# N

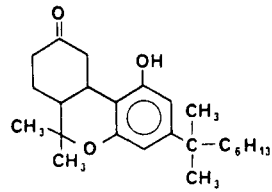
## NABILONE

**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 | U.K. | 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)-6,6a$\beta$,7,8,10,10a$\beta$-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)-6,6a$\beta$,7,8,10,10a$\beta$-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.; U.S. 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.

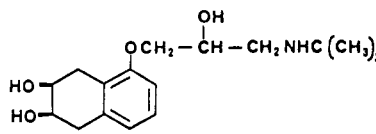
# NADOLOL

**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 | U.K. | 1979 |
| Corgard | Squibb | U.S. | 1979 |
| Corgard | Squibb | Italy | 1980 |
| Corgard | Squibb | France | 1982 |
| Betadol | Fako | Turkey | — |
| Corzide | Squibb | U.S. | — |

**Raw Materials**

5,8-Dihydro-1-naphthol
Silver acetate
Sodium hydroxide
Epichlorohydrin
Acetic anhydride
Iodine
Sodium methoxide
tert-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.; U.S. Patent 3,935,267; January 27, 1976; assigned to E.R. Squibb & Sons, Inc.

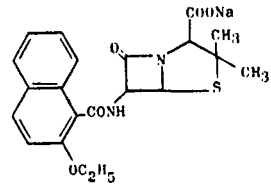
# NAFCILLIN SODIUM

**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 | U.S. | 1964 |
| Nafcil | Bristol | U.S. | 1976 |
| Nallpen | Beecham | U.S. | 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.; U.S. Patent 3,157,639; November 17, 1964; assigned to Beecham Group Limited, England

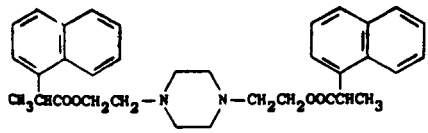
## NAFIVERINE

**Therapeutic Function:** Antispasmodic

**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

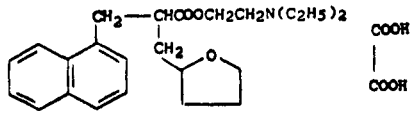
## NAFRONYL OXALATE

**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 |

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Prazilene | Lipha | U.K. | 1972 |
| Praxilene | Formenti | Italy | 1973 |
| Praxilene | Biochimica | Switz. | 1980 |
| Citoxid | Disprovent | Argentina | — |

**Raw Materials**

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

**Manufacturing Process**

30 grams (0.106 mol) of β-(1-naphthyl)-β'-tetrahydrofuryl isobutyric acid are heated under reflux for 8½ 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.; U.S. Patent 3,334,096; August 1, 1967; assigned to Lipha, Lyonnaise Industrielle Pharmaceutique, France

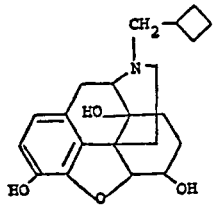
## NALBUPHINE

**Therapeutic Function:** Analgesic

**Chemical Name:** N-cyclobutylmethyl-14-hydroxydihydronormorphinone

**Common Name:** —

**Structural Formula:**



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

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Nubain | Du Pont | U.S. | 1979 |
| Nubain | Du Pont | U.K. | 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.; U.S. Patent 3,332,950; July 25, 1967; assigned to Endo Laboratories, Inc.

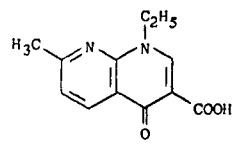
# NALIDIXIC ACID

**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 | U.S. | 1964 |
| Nalidixique | Winthrop | France | 1974 |
| *Jicsron* | *Towa Yakuhin* | *Japan* | 1981 |
| Baktogram | Farmakos | Yugoslavia | – |
| Betaxina | Amelix | Italy | – |
| Chemiurin | Cifa | Italy | – |
| Cybis | Breon | U.S. | – |
| Dixiben | Benvegna | Italy | – |
| Dixurol | I.T.I. | Italy | – |
| Enexina | S.I.T. | Italy | – |
| Entolon | Sawai | Japan | – |
| 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 | Yugoslavia | – |
| Restelon | Maruishi | Japan | – |
| Sicmylon | Niichiko | Japan | – |
| Specifin | Bergamon | Italy | – |
| Unaserus | Isei | Japan | – |
| Uralgin | Ceccarelli | Italy | – |
| Uretrene | Mitim | Italy | – |
| Uriben | R.P. Drugs | U.K. | – |
| 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 | – |

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Wintomylon | Daiichi | Japan | – |
| Wintron | Tobishi | Japan | – |

**Raw Materials**

2-Amino-6-methylpyridine
Ethoxymethylenemalonic 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.; U.S. Patent 3,149,104; September 15, 1964; assigned to Sterling Drug Inc.

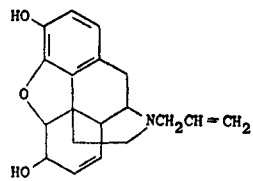
# NALORPHINE

**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)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Nalline | MSD | U.S. | 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 5½ 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 U.S. 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.; U.S. Patent 2,364,833; December 12, 1944; assigned to Merck & Co., Inc.
Weijlard, J.; U.S. Patent 2,891,954; June 23, 1959; assigned to Merck & Co., Inc.

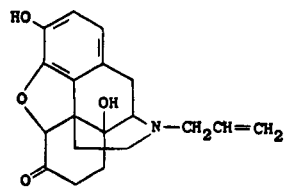
## NALOXONE

**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)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Narcan | Du Pont | U.S. | 1971 |
| Narcan | Du Pont | U.K. | 1975 |
| Narcanti | Winthrop | W. Germany | 1978 |
| Narcan | Winthrop | France | 1980 |
| Narcan | Crinos | Italy | 1980 |
| Nalone | End | U.S. | — |
| Talwin | Winthrop-Breon | U.S. | — |

**Raw Materials**

Oxymorphone
Cyanogen bromide
Allyl bromide
Acetic anhydride
Hydrogen chloride

**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.; U.S. Patent 3,254,088; May 31, 1966

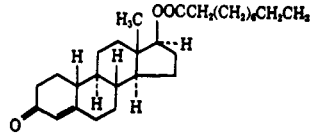
# NANDROLONE DECANOATE

**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; 434-22-0 (Base)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Deca-Durabolin | Organon | U.S. | 1962 |
| Deca-Hybolin | Hyrex | U.S. | 1979 |
| Deca-Noralone | Taro | Israel | – |
| Fortabolin | Deva | Turkey | – |
| Iebolan | I.E. Kimya Evi | Turkey | – |
| Kabolin | Legere | U.S. | – |
| Methybol | Mepha | Switz. | – |
| 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 U.S. 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.; U.S. Patent 2,798,879; July 9, 1957; assigned to The Upjohn Company
De Wit, E.D. and Overbeek, G.A.; U.S. 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:** See Nandrolone Decanoate for the steroid structure

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

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Durabolin | Organon | U.S. | 1959 |
| Nandrolin | Tutag | U.S. | 1979 |
| Activin | Aristegui | Spain | – |
| Anticatabolin | Falorni | Italy | – |
| Hepa-Obaton | Nourypharma | W. Germany | – |
| Hybolin Improved | Hyrex | U.S. | – |
| 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.; U.S. Patent 2,868,809; January 13, 1959; assigned to The Upjohn Company

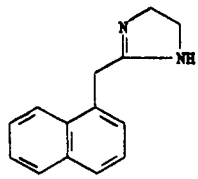
## NAPHAZOLINE

**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; 550-99-2 (Hydrochloride)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Privine | Ciba | U.S. | 1942 |
| Albalon | Allergan | U.S. | 1970 |
| Naphcon Forte | Alcon | U.S. | 1975 |
| Clera | Person Covey | U.S. | 1978 |
| Vasoclear | Smith Miller & Patch | U.S. | 1979 |
| Opcon | Muro | U.S. | 1981 |
| Nafazair | Pharmafair | U.S. | 1983 |
| Actinophtyl | Gregoire | France | – |
| Bactio-Rhin | Byk Liprandi | Argentina | – |
| Biogan | Recip | Sweden | – |
| Coldan | Sigmapharm | Austria | – |
| Degest-2 | Barnes-Hind | U.S. | – |
| Gotinal | Promeco | Argentina | – |
| Imidazyl | Tubi Lux Pharma | Italy | – |
| Imidin | Ysat Wernigerode | E. Germany | – |
| Imizol | Farmigea | Italy | – |
| Murine | Abbott | U.K. | – |
| Naftazolina | Bruschettini | Italy | – |
| Naline | Ibsa | Switz. | – |
| Nasal Yer | Yer | Spain | – |
| Nomaze | Fisons | U.K. | – |
| Ocunasal | Sam-on | Israel | – |
| Pivanol | Tek | Turkey | – |
| Privin | Ciba | W. Germany | – |
| Proculin | Ankerwerk | E. Germany | – |
| Ran | Corvi | Italy | – |

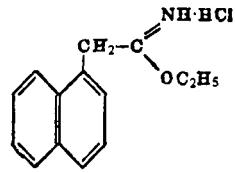
| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Rhinex S | Ysat Wernigerode | E. Germany | – |
| Rhinon | Petrasch | Austria | – |
| Rimidol | Leo | Sweden | – |
| Rinofug | Chimimport Export | Rumania | – |
| Vasoconstrictor | Pensa | Spain | – |
| Vistalbalon | Pharm-Allergan | 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. Reaction with HCl gives the hydrochloride.

**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.; U.S. Patent 2,161,938; June 13, 1939; assigned to the Society of Chemical Industry in Basle, Switzerland

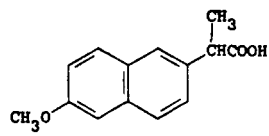
# NAPROXEN

**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 | U.K. | 1973 |
| Naprosyne | Cassenne | France | 1975 |
| Proxen | Gruenenthal | W. Germany | 1975 |
| Naprosyn | Recordati | Italy | 1975 |
| Naprosyn | Syntex | Switz. | 1975 |
| Naprosyn | Syntex | U.S. | 1976 |
| Naixan | Tanabe | Japan | 1978 |
| Congex | Nemi | Argentina | – |
| Floginax | Farmochimica | Italy | – |
| Gibixen | Gibipharm | Italy | – |
| Laser | Tosi-Novara | Italy | – |
| Madaprox | Madariaga | Spain | – |
| Naprium | Radiumfarma | 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**

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

**Manufacturing Process**

According to U.S. 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.; U.S. Patent 3,637,767; January 25, 1972; assigned to Syntex Corp., Panama
Harrison, I.T.; U.S. Patent 3,658,858; April 25, 1972; assigned to Syntex Corp., Panama
Alvarez, F.S.; U.S. Patent 3,663,584; May 16, 1972; assigned to Syntex Corp., Panama

Alvarez, F.S.; U.S. Patent 3,694,476; September 26, 1972; assigned to Syntex Corp., Panama
Halpern, O.; U.S. Patent 3,720,708; March 13, 1973

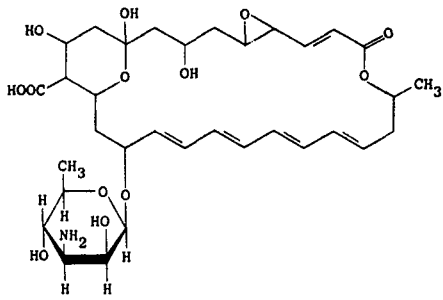
# NATAMYCIN

**Therapeutic Function:** Antibacterial (ophthalmic)

**Chemical Name:** See Structural Formula

**Common Name:** Pimaricin

**Structural Formula:**




**Chemical Abstracts Registry No.:** 7681-93-8

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Pimafucine | Beytout | France | 1964 |
| Pimafucin | Brocades | U.K. | 1965 |
| Pimafucort | Brocades | Italy | 1966 |
| Pimafucin | Basotherm | W. Germany | 1967 |
| Natacyn | Alcon | U.S. | 1979 |
| Myprozine | Lederle | U.S. | — |

**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 detais 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

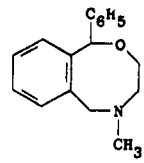
## NEFOPAM HYDROCHLORIDE

**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:**




(base)

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

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Ajan | Kettelnack | W. Germany | 1976 |
| Acupan | Carnegie | U.K. | 1978 |
| Acupan | Riker | France | 1981 |
| Lenipan | Chiesi | Italy | 1981 |
| Oxadol | I.S.I. | Italy | 1982 |
| Acupan | Boehr. Mann. | Italy | 1983 |

**Raw Materials**

2-Benzoylbenzoic acid
2-Methylaminoethanol
p-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.; U.S. Patent 3,487,153; December 30, 1969; assigned to Rexall Drug and Chemical Company

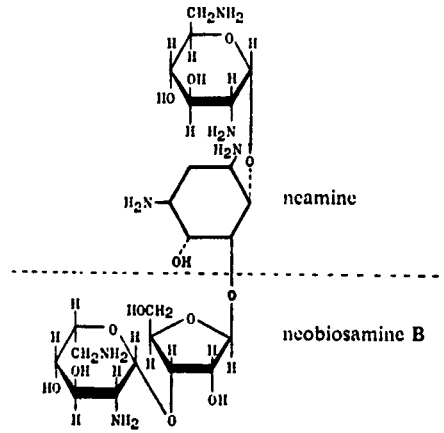
# NEOMYCIN

**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:**




neomycin B

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

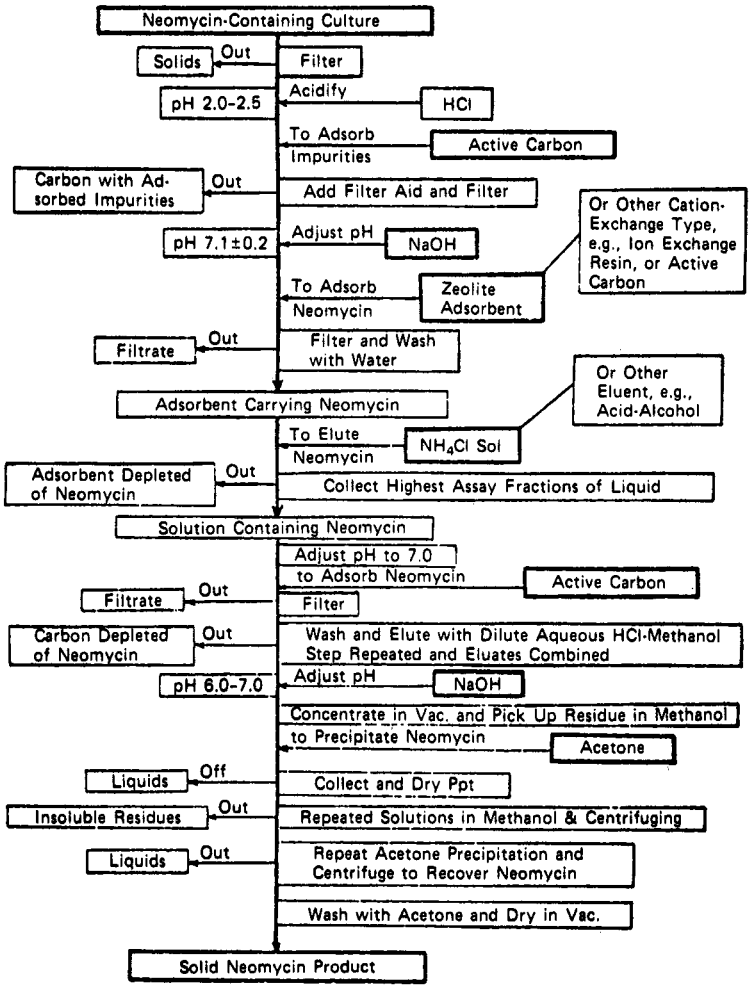
| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Myciguent | Upjohn | U.S. | 1951 |
| Otobiotic | Schering | U.S. | 1954 |
| Mycifradin | Upjohn | U.S. | 1957 |
| Neobiotic | Pfizer | U.S. | 1958 |
| Apokalin | A.L. | Norway | – |
| Biofradin | Uriach | Spain | – |
| Bykomycin | Byk-Gulden | W. Germany | – |
| Cortisporin | Burroughs-Wellcome | U.S. | – |
| Dexmy | Takeda | Japan | – |
| Endomixin | Lusofarmaco | Italy | – |
| Fradio | Nippon Kayaku | Japan | – |
| Fradyl | Christiaens | Belgium | – |
| Ivax | Boots | U.K. | – |
| Larmicin | Larma | Spain | – |
| Myacyne | Werner Schnur | W. Germany | – |
| Mytrex | Savage | U.S. | – |
| Neobretin | Norbrook | U.K. | – |
| Neodecadron | MSD | U.S. | – |
| Neointestin | Hosbon | Spain | – |
| Neolate | Therafarm | U.K. | – |
| Neomicina Roger | Roger | Spain | – |
| Neomin | Glaxo | U.K. | – |
| Neo-Polycin | Merrell Dow | U.S. | – |
| Neopt | Sigma | Australia | – |
| Neosporin | Burroughs-Wellcome | U.S. | – |
| Neosulf | Protea | Australia | – |
| Neo-Synalar | Syntex | U.S. | – |
| Octicair | Pharmafair | U.S. | – |
| Otocort | Lemmon | U.S. | – |
| Siquent | Sigma | Australia | – |
| Tampovagan | Norgine | U.K. | – |
| Topisporin | Pharmafair | U.S. | – |
| Tri-Thalmic | Schein | U.S. | – |

**Raw Materials**

Bacterium *Streptomyces fradiae*
Nutrient medium

**Manufacturing Process**

Neomycin has been produced by growing the organism, *Streptomyces* 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.; U.S. Patent 2,799,620; July 16, 1957; assigned to Rutgers Research and Educational Foundation
Jackson, W.G.; U.S. Patent 2,848,365; August 19, 1958; assigned to The Upjohn Company
Miller, T.W.; U.S. Patent 3,005,815; October 24, 1961; assigned to Merck & Co., Inc.
Moses, W.; U.S. Patent 3,022,228; February 20, 1962; assigned to S.B. Penick & Company
Haak, W.J.; U.S. Patent 3,108,996; October 29, 1963; assigned to The Upjohn Company

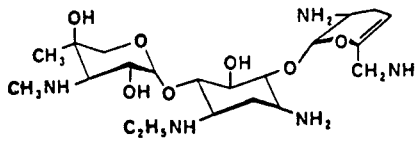
# NETILMICIN

**Therapeutic Function:** Antibiotic

**Chemical Name:** 1-N-Ethylisomicin

**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 | U.K. | 1981 |
| Netromicine | Unicet | France | 1981 |
| Nettacin | Essex | Italy | 1982 |
| Netromycin | Schering | U.S. | 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 chloroform-methanol-7% aqueous ammonium hydroxide (2:1:1) system. Combine the eluates as deter-

mined 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.; U.S. Patent 4,002,742; January 11, 1977; assigned to Schering Corp.

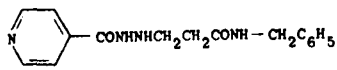
# NIALAMIDE

**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 | U.S. | 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.; U.S. Patent 2,894,972; July 14, 1959; assigned to Chas. Pfizer & Co., Inc.

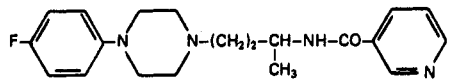
## NIAPRAZINE

**Therapeutic Function:** Antihistamine

**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**

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

**Manufacturing Process**

*1st Stage:* 10 ml of concentrated (10N) 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.; U.S. Patent 3,712,893; January 23, 1973; assigned to SA Centre Europeen De Recherches Mauvernay, CERM

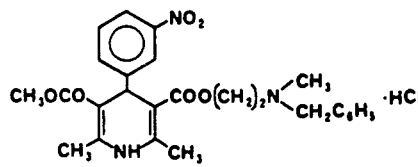
## NICARDIPINE

**Therapeutic Function:** Cerebral 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.; U.S. Patent 3,985,758; October 12, 1976; assigned to Yamanouchi Pharmaceutical Co., Ltd.

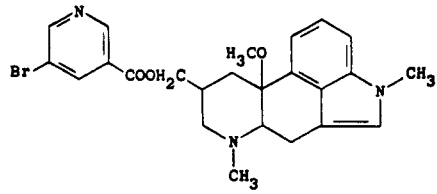
# NICERGOLINE

**Therapeutic Function:** Peripheral vasodilator

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

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

**Structural Formula:**




**Chemical Abstracts Registry No.:** 27848-84-6

| 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
Lithium aluminum hydride
5-Bromonicotinyl chloride
Methanol
Hydrogen chloride

**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 wtih 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.; U.S. Patent 3,228,943; January 11, 1966; assigned to Societa Farmaceutici Italia, Italy

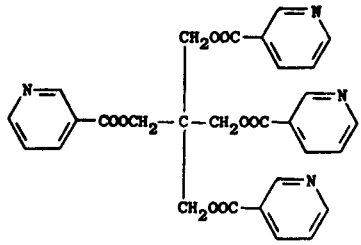
## NICERITROL

**Therapeutic Function:** Cholesterol reducing agent

**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. Pyridinehydrochloride, 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 tetra-acetic 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

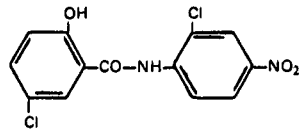
## NICLOSAMIDE

**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 | U.K. | 1961 |
| Yomesan | Bayer | Italy | 1962 |
| Tredemine | Roger Bellon | France | 1964 |
| Niclocide | Miles | U.S. | 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.; U.S. Patent 3,147,300; September 1, 1964; assigned to Farbenfabriken Bayer A.G.

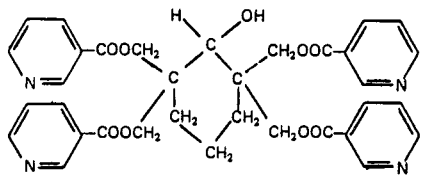
## NICOMOL

**Therapeutic Function:** Anticholesterol

**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 | 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.; U.S. Patent 3,299,077; January 17, 1967; assigned to Kyorin Seiyaku KK

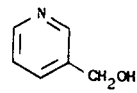
## NICOTINYL ALCOHOL

**Therapeutic Function:** Peripheral 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 | U.S. | 1949 |
| Danaden | Cascan | W. Germany | – |
| Peritard | Ikapharm | Israel | – |
| Ronicol | Roche | U.K. | – |
| Thilocombin | Thilo | W. Germany | – |

**Raw Materials**

3-Cyanopyridine
Ethyl alcohol
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-cyano-pyridine 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-amino-methyl-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.; U.S. Patent 2,509,171; May 23, 1950; assigned to Ciba Limited, Switzerland
Cohen, A.; U.S. Patent 2,520,037; August 22, 1950; assigned to Hoffmann-La Roche Inc.
Schläpfer, R.; U.S. Patent 2,547,048; April 3, 1951; assigned to Hoffmann-La Roche Inc.
Chase, G.O.; U.S. Patent 2,615,896; October 28, 1952; assigned to Hoffmann-La Roche Inc.

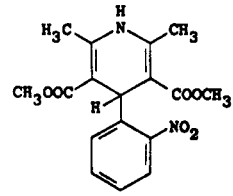
# NIFEDIPINE

**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 | U.K. | 1977 |
| Adalate | Bayer | France | 1979 |
| Procardia | Pfizer | U.S. | 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 U.S. Patent 3,485,847.

**References**

Merck Index 6374
DFU 6 (7) 427 (1981)
Kleeman & 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.; U.S. Patent 3,485,847; December 23, 1969; assigned to Farbenfabriken Bayer AG, Germany
Bossert, F. and Vater, W.; U.S. Patent 3,488,359; January 6, 1970; assigned to Farbenfabriken Bayer AG, Germany
Bossert, F. and Vater, W.; U.S. Patent 3,511,837; May 12, 1970; assigned to Farbenfabriken Bayer AG, Germany

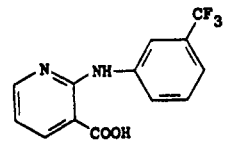
# NIFLUMIC ACID

**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 |
| 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.; U.S. Patent 3,415,834; December 10, 1968; assigned to Societe anonyme dite: Laboratoires UPSA, France

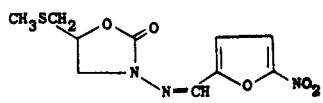
# NIFURATEL

**Therapeutic Function:** Vaginal antiinfective

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

**Common Name:** Methylmercadone

**Structural Formula:**



**Chemical Abstracts Registry No.:** 4936-47-4

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

**Raw Materials**

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

**Manufacturing Process**

In an initial step of reactions, methyl mercaptan is reacted with epichlorohydrin to give 1-chloro-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

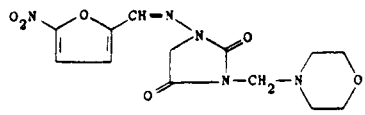
# NIFURFOLINE

**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

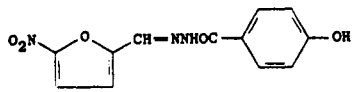
# NIFUROXAZIDE

**Therapeutic Function:** Antiseptic (intestinal)

**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 et 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.; U.S. Patent 3,290,213; December 6, 1966; assigned to S.A. des Laboratoires Robert et Carriere (France)