridine and pouring this solution into 250 ml of water.

The 5-nitrofurfurylidene hydrazide of 4-hydroxybenzoic acid obtained was washed with water and methanol and was dried at a moderate temperature. It weighed 23 g (83.7% yield), and melted at 298°C. The percentage nitrogen determined by the micro-Dumas method was 15.41% (theory 15.27%).

References

Merck Index 6383
Kleeman & Engel p. 636
I.N. p. 675
Carron, M.C.E.; US Patent 3,290,213; December 6, 1966; assigned to S.A. des Laboratoires Robert et Carriere (France)

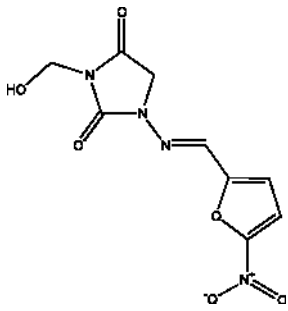
NIFURTOINOL

Therapeutic Function: Antibacterial

Chemical Name: 3-(Hydroxymethyl)-1-[[(5-nitro-2-furanyl)methylene]-amino]-2,4-imidazolidinedione

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 1088-92-2

Trade Name	Manufacturer	Country	Year Introduced
Urfadyne	Zambon	W. Germany	1969
Urfadyn	Arsac	France	1976
Urfadyne	Inpharzam	Switz.	1981
Levantin	Lek	Yugoslavia	-
Urfurine	Zambon	Spain	-

Raw Materials

Nitrofurantoin
Formaldehyde

Manufacturing Process

Three liters of 5% formaldehyde solution (2,625 cc water and 375 cc 40% formalin) containing 50 g of nitrofurantoin is refluxed for about 5 minutes, then filtered hot and cooled. The crystallized product is filtered and washed with 1% formaldehyde solution. It is air dried and then further dried at 65°C. There is obtained 33 g of 3-hydroxymethyl-1-(5-nitrofurfurylideneamino) hydantoin.

References

Merck Index 6388
I.N. p. 676
Michels, J.G.; US Patent 3,446,802; May 27, 1969; assigned to The Norwich Pharmacal Co.

NIFURZIDE

Therapeutic Function: Antibacterial, Antidiarrheal

Chemical Name: N1-[5'-Nitro-2'-thenoyl]-N2-[5''-nitro-2''-furylacrylidene] hydrazine

Common Name: -

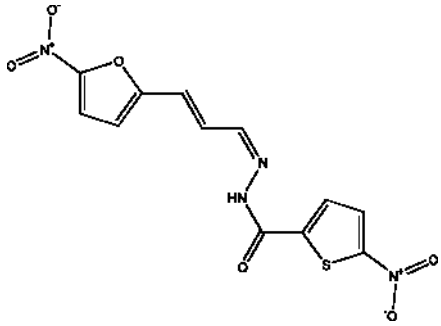
Chemical Abstracts Registry No.: 39978-42-2

Trade Name	Manufacturer	Country	Year Introduced
Ricridene	Anphar	Switz.	1981
Ricridene	Lipha	France	-

Raw Materials

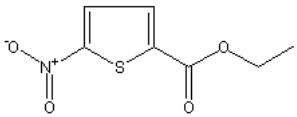
Hydrazine
Ethanol
5-Nitrothiophene carboxylic acid
5-Nitro-2-furylacrolein

Structural Formula:



Manufacturing Process

(a) Ethyl-5-nitro-2-thiophene carboxylate:



17.4 g (mol/10 = 17.31 g) of 5-nitrothiophene carboxylic acid are dissolved in 85 ml of absolute ethanol. A stream of gaseous hydrochloric acid is caused to enter the boiling solution to the point of saturation, and for 5 hours. Evaporation to dryness takes place and then the solid residue is washed with a sodium bicarbonate solution. It is suction-filtered and washed with water. After drying, there are obtained 17.7 g of a yellow product with a melting point of 63°C to 65°C and the yield is 88% (theoretical yield = 88%).

The N'-(5'-nitro-2'-thenoyl)hydrazide is prepared by reacting hydrazine with ethyl 5-nitro-2-thiophene carboxylate.

(b) 6.3 g (mol/30 = 6.5 g) of N1-[5'-nitro-2'-thenoyl]hydrazide are dissolved in 100 ml of dry tetrahydrofuran. 5.6 g (mol/30 = 5.55 g) of 5-nitro-2-furyl acrolein in 56 ml of tetrahydrofuran are added. Heating under reflux takes place for 1 hour and, 25 minutes after starting the heating, the crystallization commences; the crystals are suction-filtered, washed with ether and dried. There are obtained 7.9 g (yield 70%-theoretical yield = 11.2 g) of a yellow solid of melting point 235°C to 236°C.

Recrystallization (tepid dimethylformamide + ether) leaves the melting point unchanged.

References

Merck Index 6389
DFU 6 (6) 358 (1981)
Kleeman & Engel p. 637

DOT 17 (7) 288 (1981)
Szarvasi, E. and Fontaine, L.; US Patents 3,847,911; November 12, 1974; and 3,914,379; October 21, 1975; both assigned to Lipha, Lyonnaise Industrielle Pharmaceutique

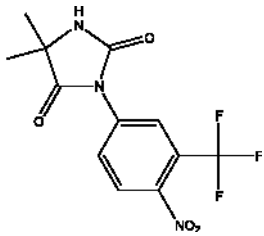
NILUTAMIDE

Therapeutic Function: Antiandrogen

Chemical Name: 2,4-Imidazolidinedione, 5,5-dimethyl-3-(4-nitro-3-(trifluoromethyl)phenyl)-

Common Name: Nilutamide

Structural Formula:



Chemical Abstracts Registry No.: 63612-50-0

Trade Name	Manufacturer	Country	Year Introduced
Anandron	Laboratoires Cassene	France	-
Anandron	Hoechst Marion Roussel	Germany	-
Nilandron	Aventis Pharmaceuticals	France	-
Nilutamide	Triquim S.A.	Argentina	-

Raw Materials

Phenyl oxide
5,5-Diphenylhydantoin
2-Nitro-5-chloro-trifluoromethylbenzene
Copper oxide
Dimethyl sulfoxide

Manufacturing Process

There are at least five methods to prepare desired compound.

1. 1-(3'-Trifluoromethyl-4'-nitropheyl)-4,4-dimethyl-imidazoline-2,5-dione

The following were introduced into 383.52 ml of phenyl oxide: 225.60 grams of 2-nitro-5-chloro-trifluoromethylbenzene, described in the German Patent

No. DRP 637,318, 128.10 grams of 5,5-dimethylhydantoin described in Beil., Vol. 24, 289 and 198.53 grams of cuprous oxide. The mixture was heated to 200°C for 24 hours, then cooled to 20°C and filtered. The residue was rinsed with phenyl oxide, then extracted with ethyl acetate. The ethyl acetate phase was concentrated to dryness under reduced pressure at 60°C and the residue was taken up in ammoniacal dichloroethane. The crystals obtained were dried at 60°C to obtain 66.55 grams of crude product which, after purification from aqueous ethanol yielded 62.55 grams of purified desired product.

2. 1-(3'-Trifluoromethyl-4'nitrophenyl)-4,4-dimethyl-imidazoline-2,5-dione

The following were introduced into 282 ml of triglyme: 112.8 grams of 2-nitro-5-chloro-trifluoromethylbenzene, 64.1 grams of 5,5-dimethyl-hydantoin and 33.5 grams of cuprous oxide. The mixture was heated to about 215°C ± 5°C for 4 hours, then cooled to 20°C and filtered. The triglyme solution was recovered and a 22 Be ammonia solution (1 volume), toluene (1 volume) and demineralized water (4 volume) were added to the solution of triglyme (1 volume). The solution was stirred at 20°C for 15 minutes, then cooled to about -10°C and stirred again at -10°C. After washing and drying, 47.6 grams of the desired product were obtained.

3. 1-(3'-Trifluoromethyl-4'-nitrophenyl)-4,4-dimethyl-imidazoline-2,5-dione

30 ml of dimethylsulfoxide and 24.8 grams of 2-nitro-5-chloro trifluoromethylbenzene were introduced at 20°C with stirring into 100 ml of dimethylsulfoxide, 12.80 grams of 5,5-dimethyl-hydantoin and 6.28 grams of potassium hydroxide in the form of flakes. The mixture was heated to 110°C for a period of time variable between 3 and 18 hours. The product was characterized and determined by thin layer chromatography.

4. 1-(3'-Trifluoromethyl-4'-nitrophenyl)-4,4-dimethyl-imidazoline-2,5-dione

71.5 grams of copper in powder form were added to 96.10 grams of 5,5-dimethyl-hydantoin and 170.86 grams of 2-nitro-5-chloro trifluoromethylbenzene. The mixture was heated to 200°C for about 21 hours, the pressure being maintained at 450 millibars, then, was cooled to 20°C and taken up in 480 ml of ethanol. The product was characterized and determined by thin layer chromatography of the ethanol solution.

5. 1-(3'-Trifluoromethyl-4'-nitrophenyl)4,4-dimethyl-imidazoline-2,5-dione

The following were introduced into 288 ml of phenyl oxide: 96.10 grams of 5,5-dimethyl-hydantoin, 170.86 grams of 2-nitro-5-chloro trifluoromethylbenzene and 89.40 grams of cupric oxide. The mixture was heated to 190°C for about 23 hours, then cooled to 20°C and filtered. The residue was characterized in the phenyl oxide filtrate by thin layer chromatography. The analytical results obtained for these 5 examples were identical to those obtained and indicated in French Patent No. 2,329,276.

References

Seuron P. et.al.; US Patent No. 5,166,358; Nov. 24, 1992; Assigned to Rousel Uclaf, Paris, France

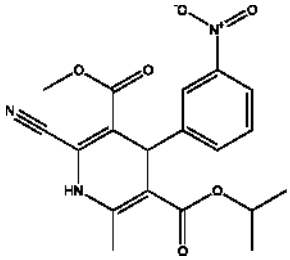
NILVADIPINE

Therapeutic Function: Calcium entry blocker, Antihypertensive

Chemical Name: 2-Cyano-1,4-dihydro-6-methyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylic acid 3-methyl- 5-(1-methyl ethyl) ester

Common Name: Nivadipine, Niprodipine

Structural Formula:



Chemical Abstracts Registry No.: 75530-68-6

Trade Name	Manufacturer	Country	Year Introduced
Nilvadipine	Fujisawa	-	-
Tensan	Klinge	-	-

Raw Materials

Isopropyl ester of 6-formyl-5-methoxycarbonyl-2-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid
Hydroxylamine hydrochloride
Sodium acetate
Acetic anhydride

Manufacturing Process

To a solution of isopropyl ester of 6-formyl-5-methoxycarbonyl-2-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine- 3-carboxylic acid (4.5 g) in acetic acid (35 ml) were added hydroxylamine hydrochloride (0.97 g) and sodium acetate (1.43 g), and the mixture was stirred at ambient temperature for 2.5 hours. After acetic anhydride (4.14 g) was added to this reaction mixture, the mixture was stirred at ambient temperature for 1.5 hours and at 95-100°C for additional 4 hours. The acetic acid and the excess of acetic anhydride were removed in vacuum, followed by adding water to the residue and it was neutralized with a saturated aqueous solution of sodium bicarbonate. This aqueous suspension was extracted twice with ethyl acetate, and the combined extract was washed with water, dried over anhydrous magnesium sulfate and evaporated to dryness under reduced pressure to give a reddish-brown oil (4.88 g), which was chromatographed over silica gel (150 g) with a mixture of

benzene and ethyl acetate (10:1 by volume) as an eluent to give a crude crystals (2.99 g). These were recrystallized from ethanol to give yellow prisms (1.89 g) of isopropyl ester of 6-cyano-5-methoxycarbonyl-2-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid melting point 148-150°C (yellow prisms from ethanol); $[\alpha]_D^{20}$ = 222.4° (c = 1 in methanol).

References

Sato Yoshinari; US Patent No. 4,338,322; July 6, 1982; Assigned to Fujisawa Pharmaceutical Co., Ltd. (Osaka, JP)

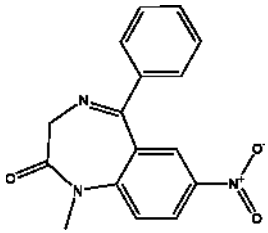
NIMETAZEPAM

Therapeutic Function: Tranquilizer

Chemical Name: 1,3-Dihydro-1-methyl-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one

Common Name:-

Structural Formula:



Chemical Abstracts Registry No.: 2011-67-8

Trade Name	Manufacturer	Country	Year Introduced
Erimin	Sumitomo	Japan	1977

Raw Materials

Hydrogen chloride	1-Methyl-5-nitro-3-phenylindole-2-carbonitrile
Chromic anhydride	Boron trifluoride etherate

Manufacturing Process

To a suspension of 73.9 g of 1-methyl-5-nitro-3-phenylindole-2-carbonitrile in 1.5 liters of dry tetrahydrofuran is added dropwise a solution of 126 g of boron trifluoride etherate in 220 ml of dry tetrahydrofuran with stirring for 2 hours. After addition, stirring is continued for an additional 3 hours. To the

reaction mixture is added dropwise 370 ml of water and then 370 ml of concentrated hydrochloric acid with stirring under ice-cooling.

The resulting precipitate is collected by filtration, washed with water followed by ethanol, and dried to give 56.3 g of crude 2-aminomethyl-1-methyl-5-nitro-3-phenylindole hydrochloride, melting point 263°C to 267°C.

To a suspension of 6.5 g of 2-aminomethyl-1-methyl-5-nitro-3-phenylindole in 65 ml of glacial acetic acid is added dropwise a solution of 6.5 g of chromic anhydride in 6.5 ml of water at 20°C with stirring. The mixture is stirred at room temperature overnight and thereto is added 195 ml of water. To the mixture is added dropwise 100 ml of 28% ammonia water with stirring under cooling. The resultant precipitate is collected by filtration, washed with water and dried to give 5.9 g of a crude product having melting point 135°C to 140°C. Fractional recrystallization from ethanol gives 3.8 g of 1-methyl-7-nitro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-one as yellow plates, melting point 153°C to 156°C. Further recrystallization from the same solvent gives pale yellow plates having melting point 156°C to 156.5°C.

References

Merck Index 6395
Kleeman & Engel p. 637
DOT 8 (9) 350 (1972); 11 (5) 195 (1975) & 13 (1) 31 (1977)
I.N. p. 676
Yamamoto, H., Inaba, S., Okamoto, T., Hironashi, T., Ishizumi, K., Yamamoto, M., Maruyama, I., Mori, K. and Kobayashi, T.; US Patents 3,770,767; November 6, 1973; and 3,652,551; March 28, 1972; both assigned to Sumitomo Chemical Co.

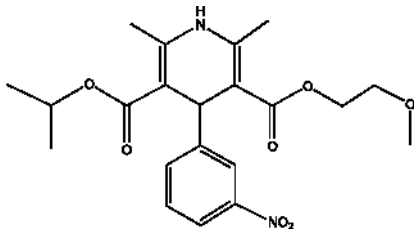
NIMODIPINE

Therapeutic Function: Vasodilator

Chemical Name: 3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-, 2-methoxyethyl 1-methylethyl ester

Common Name: Nimodipine

Structural Formula:



Chemical Abstracts Registry No.: 66085-59-4

Trade Name	Manufacturer	Country	Year Introduced
Brainox	Euro-Labor.	-	-
Curban	Rafarm	Greece	-
Grifonmod	Laboratorio Chile S.A.	Chile	-
Modina	Pentafarma	Chile	-
Modus	Berenguer	-	-
Myodipine	Help	Greece	-
Nemotan	Medochemie Ltd.	Cyprus	-
Nimotop	Bayer AG	Germany	-
Nimotop	Miles	-	-
Nimodipine	Bayer AG	Germany	-
Norton	Farmasa	Brazil	-
Regental	Tecnofarma S.A.	Chile	-
Sobrepina	Farmoz	Portugal	-
Trinalion	Tecnimede	Portugal	-
Tropocer	Laboratorios Leti	Venezuela	-
Vasotop	Cipla Limited	India	-
Ziremex	Demo	-	-
Nimocer	Synapse (A Div. of Microlabs)	India	-

Raw Materials

3'-Nitro-benzylideneacetoacetic acid isopropylester
Acetoacetic acid β-metoxyethyl ester
Ammonium hydroxide

Manufacturing Process

After 8 hours boiling of solution of 3.8 g of 3'-nitro-benzylideneacetoacetic acid isopropylester, 8 grams of acetoacetic acid β-metoxyethyl ester and 6 ml conc ammonia in 80 ml ethanol under reflux, 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine 3-β-methoxyethyl ester 5-isopropyl ester of melting point 125°C (petroleum ether/ acetic ester) was obtained. Yield 49% of theory.

References

Meyer H. et al.; US Patent No. 3,799,934; March 26, 1974; Assigned to Farbenfabriken Bayer Aktiengesellschaft, Leverkusen, Germany
Meyer H. et al.; US Patent No. 4,406,906; Sep. 27, 1983; Assigned to Bayer Aktiengesellschaft, Leverkusen, Fed. Rep. of Germany

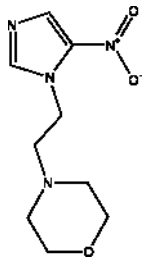
NIMORAZOLE

Therapeutic Function: Trichomonacidal

Chemical Name: N-β-Ethylmorpholino-(5)-nitroimidazole

Common Name: Nitrimidazine

Structural Formula:



Chemical Abstracts Registry No.: 6506-37-2

Trade Name	Manufacturer	Country	Year Introduced
Naxogin	Carlo Erba	UK	1970
Naxogin	Carlo Erba	Italy	1972
Esclama	Farmitalia	W. Germany	1973
Aceterol Forte	Bristol-Myers	W. Germany	1973
Naxofem	Ikapharm	Israel	-
Nulogyl	Bristol	UK	-
Sirledi	Causyth	Italy	-

Raw Materials

Ethylene oxide
Morpholine
4(5)-Nitroimidazole sodium salt
β-Chloroethyl morpholine
p-Toluenesulfonyl chloride

Manufacturing Process

6 g 4(5)-nitroimidazole sodium salt and 9 g β-chloroethylmorpholine are allowed to react in 200 ml dry toluene. The mixture is refluxed for 50 hours, then cooled and filtered from the solid residue. The solvent is evaporated under reduced pressure. The half-solid product thus obtained solidifies by addition of petroleum ether and ethyl ether.

Crystallization from water results in N-β-ethylmorpholino-(5)-nitroimidazole (melting point 110°C to 111°C); from mother liquors N-β-ethylmorpholino-(4)-nitroimidazole (melting point 104°C to 106°C) is obtained.

The following procedure is given in US Patent 3,458,528: 78 grams (0.675 mol) of 5-nitroimidazole is dissolved in 1,500 ml of acetic acid upon the addition of 72 ml (0.57 mol) of boron trifluoride etherate. 175 ml (3.5 mols) of ethylene oxide in 175 ml of hexane, in a dropping funnel topped with a cold

finger, is added slowly over 1 hour to the above solution maintained at 32° to 35°C with a water cooling bath. The mixture is concentrated under high vacuum to 100 to 150 ml volume. The residue is diluted with 500 ml of water, neutralized to pH 7 with aqueous sodium hydroxide, and extracted with 1.5 liters of ethyl acetate. The extract is dried and evaporated to yield 1-(2'-hydroxyethyl)-5-nitroimidazole.

20 grams (0.127 mols) of 1-(2'-hydroxyethyl)-5-nitroimidazole in 50 ml of dry pyridine is reacted with 75 grams of p-toluenesulfonyl chloride at 15°C for 4 hours. The reaction mixture is poured into ice and water and the crystalline precipitate is separated by filtration, washed with water and air dried to yield 1-(2'-p-toluenesulfonyloxyethyl)-5-nitroimidazole; MP 126° to 127°C.

16 grams, (0.057 mol) of 1-(2'-p-toluenesulfonyloxyethyl)-5-nitroimidazole and 9.3 ml of morpholine are heated at 95°C for 4 hours. The reaction mixture is taken up in water and extracted with ether. Evaporation of the ether yields 1-(2'-N-morpholinylethyl)-5-nitroimidazole; MP 109° to 110°C.

References

Merck Index 6398
Kleeman & Engel p. 638
OCDS Vol. 2 p. 244 (1980)
DOT 6 (5) 185 (1970) & 7 (5) 193 (1971)
I.N. p.677
Giraldi, P.N. and Mariotti, V.; US Patent 3,399,193; August 27, 1968; assigned to Carlo Erba SpA, Italy
Gal, G.; US Patent 3,458,528; July 29, 1969; assigned to Merck & Co., Inc.
Carlson, J.A., Hoff, D.R. and Rooney, C.S.; US Patent 3,646,027; February 29, 1972; assigned to Merck & Co., Inc.

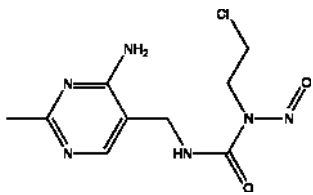
NIMUSTINE

Therapeutic Function: Antitumor, Antileukemic

Chemical Name: 1-(2-Chloroethyl)-1-nitroso-3-[(2-methyl-4-aminopyrimidin-5-yl)-methyl]urea

Common Name: ACNU

Structural Formula:



Chemical Abstracts Registry No.: 42471-28-3

Trade Name	Manufacturer	Country	Year Introduced
Nidran	Sankyo	Japan	1979

Raw Materials

1-(2-Chloroethyl)-3-[(2-methyl-4-aminopyridin-5-yl)methyl]urea
Sodium nitrite
Hydrogen chloride

Manufacturing Process

0.4 g of sodium nitrite was added with stirring, at 0°C to 5°C, to a solution of 450 mg of 1-(2-chloroethyl)-3-[(2-methyl-4-aminopyridin-5-yl)methyl]urea in 8 ml of 5% hydrochloric acid, and the reaction mixture was then stirred at 0°C to 10°C for an additional 1.5 hours.

After completion of the reaction, the reaction mixture was made alkaline by the addition of sodium carbonate, whereupon crystals separated out in situ. The crystals were recovered by filtration, washed with water and then recrystallized from 6 ml of ethanol, to give 0.1 g of the pale yellow pure desired product having a decomposition point of 125°C.

References

Merck Index 6399
DFU 3 (1) 52 (1978)
Kleeman & Engel p. 639
DOT 16 (12) 426 (1980)
I.N. p. 677
Sankyo Co., Ltd.; British Patent 1,374,344; November 20, 1974
Nakao, H., Arakawa, M. and Fukushima, M.; US Patent 4,003,901; January 18, 1977; assigned to Sankyo Co., Ltd.

NISOLDIPINE

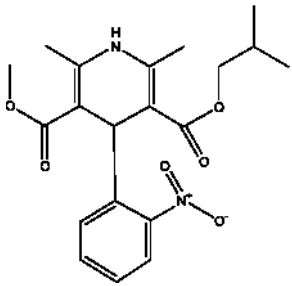
Therapeutic Function: Coronary vasodilator

Chemical Name: 3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, methyl 2-methylpropyl ester

Common Name: Nisoldipine

Chemical Abstracts Registry No.: 63675-72-9

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Baymycard	Bayer Vital	Germany	-
Corasol	Sanitas	Chile	-
Nisoldipine	Pharmax	-	-
Norvasc	Miles	-	-
Sular	AstraZeneca	-	-
Syscor	AstraZeneca	-	-
Zadipina	SmithKline Beecham	-	-

Raw Materials

2'-Nitrobenzylideneacetoacetic acid methyl ester
β-Aminocrotonic acid isopropyl ester

Manufacturing Process

Boiling a solution of 12.7 g of 2'-nitrobenzylideneacetoacetic acid methyl ester and 7.1 g of β-amino-crotonic acid isopropyl ester in 50 ml of methanol for 10 hours yielded 2,6-dimethyl-4-(2'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl ester-5-isopropyl ester of melting point 174°C (from ethanol). Yield 48% of theory.

References

Meyer H. et al.; US Patent No. 3,932,645; Jan. 13, 1976; Assigned to Farbenfabriken Bayer A G, Germany
Kutsuma T. et al.; US Patent No. 4,672,068; Jun. 9, 1987; Assigned to Fujirebio Kabushiki Kaisha, Tokyo, Japan

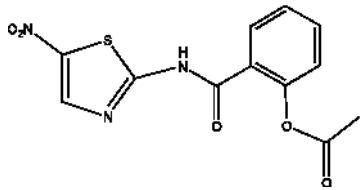
NITAZOXANIDE

Therapeutic Function: Anthelmintic

Chemical Name: 2-[(5-Nitro-2-thiazolyl)carbamoyl]phenyl acetate

Common Name: Nitazoxanide

Structural Formula:



Chemical Abstracts Registry No.: 55981-09-4

Trade Name	Manufacturer	Country	Year Introduced
Alinia	Romark Laboratories, L.C.	-	-
Cryptaz	Unimed Pharmaceuticals, Inc.	USA	-
Nitazoxanide	Romark Laboratories	USA	-
NTZ	Romark Laboratories	USA	-
NTZ	Unimed Pharmaceuticals, Inc.	USA	-

Raw Materials

p-Metoxy-benzoyl chloride
2-Amino-5-nitrothiazole
Triethylamine

Manufacturing Process

To a solution containing one mole p-metoxy-benzoyl chloride and one mole of carefully purified 2-amino-5-nitro-triazole in 200 ml of anhydrous tetrahydrofuran, one mole of triethylamine has been slowly added (about 10 minutes) while stirring. The reaction mixture, which became slightly warm, was stirred during 45 minutes and then poured under agitation, into 2 liters of distilled water. The stirring was continued until the precipitation of salicylamide, N-(5-nitro-2-thiazolyl)-, acetate (ester) was complete. The obtained precipitate was dried, washed with water, dried again and recrystallized from methanol. The yield about 60%; melting point 202°C.

References

Rossignol J.-F. et al.; US Patent No. 3,950,351; Apr. 13, 1976; Assigned to S.P.R.L. Phavic, Mouscron, Belgium
Rossignol J.-F.; US Patent No. 5,578,621; Nov. 26, 1996

NITRAZEPAM

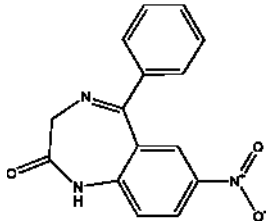
Therapeutic Function: Anticonvulsant, Hypnotic

2456 Nitrazepam

Chemical Name: 1,3-Dihydro-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 146-22-5

Trade Name	Manufacturer	Country	Year Introduced
Mogadan	Roche	W. Germany	1965
Mogadon	Roche	France	1965
Mogadon	Roche	UK	1965
Mogadon	Roche	Italy	1967
Apodorm	A.L.	Norway	-
Arem	Lennon	S. Africa	-
Atempol	Norgine	UK	-
Benzalin	Shionogi	Japan	-
Cerson	Belupo Ltd.	Yugoslavia	-
Dormicum	Glebe	Australia	-
Dormo-Puren	Klinge	W. Germany	-
Dumolid	Dumex	Denmark	-
Eatan-N	Desitin	W. Germany	-
Hipsal	Salvat	Spain	-
Hypnotin	Protea	S. Africa	-
Imadorm	Scheurich	W. Germany	-
Imeson	Desitin	W. Germany	-
Insomin	Orion	Finland	-
Ipersed	Sidus	Italy	-
Ipnozem	Biofarma	Turkey	-
Lagazepam	Lagap	Switz.	-
Lyladorm	M.P.S. Labs	S. Africa	-
Mitidin	Savoma	Italy	-
Nelbon	Sankyo	Japan	-
Nelmat	Sawai	Japan	-
Neuchlonic	Taiyo	Japan	-
Nitrados	Berk	UK	-
Nitrempax	Lafi	Brazil	-
Noctem	Alfa Farm.	Italy	-
Noctene	Rio Ethicals	S. Africa	-
Numbon	Ikapharm	Israel	-

Trade Name	Manufacturer	Country	Year Introduced
Ormodon	Ormed	S. Africa	-
Pacisyn	Medica	Finland	-
Paxisyn	Syntetic	Denmark	-
Pelson	Infale	Spain	-
Persopir	Ion	Italy	-
Prosonno	Von Boch	Italy	-
Quill	Ellea	Italy	-
Relact	Lemonier	Argentina	-
Remnos	D.D.S.A.	UK	-
Rindepres	Disprovent	Argentina	-
Somitran	Farmos	Finland	-
Somnased	Duncan Flockhart	UK	-
Somnite	Norgine	UK	-
Sonnolin	Dima	Italy	-
Surem	Galen	UK	-
Tri	Vita	Italy	-
Unisomnia	Unigreg	UK	-

Raw Materials

2-Aminobenzophenone
Glycine ethyl ester hydrochloride
Nitric acid

Manufacturing Process

A mixture of 16.8 g of 2 -aminobenzophenone, 11.9 g of glycine ethyl ester hydrochloride and 200 cc of pyridine was heated to reflux. After one hour, 20 cc of pyridine was distilled off. The solution was refluxed for 15 hours, then 11.9 g of glycine ethyl ester hydrochloride was added and the refluxing was continued for an additional 4 hours. The reaction mixture was continued for an additional 4 hours. The reaction mixture was concentrated in vacuo, then diluted with ether and water. The reaction product, 5-phenyl-3H-1,4-benzodiazepin-2(1H)-one, crystallized out, was filtered off, and then recrystallized from acetone in the form of colorless rhombic prisms, MP 182°C to 183°C.

48 g (0.2 mol) of 5-phenyl-3H-1 ,4-benzodiazepin-2(1 H)-one was dissolved in 250 cc of concentrated sulfuric acid by stirring at 15°C for ½ hour. The solution was then cooled to 0°C and a mixture of 9.1 cc of fuming nitric acid (90%, sp. gr. = 1.50) and 11.8 cc of concentrated sulfuric acid was added dropwise with stirring, keeping the temperature of the reaction mixture between -5°C and 0°C. After completion of the addition of the nitric acid-sulfuric acid mixture, stirring was continued for 1 hour and the reaction mixture was stored in the refrigerator overnight.

The mixture was then added dropwise to 2 kg of crushed ice with stirring and cooling, keeping the temperature at 0°C. After 1 hour of stirring in the cold, 640 cc of concentrated ammonium hydroxide was added dropwise at 0°C to pH 8. Stirring was continued for ½ hour and the crude product was filtered

off, washed with a small amount of ice water and sucked dry overnight. The crude product was suspended in a mixture of 100 cc of methylene chloride and 1,700 cc of alcohol. 50 g of decolorizing charcoal was added and the mixture was refluxed with stirring for 2 hours. After standing overnight at room temperature 15 g of diatomaceous earth filter aid was added and the refluxing was resumed for 1½ hours. The mixture was filtered while hot. The clear, light yellow filtrate was concentrated in vacuo on the steam bath with stirring to about 600 cc. The concentrate was stirred and cooled in ice for about 2 hours; the precipitated crystalline product was filtered off, washed with some petroleum ether and sucked dry. The product, 7-nitro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one, was recrystallized from a mixture of 1,000 cc of alcohol and 50 cc of methylene chloride to obtain white prisms melting at 224°C to 225°C.

References

Merck Index 6418
Kleeman & Engel p. 640
OCDS Vol. 1 p. 366 (1977)
DOT 1 (4) 132 (1965) & 9 (6) 237 (1973)
I.N. p. 678
REM p. 1064
Kariss, J. and Newmark, H.L.; US Patent 3,116,203; December 31, 1963; assigned to Hoffmann-LaRoche, Inc.

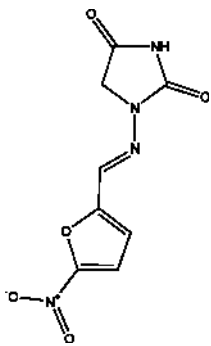
NITROFURANTOIN

Therapeutic Function: Antibacterial (urinary)

Chemical Name: 1-[[(5-Nitro-2-furanyl)methylene]amino]-2,4-imidazolidinedione

Common Name: N-(5-Nitro-2-furfurylidene)-1-aminohydantoin

Structural Formula:



Chemical Abstracts Registry No.: 67-20-9

Trade Name	Manufacturer	Country	Year Introduced
Furadantin	Norwich Eaton	US	1953
Furadoine	Oberval	France	1954
Trantoin	McKesson	US	1969
Cyantin	Lederle	US	1970
Furachel	Rachelle	US	1970
N-Toin	Upjohn	US	1971
Parfuran	Warner Lambert	US	1974
Alfuran	Alkaloid	Yugoslavia	-
Berkfurin	Berk	UK	-
Ceduran	Cedona	Netherlands	-
Chemiofuran	Italfarmaco	Italy	-
Chemiofurin	Torlan	Spain	-
Cistofuran	Crosara	Italy	-
Cystit	Heyden	W. Germany	-
Dantafur	Norwich Eaton	US	-
Fua Med	Med	W. Germany	-
Furadoine	Oberval	France	-
Furalan	Lannett	US	-
Furaloid	Edwards	US	-
Furanex	Elliott-Marion	Canada	-
Furanite	Saunders	Canada	-
Furantoin	Spofa	Czechoslovakia	-
Furatin	Hemofarm	Yugoslavia	-
Furedan	Scharper	Italy	-
Furil	Off	Italy	-
Furobactina	Esteve	Spain	-
Furophen	Pharbil	Netherlands	-
Gerofuran	Gerot	Austria	-
Ituran	Promonta	W. Germany	-
Macrodantin	Eaton	US	-
Microdoine	Gomenol	France	-
Micturol	Liade	Spain	-
Nephronex	Cortunon	Canada	-
Nierofu	Hoyer	W. Germany	-
Nifuran	Paul Maney	Canada	-
Nifurantin	Apogepha	E. Germany	-
Nitrofur C	Leiras	Finland	-
Novofuran	Novopharm	Canada	-
Phenurin	Merckle	W. Germany	-
Profura	Rachelle	US	-
Trantoin	McKesson	US	-
Trocurine	Labatec	Switz.	-
Urantoin	D.D.S.A.	UK	-

Trade Name	Manufacturer	Country	Year Introduced
Uretoin	Tokyo Tanabe	Japan	-
Urodil	Pharma-Selz	W. Germany	-
Urodin	Streuli	Switz.	-
Urofuran	Farmos	Finland	-
Urolisa	Lisapharma	Italy	-
Urolong	Thiemann	W. Germany	-
Uro-Tablinen	Sanorania	W. Germany	-
Uvamin	Mepha	Switz.	-

Raw Materials

n-Heptaldehyde
1-Aminohydantoin
5-Nitro-2-furaldoxime

Manufacturing Process

To a solution of 18.9 grams (0.166 mol) n-heptaldehyde in 25 ml of isopropanol is added, with stirring, a solution of 19.1 grams (0.166 mol) of 1-aminohydantoin in 110 ml water acidified with concentrated HCl. The heavy white precipitate formed is filtered and washed, until acid free, with small amounts of water and ether. The yield of N-(n-heptylidene)-1-aminohydantoin is 14 grams of MP 150°C (with decomposition). This may be recrystallized from dimethylformamide.

A mixture of 2.5 grams (0.016 mol) of 5-nitro-2-furaldoxime, 3.9 grams (0.018 mol) of N-(n-heptylidene)-1-aminohydantoin and 5 cc of sulfuric acid (density 1.84) is placed in a 250 cc beaker. It is heated with stirring at steam bath temperature for about 1.5 hours. Upon cooling, a solid precipitates which is collected by filtration, washed with water, isopropanol and ether in turn and dried at 110°C for 4 hours. There is obtained N-(5-nitro-2-furfurylidene)-1-aminohydantoin in 96 to 98% yield, according to US Patent 2,927,110.

References

Merck Index 6445
Kleeman & Engel p. 641
PDR pp. 1278, 1606
OCDS Vol. 1 p. 230 (1977)
I.N. p. 680
REM p. 1215
Hayes, K.J.; US Patent 2,610,181; September 9, 1952; assigned to Eaton Laboratories, Inc.
Michels, J.G.; US Patent 2,898,335; August 4, 1959; assigned to The Norwich Pharmacal Company
Gever, G. and O'Keefe, C.; US Patent 2,927,110; March 1, 1960; assigned to The Norwich Pharmacal Company

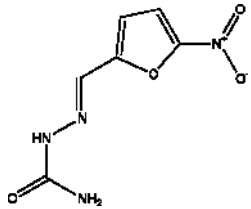
NITROFURAZONE

Therapeutic Function: Topical antiinfective

Chemical Name: 2-[(5-Nitro-2-furanyl)methylene]hydrazinecarboxamide

Common Name: Nitrofural

Structural Formula:



Chemical Abstracts Registry No.: 59-87-0

Trade Name	Manufacturer	Country	Year Introduced
Furacin	Norwich Eaton	US	1946
Actin-N	Chesebrough-Pond	US	1981
Amifur	Norwich Eaton	US	-
Escofuron	Streuli	Switz.	-
Furesol	A.F.I.	Norway	-
Germex	Lennon	S. Africa	-
Monofuracin	Dainippon	Japan	-
Muldacin	Mulda	Turkey	-
Nifucin	Jenapharm	E. Germany	-
Nifuzon	Pharmacia	Sweden	-
Nitrozone	Century	US	-
Yatrocin	Italfarmaco	Italy	-

Raw Materials

Semicarbazide hydrochloride
2-Formyl-5-nitrofuran

Manufacturing Process

A mixture of 43 grams of semicarbazide hydrochloride and 31 grams of sodium acetate is dissolved in 150 cc of water. The pH of this solution is approximately 5. Ethyl alcohol (95% by volume) in the amount of 250 cc is added and the mixture is stirred mechanically. A solution of 53.5 grams of carefully purified 2-formyl-5-nitrofuran in 250 cc of the said alcohol is added dropwise to the semicarbazide solution at room temperature. After completing the addition of the aldehyde solution, the mixture is stirred for another hour. The precipitate is removed from the reaction mixture by filtration. It is washed

well with ethyl alcohol and dried to constant weight at 70°C in an oven. The product weighs 73 grams, corresponding to a yield of 97%. It is obtained in the form of pale yellow needles, which are not subjected to further purification, according to US Patent 2,416,234.

References

Merck Index 6446
Kleeman & Engel p. 641
PDR p. 1278
OCDS Vol. 1 p. 229 (1977)
I.N. p. 680
REM p. 1163
Stillman, W.B. and Scott, A.B.; US Patent 2,416,234; February 18, 1947; assigned to Eaton Laboratories, Inc.
Gever, G. and O'Keefe, C.; US Patent 2,927,110; March 1, 1960; assigned to The Norwich Pharmacal Company

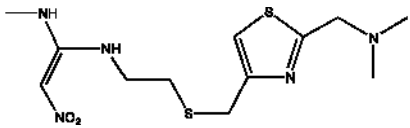
NIZATIDINE

Therapeutic Function: Antiulcer

Chemical Name: 1,1-Ethenediamine, N-(2-(((2-((dimethylamino)methyl)-4-thiazolyl)methyl)thio)ethyl)-N'-methyl-2-nitro-

Common Name: Nizatidine

Structural Formula:



Chemical Abstracts Registry No.: 76963-41-2

Trade Name	Manufacturer	Country	Year Introduced
Acinon	Zeria	-	-
Antizid	Eli Lilly	-	-
Axid	Eli Lilly	-	-
Axid	Norgine Pharma	France	-
Calmaxid	Norgine AG	-	-
Flectar	Biomedica	Greece	-
Nizatidine	Eli Lilly	USA	-
Nizatidine	Pharmascience	Canada	-
Nizax	Eli Lilly	-	-
Nizaxid	Norgine Pharma	France	-
Panaxid	Norgine Pharma	France	-

Trade Name	Manufacturer	Country	Year Introduced
Peptodin	Kleva Ltd.	Greece	-
Tazac	Eli Lilly Australia Pty Limited	Australia	-
Ulxit	Tyrol Pharma GmbH	Germany	-
Zanizal	Bruno Farmaceutici S.p.A.	Italy	-

Raw Materials

2-Nitromethylenethiazolidine
Methylamine
4-Chloromethyl-2-dimethylaminomethylthiazole dihydrochloride

Manufacturing Process

Nizatidine may be prepared by 2 ways.

1. A mixture of (25.7 g) 2-nitromethylenethiazolidine and acetonitrile (50 ml) was stirred and heated at 40°C under nitrogen. Methylamine gas (16.0 g) was passed into the stirred mixture over 45 minutes to give a solution. A slurry of 4-chloromethyl-2-dimethylaminomethylthiazole hydrochloride (40.0 g) (prepared as described in EP 49,618) in acetonitrile (50 ml) was added to the solution over a period of 4.5 hours whilst methylamine gas was bubbled through the reaction mixture such that methylamine (38.3 g) was added over the period (total methylamine added was 54.3 g). The temperature of the reaction mixture varied between 24° and 35°C during the addition. After the addition, the mixture was diluted with acetonitrile (50 ml) and stirred at ambient temperature for 17 hours. A solid was removed by filtration and the filtrate was split into 2 equal portions.

Portion 1: The solution was evaporated to give a black oil which was partitioned between water (200 ml) and chloroform (200 ml). The separated chloroform phase was washed with saturated brine, then dried over magnesium sulphate, filtered and evaporated to give a reddish oil which was dissolved in acetone (200 ml), boiled under reflux, cooled to 40°C and then seeded with nizatidine. The mixture was left to stand at 0°-5°C for 64 hours. The mixture was filtered to give nizatidine (10.4 g, 37%) m.p. 118-122°C. The structure was confirmed by1H NMR. The product was 95.4% pure by HPLC.

Portion 2: The mixture was evaporated to give an oil which was taken up in chloroform (200 ml) then washed with water (100 ml). The chloroform solution was washed with brine (100 ml), dried over magnesium sulphate, and then concentrated under reduced pressure at 45°C to give a brown oil. The oil was dissolved in acetone (200 ml) and activated charcoal (0.5 g) was added to the solution. The mixture was boiled under reflux for 10 minutes, then cooled to 45°C and filtered at this temperature to remove the charcoal. The filtrate was cooled to 20°C, seeded with nizatidine (0.05 g), then cooled 0°-5°C for 45 minutes during which time crystallisation occurred. The mixture was filtered to give nizatidine (9.4 g, 32.2%).

2. A mixture of 2-nitromethylenethiazolidine (12.6 g) and water (30.0 ml) was stirred and heated at 40°C under argon. Methylamine (20.0 g of a 40% w/w aqueous solution) was added slowly over 30 minutes to the reaction mixture

at 40°C. The mixture was cooled at ambient temperature and further methylamine (23.6 g of 40% w/w aqueous solution) was added over 2.5 hours and a solution of 4-chloromethyl-2-dimethylaminomethylthiazole dihydrochloride (25.0 g) in water (30 ml) was added over 5.5 hours with the addition of the thiazole starting simultaneously with the addition of the methylamine. The reaction mixture was left to stir for a further 15 minutes and then was concentrated under reduced pressure. The solid obtained was dissolved in a mixture of methyl ethyl ketone (200 ml), aqueous potassium carbonate solution (43 ml, 10% w/w). The mixture was warmed slightly to obtain a solution. The mixture was separated and the aqueous layer was washed with methyl ethyl ketone (2 times 130 ml and then 1 times 100 ml). The combined organic layers were evaporated under reduced pressure to yield crude nizatidine (approximately 25.2 g), which was shown to be 89.4% pure by HPLC. The crude solid was dissolved in dichloromethane (300 ml). The solution was washed with water (3 times 75 ml). The combined aqueous layer and the washings were back extracted with dichloromethane and the combined organic layers were dried and concentrated under reduced pressure to give nizatidine (21.1 g, 74.3% yield). The solid was dissolved in ethanol (45 ml) by warming on a steam bath. The solution was removed from the steam bath treated with activated charcoal (2.3 g) and the mixture was boiled for a further 8 minutes. The mixture was hot filtered. The filtrate was cooled and filtered to give nizatidine (13.8 g, 48% yield) which was shown to be 99.8% pure by HPLC.

References

Ph. Cornwall; U. S. Patent No. 6,069,256; May 30 2000; assigned Knoll aktiengesellshaft (Lundeligshaffen, D.E.)

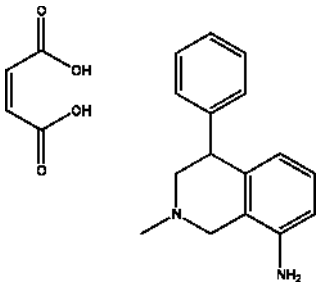
NOMIFENSINE MALEATE

Therapeutic Function: Psychostimulant

Chemical Name: 8-Amino-1,2,3,4-tetrahydro-2-methyl-4-phenyl-isoquinoline maleate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 32795-47-4; 24526-64-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Alival	Hoechst	W. Germany	1976
Merital	Hoechst	UK	1977
Alival	Hoechst	France	1977
Psicronizer	Albert Pharma	Italy	1977
Merital	Hoechst	Canada	1982
Neurolene	Magis	Italy	-
Nomival	Leiras	Finland	-

Raw Materials

Sulfuric acid	α-Bromoacetophenone
Hydrogen	(2-Nitrobenzyl)methylamine
Maleic acid	Sodium borohydride

Manufacturing Process

A solution of N-(2-aminobenzyl)-1-phenyl-2-methylaminoethanol-1 was prepared by the reaction of α-bromo-acetophenone and (2-nitrobenzyl)methylamine, followed by hydrogenation of the nitro group by means of nickel on diatomaceous earth at room temperature and reduction of the CO group by means of sodium borohydride. The intermediate thus produced was dissolved in 100 ml of methylene chloride and introduced dropwise into 125 ml of sulfuric acid at 10° to 15°C. After a short standing, the reaction mixture was poured onto ice and rendered alkaline by means of a sodium hydroxide solution. By extraction with ether, there was obtained 1,2,3,4-tetrahydro-2-methyl-4-phenyl-8-amino-isoquinoline. The base is reacted with maleic acid to give the maleate; melting point of the maleate 199° to 201°C (from ethanol).

References

Merck Index 6515
DFU 1 (2) 72 (1976)
Kleeman and Engel p. 642
PDR p. 941
DOT 13 (2) 77 (1977)
I.N. p. 685
Farbwerke Hoechst AG, Germany; British Patent 1,164,192; September 17, 1969
Ehrhart, G., Schmitt, K., Hoffmann, I. and Ott, H.; US Patent 3,577,424; May 4, 1971; assigned to Farbwerke Hoechst AG.

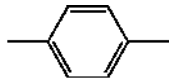
NONOXYNOL

Therapeutic Function: Spermatocide (vaginal)

Chemical Name: α-(Nonylphenyl)-ω-hydroxypoly(oxy-1,2-ethanediyl)

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 26027-38-3

Trade Name	Manufacturer	Country	Year Introduced
Ortho-Delfen	Cilag	France	1971
Semicid	Whitehall	US	1978
Intercept	Ortho	US	1980
Gynol	Ortho	US	1982
Shur-Seal	Milex	US	1983
C-Film	Hommel	Switz.	-
Emko	Emko-Schering	US	-
Encare Oval	Patentex	W. Germany	-
Glovan	Teva	Israel	-
Igepal	G.A.F.	US	-
Ortho-Creme	Cilag	US	-

Raw Materials

Isononylphenol
Sodium hydroxide
Ethylene oxide

Manufacturing Process

220 parts of isononylphenol prepared by condensation of phenol with an olefin mixture obtained by polymerization of propylene and containing essentially isononylenes are caused to react with 0.5 part of caustic alkali powder. The whole is heated to about 130°C to 135°C and the water formed is removed under reduced pressure, while stirring. Thereupon, ethylene oxide is introduced into the melt, while well stirring, during which operation care must be taken, that the temperature of the reaction mass is maintained between 180°C and 200°C. When about 300 parts of ethylene oxide are taken up, the reaction is interrupted. A water-soluble oil is obtained.

References

Merck Index 6518
PDR pp. 1661, 1900
I.N. p. 686
REM p. 1163

Steindorff, A., Balle, G., Horst, K. and Michel, R.; US Patent 2,413,477; September 3, 1940; assigned to General Aniline & Film Corp.

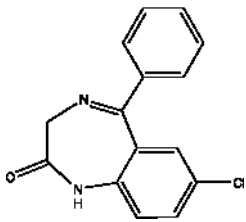
NORDAZEPAM

Therapeutic Function: Tranquilizer

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

Common Name: Nordiazepam; Desmethyldiazepam

Structural Formula:



Chemical Abstracts Registry No.: 1088-11-5

Trade Name	Manufacturer	Country	Year Introduced
Madar	Ravizza	Italy	1973
Vegesan	Mack	Switz.	1981

Raw Materials

(2-Benzoyl-4-chlorophenyl-carbamoylmethyl)carbamic acid benzyl ester
Hydrogen bromide
Acetic acid

Manufacturing Process

A solution of 3.1 g of (2-benzoyl-4-chlorophenyl-carbamoylmethyl)carbamic acid benzyl ester in 30 cc of 20% hydrobromic acid in glacial acetic acid was stirred for 45 minutes at room temperature. On addition of 175 cc of anhydrous ether, a gummy solid precipitated. After several minutes the ether solution was decanted. The resultant 5-chloro-2-glycylaminobenzophenone was not isolated, but about 155 cc of ether was added to the residue and after chilling in an ice bath, 10% sodium hydroxide was added until the mixture was alkaline. The ether layer was then separated, washed twice with water and dried over sodium sulfate. After filtration, the ether solution was concentrated to dryness in vacuo. The residue was crystallized from benzene

to yield 7-chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one.

References

Merck Index 6531
DOT 9 (6) 239 (1973)
I.N. p. 688
Stempel, A.; US Patent 3,202,699; August 24, 1965; assigned to Hoffmann-LaRoche Inc.

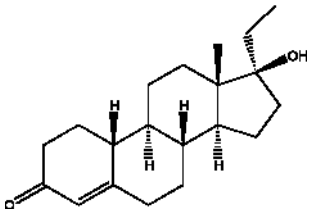
NORETHANDROLONE

Therapeutic Function: Androgen

Chemical Name: 17-Hydroxy-19-norpregn-4-ene-3-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 52-78-8

Trade Name	Manufacturer	Country	Year Introduced
Nilevar	Searle	US	1956
Nilevar	Searle	France	1960

Raw Materials

Norethindrone
Hydrogen

Manufacturing Process

Through a mixture of 11 parts of charcoal containing 5% palladium and 2,000 parts of dioxane a stream of hydrogen is passed for 60 minutes. Then 86 parts of 17-ethynyl-19-nortestosterone (Norethindrone) in 1,500 parts of dioxane are added and the mixture is hydrogenated until 2 mols of hydrogen are absorbed. The catalyst is then removed by filtration and the solvent is

evaporated under vacuum. The crystalline residue is dissolved in 2,700 parts of benzene and thus applied to a chromatography column containing 5,000 parts of silica gel. The column is washed with 2,700 parts of benzene, 4,500 parts of a 10% solution of ethyl acetate in benzene and 27,000 parts of a 20% solution of ethyl acetate in benzene and is then eluted with 30,000 parts of a 30% solution of ethyl acetate in benzene. The resulting eluate is concentrated under vacuum and the residue is recrystallized from methanol and dried to constant weight at 75°C. The 17-ethyl-19-nortestosterone thus obtained melts at about 140°C to 141°C.

References

Merck Index 6537
Kleeman & Engel p. 644
OCDS Vol. 1 p. 170 (1977)
I.N. p. 688
Colton, F.B.; US Patent 2,721,871; October 25, 1955; assigned to G.D. Searle & Co.

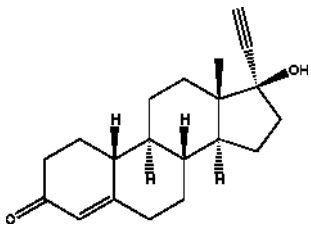
NORETHINDRONE

Therapeutic Function: Progestin

Chemical Name: 17-Hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one

Common Name: Norethisteron

Structural Formula:



Chemical Abstracts Registry No.: 68-22-4

Trade Name	Manufacturer	Country	Year Introduced
Norlutin	Parke Davis	US	1957
Ortho-Novum	Ortho	US	1963
Norinyl	Syntex	US	1964
Nor-QD	Syntex	US	1973
Brevicon	Syntex	US	-
Conceplan	Gruenenthal	W. Germany	-
Gesta-Plan	D.A.K.	Denmark	-

Trade Name	Manufacturer	Country	Year Introduced
Micronor	Ethnor	Australia	-
Micronor	Ortho	US	-
Micronovum	Cilag	W. Germany	-
Modicon	Ortho	US	-
Monogest	Spofa	Czechoslovakia	-
Norfor	Gremy-Longuet	France	-
Norgestin	Janus	Italy	-
Noriday	Syntex	US	-
Norlestrin	Parke Davis	US	-
Ovcon	Mead Johnson	US	-
Primolut N	Schering	UK	-
Tri-Norinyl	Syntex	US	-
Utovlan	Syntex	UK	-

Raw Materials

3-Methoxyestrone
Ethyl orthoformate
Lithium
Potassium
Ammonia
Acetylene
Chromic acid

Manufacturing Process

7.5 grams of 3-methoxyestrone were dissolved in 750 cc of anhydrous dioxane in a three-neck flask, placed in a box and insulated with cotton wool. 2 liters of anhydrous liquid ammonia and 15 grams of lithium metal in the form of wire were added to the mechanically stirred solution. After stirring for one hour, 150 cc of absolute ethanol were added at such speed that no bumping occurred; when the blue color had disappeared, 500 cc of water were added in the same way. The ammonia was evaporated on the steam bath and the product collected with 2 liters of water. It was extracted with ether and then with ethyl acetate and the combined extract was washed to neutral and evaporated to dryness under vacuum, leaving 7.4 grams of a slightly yellow oil.

The oil thus obtained was dissolved in 400 cc of methanol and refluxed during one hour with 150 cc of 4N hydrochloric acid. The mixture was poured into a sodium chloride solution and extracted with ethyl acetate, washed to neutral, dried and evaporated to dryness. The product was a yellow oil which showed an ultraviolet absorption maximum characteristic of a Δ^4-3-ketone.

A solution of 2.7 grams of chromic acid in 20 cc of water and 50 cc of acetic acid was added to the stirred solution of the above oil in 100 cc of acetic acid, maintaining the temperature below 20°C. After 90 minutes standing, 50 cc of methanol were added and the mixture concentrated under vacuum (20 mm). The residue was extracted with ether, washed to neutral and evaporated to dryness. The residual semicrystalline product (7 grams) was chromatographed over alumina and the fractions eluted with ether yielded 3.2 grams of Δ^4-19-norandrosten-3,17-dione having a MP of 163° to 167°C.

A solution of 2 grams of Δ^4-19-norandrosten-3,17-dione and 0.4 gram of pyridine hydrochloride in 50 cc of benzene free of thiophene was made free of moisture by distilling a small portion; 4 cc of absolute alcohol and 4 cc of ethyl orthoformate were added and the mixture was refluxed during 3 hours. 5 cc of the mixture were then distilled and after adding an additional 4 cc of ethyl orthoformate the refluxing was continued for 2 hours longer. The mixture was evaporated to dryness under vacuum and the residue was taken up in ether, washed, dried and evaporated to dryness. The residue was crystallized from hexane-acetone and then from ether to give $\Delta^{3,5}$-19-nor-3-ethoxy-androstadien-17-onewith a MP of 140° to 142°C.

One gram of potassium metal was dissolved in 25 cc of tertiary amyl alcohol by heating under an atmosphere of nitrogen. One gram of $\Delta^{3,5}$-19-nor-3-ethoxyandrostadien-17-onein 25 cc of anhydrous toluene was added and nitrogen was passed during 15 minutes. Then acetylene (especially dried and purified) was passed during 14 hours through the mechanically stirred solution, at room temperature.

The mixture was poured in water, acidified to pH 1 with dilute hydrochloric acid, heated on the steam bath for 30 minutes and then subjected to steam distillation to remove the organic solvents. The residue was filtered, dried and recystallized several times from ethyl acetate. The Δ^4-19-nor-17α-ethinylandrosten-17β-ol-3-onethus obtained had a MP of 198° to 200°C (in sulfuric acid bath), 200° to 204°C (Kofler).

References

Merck Index 6538
Kleeman & Engel p. 644
PDR pp. 1104, 1297, 1358, 1372, 1793
OCDS Vol. 1 p. 164 (1977) & 2, 145 (1980)
DOT 4 (1) 19 (1968) & 9 (4) 144 (1973)
I.N. p. 688
REM p. 992
Djerassi, C., Miramontes, L. and Rosenkranz, G.; US Patent 2,744,122; May 1, 1956; assigned to Syntex SA, Mexico
de Ruggieri, P.; US Patent 2,849,462; August 26, 1958

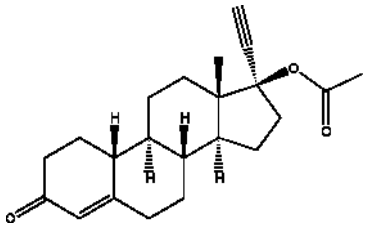
NORETHINDRONE ACETATE

Therapeutic Function: Chemical Name: 19-Nor-17α-pregn-4-en-20-yn-3-one, 17-hydroxy-, acetate

Common Name: -

Chemical Abstracts Registry No.: 51-98-9

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Norlestrin	Parke Davis	US	1964
Milligynon	Schering	France	1978
Aygestrin	Ayerst	US	1982
Brevicon	Syntex	US	-
Norlutin-A	Parke Davis	UK	-
Primolut-Nor	Schering	W. Germany	-

Raw Materials

Norethindrone
Acetic anhydride
Hydrogen chloride

Manufacturing Process

2.98 grams of 17-ethinyl-19-nor-testosterone (norethindrone) are suspended in 30 cc of acetic anhydride and a solution of 1.9 grams of p-toluenesulfonic acid in 19 cc of acetic anhydride is gradually added while cooling and stirring. Complete dissolution takes place after about one hour. After additional 30 to 60 minutes, a thick, pasty mass separates. The reaction is permitted to continue for a total period of 5 hours, whereupon water is added to the reaction mixture and the 3-enol-17-diacetate which separates after stirring for 1 to 2 hours is filtered off, washed until neutral and dried in vacuo over calcium chloride at room temperature.

In order to prepare the monoacetate, the crude diacetate is suspended in 150 cc of methanol and, after adding 1.5 cc, concentrated hydrochloric acid, heated to boiling for 15 minutes in a nitrogen atmosphere. The crude monoacetate which separates upon the addition of water after cooling is filtered off, washed and dried in vacuo over calcium chloride at room temperature. The pure 17-acetete, obtained after repeated recrystallizations from methylene chloride/hexane has a MP of 161° to 162°C.

References

Merck Index 6538
Kleeman & Engel p. 645
PDR pp. 615, 1378
OCDS Vol. 1 p. 165 (1977)

I.N. p. 689
REM p. 992
Engelfried, O., Kaspar, E., Schenck, M. and Popper, A.; US Patent 2,964,537; Dec. 13, 1960; assigned to Schering AG, Germany

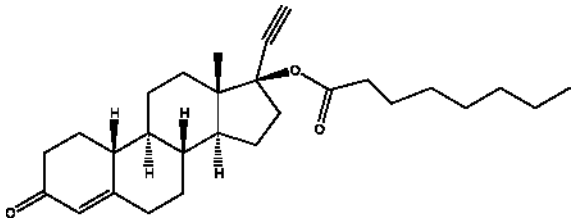
NORETHISTERONE ENANTHATE

Therapeutic Function: Progestin

Chemical Name: 19-Norpregn-4-en-20-yn-3-one, 17-((1-oxoheptyl)oxy)-, (17α)-

Common Name: Norethindrone enanthate; Norethisterone enanthate; Norethisterone heptanoate

Structural Formula:



Chemical Abstracts Registry No.: 3836-23-5

Trade Name	Manufacturer	Country	Year Introduced
Norigest	Schering	-	-

Raw Materials

17-Ethinyl-19-nor-testosteron
Enanthic acid

Manufacturing Process

1 g 17-ethinyl-19-nor-testosteron was refluxed with 5 ml of enanthic acid anhydride on an oil bath at temperature 180°C 17 hours. Then the reaction mixture was distilled with water steam to the full disappearence of smell of enantic acid. After that it was washed with 2 N sodium hydroxide and finally with water to neutral, dried over sodium sulfate and evaporated to dryness. The oily residue was rubbed with some drops of methanol and stood at -8°C 24 hours to give the crystals of 3-endol diester; MP: 82°-84°C, 2 g of it was dissolved in 120 ml of methanol and heated with 1.2 ml concentrated hydrochloric acid. The partly saponified product was distilled with water steam

to full disappearence of smell of enantic acid. The residue was mixed with ether, washed with 2 N sulfuric acid, 2 N sodium hydroxide, finally with water to neutral dried over sodium sulfate and evaporated to dryness. The residue was stirred with pentane and cooled for crystallization. Pure enanthate was crystallized after repeated solution in pentane. 17-α-Ethinyl-19-nortestosterone enanthate had MP: 68°-71°C.

References

Engelfried O. et al.; D.B. Patent No. 1,017,166; June 16, 1956; Schering Aktiengesellschaft, Berlin

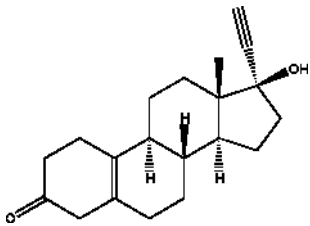
NORETHYNODREL

Therapeutic Function: Progestin

Chemical Name: 17-Hydroxy-19-nor-17α-pregn-5(10)-en-20-yn-3-one

Common Name: 13-Methyl-17-ethynyl-17-hydroxy-1,2,3,4,6,7,8,9,11,12,13,14,16,17-tetradecahydro-15H-cyclopenta-α-phenanthren-3-one

Structural Formula:



Chemical Abstracts Registry No.: 68-23-5

Trade Name	Manufacturer	Country	Year Introduced
Enovid	Searle	US	1957

Raw Materials

3-Methoxy-17-oxo-2,5-estradiene
Acetylene
Acetic acid

Manufacturing Process

Convenient starting materials are the ethers of 3-hydroxy-13-methyl-1,4,6,7,8,9,11,12,13,14,16,17-dodecahydro-15H-cyclopenta-α-phenanthren-

17-one described in US Patent 2,655,518, according to US Patent 2,691,028 where the following preparation is also described. The methyl ether is also designated as 3-methoxy-17-oxo-2,5-estradiene.

A stirred solution of 10.6 parts of 3-methoxy-13-methyl-1,4,6,7,8,9,11,12,13, 14,16,17dodecahydro-15H-cyclopenta-α-phenanthren-17-one in 700 parts of anhydrous ether and 45 parts of dry toluene is cooled to 0°C and saturated with dry acetylene. While a slow stream of acetylene is passed through the reaction mixture, a solution of 20 parts of potassium t-amylate in 135 parts of anhydrous t-pentanol is added in the course of 15 minutes with stirring. Passage of acetylene and stirring are continued for an additional 4½ hours. After standing at 0°C for 16 hours, the mixture is washed with aqueous ammonium chloride solution until the aqueous phase is neutral, then with water and saturated sodium chloride solution. The organic layer is dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to a residue of about 250 parts. 500 parts of petroleum ether are added and after standing at 0°C for an hour, the mixture is filtered. The collected precipitate is recrystallized from ether. The resulting 3-methoxy-13-methyl-17-ethynyl-1,4,6,7,8,9,11,12,13,14,16,17-dodecahydro-15H-cyclopenta-α-phenanthren-17-ol melts at about 181° to 182°C.

To a refluxing solution of 10 parts of 3-methoxy-17-ethynyl-17-hydroxy-13-methyl-1,4,6,7,8,9,11,12,13,14,16,17-dodecahydro-15H-cyclopenta-α-phenanthrene in 500 parts of methanol, 20 parts of glacial acetic acid are added. Refluxing is continued for 7 minutes, water is added to the point of turbidity and the reaction mixture is permitted to come to room temperature. The precipitate is collected on a filter and recrystallized from aqueous methanol. The 13-methyl-17-ethynyl-17-hydroxy-1,2,3,4,6,7,8,9,11,12,13,14, 16,17-tetradecahydro-15H-cyclopenta-α-phenanthren-3-one thus obtained melts at about 169° to 170°C.

References

Merck Index 6539
Kleeman & Engel p. 647
PDR p. 1680
OCDS Vol. 1 p. 186 (1977)

DOT 4 (1) 22 (1968)
I.N. p. 689
REM p. 993
Colton, F.B.; US Patent 2,691,028; October 5, 1954; assigned to G.D. Searle & Co.
Colton, F.B.; US Patent 2,725,389; November 29, 1955; assigned to G.D. Searle & Co.

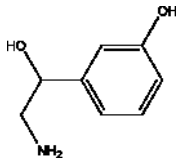
NORFENEFRINE

Therapeutic Function: Adrenergic

Chemical Name: α-(Aminomethyl)-3-hydroxybenzenemethanol

Common Name: Norphenylephrine

Structural Formula:



Chemical Abstracts Registry No.: 536-21-0; 4779-94-6 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Zordel	Grelan	Japan	1970
Coritat	Green Cross	Japan	-
Esbufon	Schaper and Brummer	W. Germany	-
Euro-Cir	Virgiliano	Italy	-
Molycor R	Mepha	Switz.	-
Nevadral	Pharmacia	Sweden	-
Normetolo	Selvi	Italy	-
Novadral	Goedecke	W. Germany	-
Stagural	Stada	W. Germany	-
Sympatosan	Kwizda	Austria	-
Tonolift	Teisan	Japan	-

Raw Materials

Sodium iodide
Hydrogen
Hexamethylenetetramine
m-Acetoxyacetophenone
Bromine

Manufacturing Process

100 parts of the hydrochloride of meta-hydroxy-ω-aminoacetophenone of melting point 220°C to 222°C (obtainable by brominating meta-acetoxyacetophenone, causing the bromoketone to react with sodium iodide, adding hexamethylenetetramine to the iodide in an indifferent solvent and scission of the addition product in acid solution) are shaken in aqueous solution with hydrogen in presence of 2 parts of palladium catalyst until 2 atomic proportions of hydrogen have been absorbed. The catalyst is now filtered and the filtrate evaporated in a vacuum; and the crystalline and completely dry residue is dissolved in absolute alcohol and a precipitate is produced by adding dry ether. The hydrochloride of meta-hydroxyphenylethanolamine thus obtained forms white crystals of melting point 159°C to 160°C.

References

Merck Index 6540

Kleeman & Engel p. 647
I.N. p.689
Legerlotz, H.; US Patent 2,312,916; March 2, 1943; assigned to Ciba Pharmaceutical Products Inc.

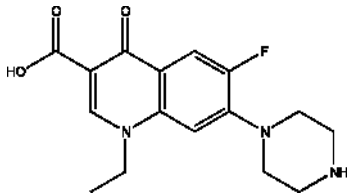
NORFLOXACIN

Therapeutic Function: Antibacterial

Chemical Name: 1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 70458-96-7

Trade Name	Manufacturer	Country	Year Introduced
Noroxin	MSD	Italy	1983
Sebercim	I.S.F.	Italy	1983
Primoxin	Sharp and Dohme	W. Germany	1983
Noroxin	MSD	Switz.	1983
Fulgram	A.B.C.	Italy	-

Raw Materials

7-Chloro-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
Piperazine

Manufacturing Process

36 g (0.134 mol) of 7-chloro-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 46 g of piperazine and 210 cm^3 of pyridine were heated under reflux for 6 hours, while stirring. After the starting material had dissolved, a precipitate appeared after heating for about 2 hours 30 minutes. The major part of the solvent was removed by concentration in vacuo (15 mm Hg; 100°C). In order to remove the pyridine as completely as possible, the residue was taken up in 200 cm3of water and the concentration in vacuo was repeated.

The residue, resuspended in 150 cm^3 of water, was stirred. 150 cm^3 of 2N NaOH were added thereto. The solution, which was slightly turbid, was treated with 5 g of animal charcoal and stirred for 30 minutes. After filtration, the pH was brought to 7.2 by adding acetic acid while stirring. The precipitate was filtered off, washed with water and dissolved in 250 cm^3 of a 10% aqueous acetic acid. The acid solution (pH 4.4) was filtered and then brought to pH 7.2 by gradually added 2N NaOH.

The suspension was heated to 90°C, while stirring. The crystals were separated and recrystallized from 280 cm^3 of a mixture of DMF (1 volume) and ethanol (4 volumes). After drying in vacuo over phosphorus pentoxide, 29.5 g (yield 70%) of 1-ethyl-6-fluoro-4-oxo-7-piperazinyl-1,4-dihydroquinoline-3-carboxylic acid, melting point 222°C, were obtained.

In air, this product is hygroscopic and gives a hemihydrate.

References

Merck Index 6541
DFU 7 (8) 586 (1982)
DOT 19 (6) 341 (1983)
I.N. p. 689
Pesson, M.; US Patent 4,292,317; September 29, 1981; assigned to Laboratorie Roger Bellon (France) and Dainippon Pharmaceutical (Japan)

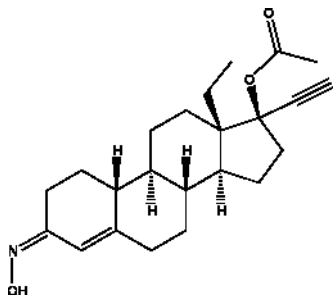
NORGESTIMATE

Therapeutic Function: Progestin

Chemical Name: 18,19-Dinorpregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-, 3-oxime, (17α)-

Common Name: Dexnorgestrel acetime; Norgestimate

Structural Formula:



Chemical Abstracts Registry No.: 35189-28-7

Trade Name	Manufacturer	Country	Year Introduced
Ortrel	Janssen Cilag	-	-

Raw Materials

D-17β-Acetoxy-13β-ethyl-17α-ethynyl-gon-4-en-3-one
Hydroxylamine hydrochloride

Manufacturing Process

A solution of 4.5 g of D-17β-acetoxy-13β-ethyl-17α-ethynyl-gon-4-en-3-one in 15 ml of pyridine and 2.0 g of hydroxylamine hydrochloride hydroxylamine hydrochloride is heated on a steam bath for 45 min. It is then cooled and poured into a large amount of ice-water, after which the solid which is thus produced is filtered off and air dried. Recrystallization from methylene chloride-ethanol gives D-17β-acetoxy-13α-ethyl-17α-ethynyl-gon-4-en-one oxime, m.p. 214-218°C; $[\alpha]_D^{25}$ = +41°.

References

Tullar B.F., Greebbush E.; US Patent Dec. 18, 1956; Assigned to Sterling Drug Inc., Del., a corporation of Delaware

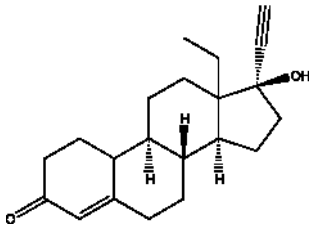
NORGESTREL

Therapeutic Function: Progestin

Chemical Name: 13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one

Common Name: 17α-Ethynyl-18-homo-19-nortestosterone

Structural Formula:



Chemical Abstracts Registry No.: 797-63-7

Trade Name	Manufacturer	Country	Year Introduced
Ovrette	Wyeth	US	1968
Eugynon	Schering	Italy	1969
Neogest	Schering	UK	1974
Microlut	Schering	W. Germany	1974
Planovar	Wyeth	Japan	1979
Duoluton	Schering	Japan	1979
Prempak	Ayerst	UK	-

Raw Materials

(+/-)-1,4-Dihydro-17α-ethynyl-18-homo-oestradiol 3-methyl ether
Hydrogen chloride

Manufacturing Process

To 0.7 gram of (+/-)-1,4-dihydro-17α-ethynyl-18-homo-oestradiol 3-methyl ether in 36 cc methanol was added 1.6 cc water and 2.4 cc concentrated hydrochloric acid. After standing at room temperature for 2 hours ether was added, and the washed and dried ethereal solution was evaporated, yielding a gum which was dissolved in 5 cc benzene and the solution absorbed on 50 grams of an activated fuller's earth. Elution with light petroleum containing increasing proportions of benzene gave a crystalline by-product: further elution with benzene containing a small proportion of ether gave a crystalline product which was recrystallized from ethyl acetate, yielding 0.11 gram of (+/-)-17α-ethynyl-18-homo-19-nortestosterone. MP 203° to 206°C.

References

Merck Index 6543
Kleeman & Engel p. 648
PDR pp. 1952, 1958, 1965
OCDS Vol. 1 p.167 (1977); 2, 151 (1980) & 3, 84 (1984)
DOT 4 (1) 24 (1968)
I.N. p. 690
REM p. 993
Hughes, G.A. and Smith, H.; British Patent 1,041,280; September 1, 1966

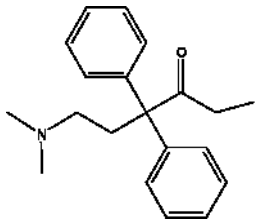
NORMETHADONE

Therapeutic Function: Narcotic analgesic, Antitussive

Chemical Name: 3-Hexanone, 6-(dimethylamino)-4,4-diphenyl-

Common Name: Desmethylmethadone; Noramidone; Normetadone; Normethadone; Phenyldimazone

Structural Formula:



Chemical Abstracts Registry No.: 467-85-6

Trade Name	Manufacturer	Country	Year Introduced
Normethadone	Isotec, Inc.	-	-

Raw Materials

Sodium amide
Magnesium
Ethyl bromide
Diphenylacetonitrile
2-Dimethyaminoethylchloride

Manufacturing Process

65 g of thin powder sodium amide was added to a solution of 289 g diphenylacetonitrile in 300 ml benzene for 15-20 minutes at temperature 45°-50°C. Then the mixture was cooled to about 25°C, 182 g 2-dimethyaminoethylchloride was added dropwise. On ending the reaction it was heated to reflux for 15 minutes, diluted with water, the benzene layer separated and washed with diluted hydrochloric acid. The acid layer was alkalified with sodium hydroxide, extracted with ether and dried over potash. The ether was distilled off to dryness and the residue solidified to give colorless crystals of 4-dimethylamino-2,2-diphenylbutyronitrile. The C_2H_5MgBr was made from 66.5 g of magnesium, 300 ml dry ether and 33 g ethyl bromide and mixed with above prepared nitrile in 150 ml toluene. After the ending of reaction, the mixture was heated for 1.5 hour on the steam bath to give hard-grained bulk. It was mixed with 600 ml concentrate hydrochloric acid in 1500 ml water. On cooling 500 ml benzene was added and three layers arose. The middle layer crystallized shortly. The crystals were filtered off, washed with 100 ml 2 N hydrochloric acid and 3 x 100 ml acetone. 6-Dimethylamino-4,4-diphenyl-3-hexanone was prepared as a hydrochloride. MP: 231°C. The salt may be transformed into the base by adding of an equivalent of any basic compound (triethyl amine, soda and so on).

References

Bockmuhl M., Ehrhart G.; D.B. Patent No. 865,314; July 8, 1949; Farbwerke Hoechst, vormals Meister Lucius and Bruning, Frankfurt/M.-Hochst

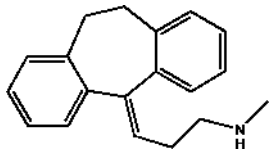
NORTRIPTYLINE

Therapeutic Function: Antidepressant

Chemical Name: 3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-N-methyl-1-propanamine

Common Name: Desmethylamitriptyline; Desitriptyline

Structural Formula:



Chemical Abstracts Registry No.: 72-69-5; 894-71-3 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Aventyl	Lilly	UK	1963
Nortrilen	Tropon	W. Germany	1964
Aventyl	Lilly	US	1965
Psychostyl	Lilly	France	1966
Vividyl	Lilly	Italy	1967
Noritren	Dainippon	Japan	1971
Altilev	Squibb	France	1976
Pamelor	Sandoz	US	1977
Allegron	Dista	UK	-
Ateben	Sintyal	Argentina	-
Martimil	Lafarquin	Spain	-
Nortylin	Ikapharm	Israel	-
Norzepine	Bial	Portugal	-
Sensaval	Pharmacia	Sweden	-

Raw Materials

5-(3-Chloropropylidene)dibenzo[a,d]cyclohepta[1,4]diene
Methylamine

Manufacturing Process

A mixture of 114.5 g of 5-(3-chloropropylidene)dibenzo[a,d]cyclohepta[1,4] diene, 75 ml of benzene, and about 400 ml of methylamine is heated in an autoclave at 120°C for six hours. The excess methylamine is distilled from the reaction mixture under vacuum and the residue is stirred with 300 ml of water. Acidification of the mixture with hydrochloric acid causes the separation of the hydrochloride of 5-(3-methylaminopropylidene)dibenzo[a,d]

cyclohepta[1,4]diene. The product is collected by filtration and is purified by recrystallization from a mixture of absolute ethanol and ethyl acetate. MP 210°C to 212°C.

References

Merck Index 6558
Kleeman & Engel p. 651
PDR p. 1588
OCDS Vol. 1 p. 151 (1977)
DOT 1 (1) 22 (1965) & 9 (6) 219 (1973)
I.N. p. 691
REM p. 1096
Peters, L.R. and Hennion, G.F.; US Patent 3,281,469; October 25, 1966; assigned to Eli Lilly & Co.

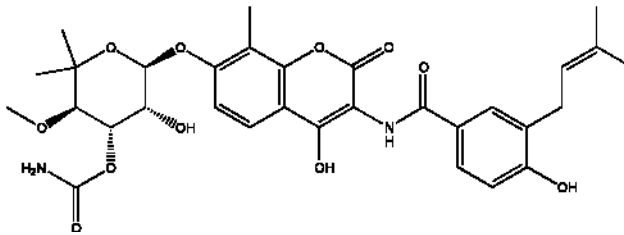
NOVOBIOCIN

Therapeutic Function: Antibiotic

Chemical Name: N-[7-[[3-O-(Aminocarbonyl)-5,5-di-C-methyl-4-O-methyl-α-L-lyxopyranosyl]oxy]-4-hydroxy-8-methyl-2-oxo-2H-1-benzopyran-3-yl]-4-hydroxy-3-(3-methyl-2-butenyl)benzamide

Common Name: Streptonivicin

Structural Formula:



Chemical Abstracts Registry No.: 303-81-1

Trade Name	Manufacturer	Country	Year Introduced
Albamycin	Upjohn	US	1956
Cathomycin	MSD	US	1956
Cathomycine	Theraplix	France	1957
Albiocin	Upjohn	Japan	-
Inamycin	Hoechst	W. Germany	-
Robiocina	San Carlo	Italy	-
Stilbiocina	Donatello	Italy	-

Raw Materials

Bacterium Streptomyces spheroides
Soybean meal
Dextrose

Manufacturing Process

The preparation of novobiocin by fermentation is described in US Patent 3,049,534 as follows: A medium containing 2% soybean meal, 1% dextrose, 0.25% sodium chloride and 0.75% distiller's solubles was made up in tap water. About 25 ml of the prepared medium was placed in a 75 ml vial and sterilized by heating at 120°C for 20 minutes. The sterilized medium was then inoculated with a vegetative culture of Streptomyces spheroides MA-319 (NRRL 2449), and the vial loosely stoppered with cotton. The vial was then placed on a shaking machine with an amplitude of 1½ inches at 28°C for 6 days. At the end of this fermentation time, the fermented broth was assayed using the cylinder-plate method with Bacillus megatherium ATCC 9885 as the assay organism and found to have an activity of 600 units/ml or 30 mcg/ml of novobiocin. The production of larger quantities of novobiocin by submerged fermentation in suitable tanks is also described in US Patent 3,049,534.

The preparation of novobiocin by a synthetic route is described in US Patent 2,966,484, as well as in US Patent 2,925,411.

References

Merck Index 6563
Kleeman & Engel p. 652
I.N. p. 693
REM p. 1212
Stammer, C.H.; US Patent 2,925,411; February 16, 1960
Walton, E. and Spencer, C.; US Patent 2,966,484; December 27, 1960; assigned to Merck & Co., Inc.
Caron, E.L., Johnson, J.L., Hinman, J.W. and Hoeksema, H.; US Patent 2,983,723; May 9, 1961; assigned to The Upjohn Company
Wolf, F.J.; US Patent 3,000,873; September 19, 1961; assigned to Merck & Co., Inc.
Stammer, C.H. and Miller, I.M.; US Patent 3,049,475; August 14, 1962; assigned to Merck & Co., Inc.
Miller, I.M.; US Patent 3,049,476; August 14, 1962; assigned to Merck & Co., Inc.
Wallick, H.; US Patent 3,049,534; August 14, 1962; assigned to Merck & Co., Inc.
French, G.H.; US Patent 3,068,221; December 11, 1962; assigned to The Upjohn Co.

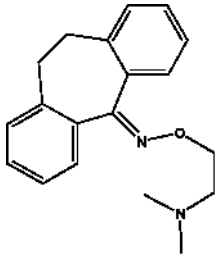
NOXIPTILIN

Therapeutic Function: Psychostimulant

Chemical Name: 10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-one O-[2-(dimethylamino)ethyl]oxime

Common Name: Dibenzoxin

Structural Formula:



Chemical Abstracts Registry No.: 3362-45-6; 4985-15-3 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Agedal	Bayer	W. Germany	1969
Agedal	Bayer	Italy	1975
Nogedal	Theraplix	France	1978
Elronon	Deutsches Hydrierwerk	E. Germany	-
Sipcar	Bernabo	Argentina	-

Raw Materials

5-Keto-10,11-dihydrodibenzo[a,d]cycloheptene
Hydroxylamine hydrochloride
Sodium amide
β-(Dimethylamino)ethyl chloride

Manufacturing Process

15 grams 5-keto-10,11-dihydrodibenzo-[a,d]cycloheptene dissolved in 225 ml of pyridine was mixed with 15 grams hydroxylamine hydrochloride, and the mixture was boiled under reflux for 22 hours. The bulk of the pyridine was then distilled off under reduced pressure, the residue was poured into water, and the aqueous mixture thus formed was extracted with ether.

The ether extract was washed with water, dried and heated to distill off the ether. The solid residue was recrystallized from a mixture of benzene and light petroleum (BP 40° to 60°C). 12.8 grams of the recrystallized oxime had a MP of 167° to 169°C.

A solution of 22 grams of the above described 5-oximino-10,11-dihydrodibenzo-[a,d]cycloheptene in 120 ml benzene was treated with 7.8

grams sodamide and the mixture was stirred and heated under reflux for 2 hours. At this stage, the 14.4 grams of hydrochloride of β-(dimethylamino) ethyl chloride was added and heating under reflux was continued for 16 hours. 50 ml water was then cautiously added to decompose unreacted sodamide and the benzene layer was separated and extracted with dilute (10%) aqueous hydrochloric acid.

The aqueous acid extracts were made alkaline with concentrated aqueous potassium hydroxide solution and then extracted with ether. The ether extracts were dried, the solvent was removed and the residual oil was distilled under reduced pressure. The product was 14.5 grams of the fraction boiling at 160° to 164°C, under a pressure of 0.05 mm of mercury.

References

Merck Index 6566
Kleeman & Engel p. 653
DOT 6 (2) 56 (1970)
I.N. p. 695
Wrigley, T.I. and Leeming, P.R.; British Patent 1,045,911; October 19, 1966; assigned to Pfizer Limited, England
Schutz, S. and Hoffmeister, F.; US Patent 3,505,321; April 7, 1970; assigned to Farbenfabriken Bayer A.G.

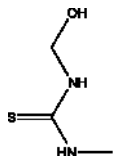
NOXYTIOLIN

Therapeutic Function: Antifungal

Chemical Name: 1-Methyl-3-hydroxymethyl-2-thiourea

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 15599-39-0

Trade Name	Manufacturer	Country	Year Introduced
Noxyflex	Geistlich	UK	1964
Noxyflex	Innothera	France	1978
Gynaflex	Geistlich	Switz.	-

Raw Materials

Methyl thiourea
Formaldehyde

Manufacturing Process

400 g methyl thiourea and 2.5 g $NaHCO_3$ are dissolved in 400 ml formaldehyde solution of 35% concentration. After having been left at ordinary temperature for 2 to 3 hours, the solution is adjusted with dilute HCl to pH 7 to 7.5. After the reaction mixture had been left overnight at 15°C some of the final product crystallized and was filtered off using a Buchner funnel. The mother liquor was concentrated by evaporation in vacuo at a bath-temperature of 30°C. The crystals obtained were again collected by filtration using a Buchner funnel and were combined with the first crystalline fraction and dried in vacuo at ordinary temperature. Yield of pure substance 400 g; melting point 84°C to 86°C.

References

Merck Index 6567
Kleeman & Engel p. 653
DOT 4 (3) 106 (1968)
I.N. p. 695
Aebi, A. and Hafstetter, E.; British Patent 970,414; January 12, 1960; assigned to Ed Geistlich Sohne AG fur Chemische Industrie.

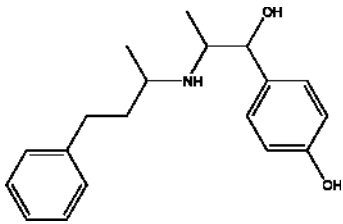
NYLIDRIN

Therapeutic Function: Vasodilator

Chemical Name: 4-Hydroxy-α-[1-[(1-methyl-3-phenylpropyl)amino]ethyl] benzenemethanol

Common Name: Buphenine

Structural Formula:



Chemical Abstracts Registry No.: 447-41-6

Trade Name	Manufacturer	Country	Year Introduced
Arlidin	U.S.V.	US	1955
Arlibide	U.S.V.	Argentina	-
Bufedon	Cosmopharma	Netherlands	-
Buphedrin	Tatsumi	Japan	-
Dilatol	Tropon	W. Germany	-
Dilatropon	Draco	Sweden	-
Dilaver	Neopharma	Finland	-
Dilydrin	Medichemie	Switz.	-
Nyderal	Kobayashi	Japan	-
Nylin	Toho	Japan	-
Opino	Bayropharm	W. Germany	-
Penitardon	Woelm	W. Germany	-
Perdilat	Abdi Ibrahim	Turkey	-
Perdilatal	Smith and Nephew	UK	-
Pervadil	I.C.N.	Canada	-
Pharmadil	Pharmacia	Sweden	-
Rudilin	Darby	US	-
Rydrin	Kodama	Japan	-
Shatorn	Seiko	Japan	-
Tacodilydrin	Swiss Pharma	W. Germany	-
Tocodrin	Medichemie	Switz.	-
Vasiten	Crinos	Italy	-
Verina	Fujisawa	Japan	-

Raw Materials

p-Benzoxy-α-bromopropiophenone
1-Phenyl-3-aminobutane
Hydrogen

Manufacturing Process

8 grams of the hydrobromide of 1-(p-benzoxyphenyl)-2-(α-methyl-γ-phenyl-propylamino)-propanone-(1) were obtained by heating equivalent quantities of p-benzoxy-α-bromopropiophenone and 1-phenyl-3-amino-butane for an hour on the water bath in the absence of solvents. The product was purified by twice boiling with five times the quantity of acetic acid and filtration at 80°C, then shaken in contact with hydrogen with 0.8 gram of Raney nickel in 70 cc of pure methanol containing 0.96 gram (corresponding to 1 mol) of KOH. After 4 hours 2 mols of hydrogen had been taken up and the solution was filtered from the catalyst, evaporated in vacuo, and the residue triturated first with water to remove potassium bromide and then with methanol to remove potassium bromide. 3.7 grams (72% of the theoretical yield) of the compound specified, melting at 110° to 112°C, were obtained, as described in US Patent 2,661,373.

References

Merck Index 6577
Kleeman & Engel p. 123
PDR pp. 830, 993, 1606, 1809, 1999
OCDS Vol. 1 p. 69 (1977)
I.N. p. 163
REM p. 892
Schopf, C. and Kunz, K.J.; US Patent 2,661,372; December 1, 1953; assigned to Troponwerke Dinklage & Co., Germany
Kulz, F. and Schopf, C.; US Patent 2,661,373; December 1, 1953

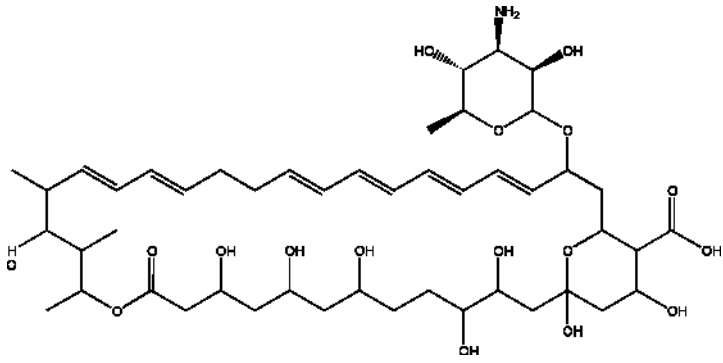
NYSTATIN

Therapeutic Function: Antifungal

Chemical Name: Nystatin

Common Name:-

Structural Formula:



Chemical Abstracts Registry No.: 1400-61-9

Trade Name	Manufacturer	Country	Year Introduced
Mycostatin	Squibb	US	1954
Mycostatine	Squibb	France	1956
Nysta-Dome	Dome	US	1964
Nilstat	Lederle	US	1970
Nysert	Norwich Eaton	US	1979
Multilind	F.A.I.R.	UK	1979

Trade Name	Manufacturer	Country	Year Introduced
Nystex	Savage	US	1983
Biofanal	Pfleger	W. Germany	-
Candex	Dome	US	-
Candio-Hermal	Hermal	W. Germany	-
Herniocid	Mayrhofer	Austria	-
Korostatin	Holland Rantos	US	-
Mycolog	Squibb	US	-
Myco-Triacet	Lemmon	US	-
Mytrex	Savage	US	-
Nadostine	Nadeau	Canada	-
Nyaderm	K-Line	Canada	-
Nystacid	Farmos	Finland	-
Nyst-Olone	Schein	US	-
Rivostatin	Rivopharm	Switz.	-
Stereomycin	Medica	Finland	-

Raw Materials

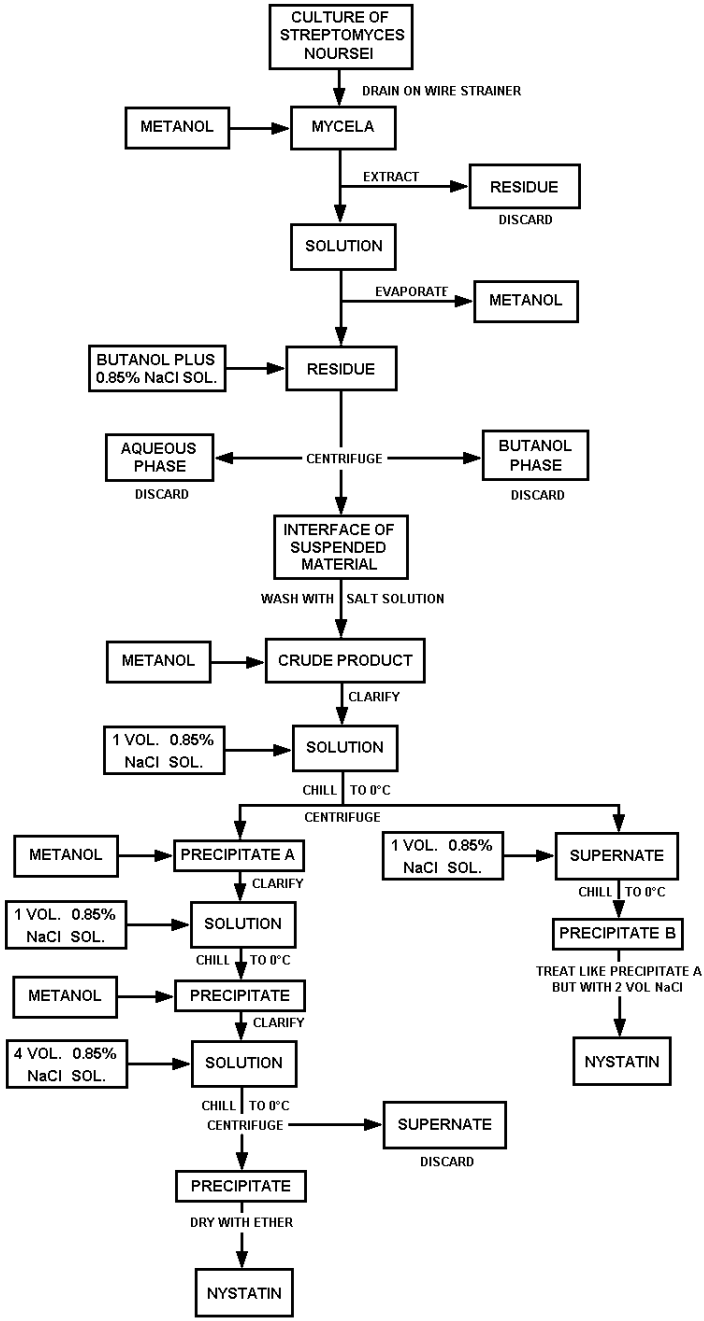
Bacterium Streptomyces noursei
Nutrient medium

Manufacturing Process

A typical isolation and recovery procedure for nystatin is described in US Patent 2,797,183 and is shown in the following diagram:

References

Merck Index 6580
Kleeman & Engel p. 654
PDR pp.888, 1022, 1034, 1429, 1604, 1751
I.N. p. 696
REM p. 1230
Vandeputte, J. and Gold, W.; US Patent 2,786,781; March 26, 1957; assigned to Olin Mathieson Chemical Corporation
Hazen, E.L. and Brown, R.F.; US Patent 2,797,183; June 15, 1957; assigned to Research Corporation
Vandeputte, J.; US Patent 2,832,719; April 29, 1958; assigned to Olin Mathieson Chemical Corporation
Renella, J.G.; US Patent 3,517,100; June 23, 1970; assigned to American Cyanamid Co.


CULTURE OF STREPTOMYCES NOURSEI
DRAIN ON WIRE STRAINER
METANOL
MYCELA
EXTRACT
RESIDUE
DISCARD
SOLUTION
EVAPORATE
METANOL
BUTANOL PLUS 0.85% NaCl SOL.
RESIDUE
AQUEOUS PHASE
DISCARD
CENTRIFUGE
BUTANOL PHASE
DISCARD
INTERFACE OF SUSPENDED MATERIAL
WASH WITH SALT SOLUTION
METANOL
CRUDE PRODUCT
CLARIFY
1 VOL. 0.85% NaCl SOL.
SOLUTION
CHILL TO 0°C
CENTRIFUGE
METANOL
PRECIPITATE A
CLARIFY
1 VOL. 0.85% NaCl SOL.
SOLUTION
CHILL TO 0°C
METANOL
PRECIPITATE
CLARIFY
4 VOL. 0.85% NaCl SOL.
SOLUTION
CHILL TO 0°C
CENTRIFUGE
SUPERNATE
DISCARD
PRECIPITATE
DRY WITH ETHER
NYSTATIN
1 VOL. 0.85% NaCl SOL.
SUPERNATE
CHILL TO 0°C
PRECIPITATE B
TREAT LIKE PRECIPITATE A BUT WITH 2 VOL NaCl
NYSTATIN