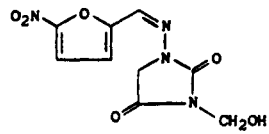
NIFURTOINOL

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.; U.S. Patent 3,446,802; May 27, 1969; assigned to The Norwich Pharmacal Co.

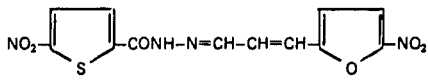
NIFURZIDE

Therapeutic Function: Antibacterial, antidiarrheal

Chemical Name: N^1-[5'-Nitro-2'-thenoyl]-N^2-[5''-nitro-2''-furylacrylidene] hydrazine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 39978-42-2

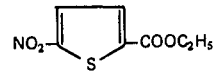
Trade Name	Manufacturer	Country	Year Introduced
Ricridene	Anphar	Switz.	1981
Ricridene	Lipha	France	—

Raw Materials

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

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 N^1-[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.; U.S. Patents 3,847,911; November 12, 1974; and 3,914,379; October 21, 1975; both assigned to Lipha, Lyonnaise Industrielle Pharmaceutique

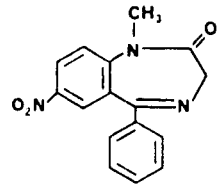
NIMETAZEPAM

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

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

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.; U.S. Patents 3,770,767; November 6, 1973; and 3,652,551; March 28, 1972; both assigned to Sumitomo Chemical Co.

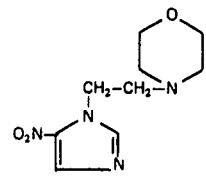
NIMORAZOLE

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	U.K.	1970
Naxogin	Carlo Erba	Italy	1972
Esclama	Farmitalia	W. Germany	1973
Aceterol Forte	Bristol Myers	W. Germany	1973
Naxofem	Ikapharm	Israel	–
Nulogyl	Bristol	U.K.	–
Sirledi	Causyth	Italy	–

Raw Materials

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

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 U.S. 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-toluene sulfonyl 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.; U.S. Patent 3,399,193; August 27, 1968; assigned to Carlo Erba SpA, Italy
Gal, G.; U.S. Patent 3,458,528; July 29, 1969; assigned to Merck & Co., Inc.
Carlson, J.A., Hoff, D.R. and Rooney, C.S.; U.S. Patent 3,646,027; February 29, 1972; assigned to Merck & Co., Inc.

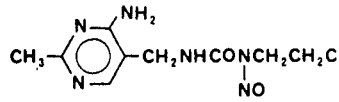
NIMUSTINE

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.; U.S. Patent 4,003,901; January 18, 1977; assigned to Sankyo Co., Ltd.

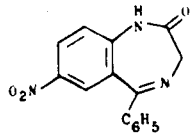
NITRAZEPAM

Therapeutic Function: Anticonvulsant, hypnotic

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	U.K.	1965
Mogadon	Roche	Italy	1967
Apodorm	A.L.	Norway	—
Arem	Lennon	S. Africa	—
Atempol	Norgine	U.K.	—
Benzalin	Shionogi	Japan	—
Cerson	Belupo	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	U.K.	—
Nitrempax	Lafi	Brazil	—
Noctem	Alfa Farm.	Italy	—
Noctene	Rio Ethicals	S. Africa	—
Numbon	Ikapharm	Israel	—
Ormodon	Ormed	S. Africa	—

Trade Name	Manufacturer	Country	Year Introduced
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.	U.K.	–
Rindepres	Disprovent	Argentina	–
Somitran	Farmos	Finland	–
Somnased	Duncan Flockhart	U.K.	–
Somnite	Norgine	U.K.	–
Sonnolin	Dima	Italy	–
Surem	Galen	U.K.	–
Tri	Vita	Italy	–
Unisomnia	Unigreg	U.K.	–

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(1H)-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.; U.S. Patent 3,116,203; December 31, 1963; assigned to Hoffmann-LaRoche, Inc.

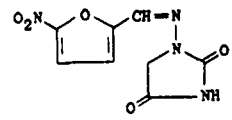
NITROFURANTOIN

Therapeutic Function: Urinary antibacterial

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	U.S.	1953
Furadoine	Oberval	France	1954
Trantoin	McKesson	U.S.	1969
Cyantin	Lederle	U.S.	1970
Furachel	Rachelle	U.S.	1970
N-Toin	Upjohn	U.S.	1971
Parfuran	Warner Lambert	U.S.	1974
Alfuran	Alkaloid	Yugoslavia	–
Berkfurin	Berk	U.K.	–
Ceduran	Cedona	Neth.	–
Chemiofuran	Italfarmaco	Italy	–
Chemiofurin	Torlan	Spain	–
Cistofuran	Crosara	Italy	–
Cystit	Heyden	W. Germany	–
Dantafur	Norwich-Eaton	U.S.	–
Fua Med	Med	W. Germany	–
Furadoine	Oberval	France	–
Furalan	Lannett	U.S.	–
Furaloid	Edwards	U.S.	–
Furanex	Elliott-Marion	Canada	–
Furanite	Saunders	Canada	–
Furantoin	Spofa	Czechoslovakia	–
Furatin	Hemofarm	Yugoslavia	–
Furedan	Scharper	Italy	–
Furil	Off	Italy	–
Furobactina	Esteve	Spain	–
Furophen	Pharbil	Neth.	–
Gerofuran	Gerot	Austria	–
Ituran	Promonta	W. Germany	–
Macrodantin	Eaton	U.S.	–

Trade Name	Manufacturer	Country	Year Introduced
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	U.S.	–
Trantoin	McKesson	U.S.	–
Trocurine	Labatec	Switz.	–
Urantoin	D.D.S.A.	U.K.	–
Uretoin	Tokyo Tanabe	Japan	–
Urodil	Pharma-Selz	W. Germany	–
Urodin	Streuli	Switz.	–
Urofuran	Farmos	Finland	–
Urolisa	Lisafarma	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 U.S. 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.; U.S. Patent 2,610,181; September 9, 1952; assigned to Eaton Laboratories, Inc.
Michels, J.G.; U.S. Patent 2,898,335; August 4, 1959; assigned to The Norwich Pharmacal Company
Gever, G. and O'Keefe, C.; U.S. Patent 2,927,110; March 1, 1960; assigned to The Norwich Pharmacal Company

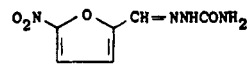
NITROFURAZONE

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	U.S.	1946
Actin-N	Chesebrough-Pond	U.S.	1981
Amifur	Norwich-Eaton	U.S.	–
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	U.S.	–
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 U.S. 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.; U.S. Patent 2,416,234; February 18, 1947; assigned to Eaton Laboratories, Inc.
Gever, G. and O'Keefe, C.; U.S. Patent 2,927,110; March 1, 1960; assigned to The Norwich Pharmacal Company

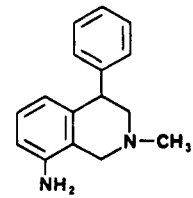
NOMIFENSINE MALEATE

Therapeutic Function: Psychostimulant

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

Common Name: –

Structural Formula:



(base)

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

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

Raw Materials

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

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 & 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.; U.S. Patent 3,577,424; May 4, 1971; assigned to Farbwerke Hoechst AG.

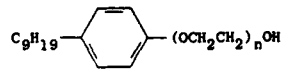
NONOXYNOL

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	U.S.	1978
Intercept	Ortho	U.S.	1980
Gynol	Ortho	U.S.	1982
Shur-Seal	Milex	U.S.	1983
C-Film	Hommel	Switz.	–
Emko	Emko-Schering	U.S.	–
Encare Oval	Patentex	W. Germany	–
Glovan	Teva	Israel	–
Igepal	G.A.F.	U.S.	–
Ortho-Creme	Cilag	U.S.	–

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.; U.S. Patent 2,413,477; September 3, 1940; assigned to General Aniline & Film Corp.

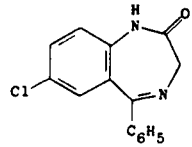
NORDAZEPAM

Therapeutic Function: Minor 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.; U.S. Patent 3,202,699; August 24, 1965; assigned to Hoffmann-LaRoche Inc.

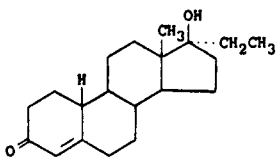
NORETHANDROLONE

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	U.S.	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.; U.S. Patent 2,721,871; October 25, 1955; assigned to G.D. Searle & Co.

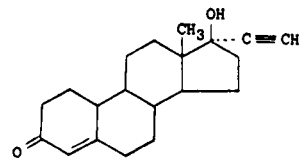
NORETHINDRONE

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	U.S.	1957
Ortho-Novum	Ortho	U.S.	1963
Norinyl	Syntex	U.S.	1964

Trade Name	Manufacturer	Country	Year Introduced
Nor-QD	Syntex	U.S.	1973
Brevicon	Syntex	U.S.	–
Conceplan	Gruenenthal	W. Germany	–
Gesta-Plan	D.A.K.	Denmark	–
Micronor	Ethnor	Australia	–
Micronor	Ortho	U.S.	–
Micronovum	Cilag	W. Germany	–
Modicon	Ortho	U.S.	–
Monogest	Spofa	Czechoslovakia	–
Norfor	Gremy-Longuet	France	–
Norgestin	Janus	Italy	–
Noriday	Syntex	U.S.	–
Norlestrin	Parke Davis	U.S.	–
Ovcon	Mead Johnson	U.S.	–
Primolut N	Schering	U.K.	–
Tri-Norinyl	Syntex	U.S.	–
Utovlan	Syntex	U.K.	–

Raw Materials

3-Methoxyestrone
Ammonia
Ethyl orthoformate
Acetylene
Lithium
Chromic acid
Potassium

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-one with 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-one in 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-one thus 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.; U.S. Patent 2,744,122; May 1, 1956; assigned to Syntex SA, Mexico
de Ruggieri, P.; U.S. Patent 2,849,462; August 26, 1958

NORETHINDRONE ACETATE

Chemical Abstracts Registry No.: 51-98-9

Trade Name	Manufacturer	Country	Year Introduced
Norlestrin	Parke Davis	U.S.	1964
Milligynon	Schering	France	1978
Aygestrin	Ayerst	U.S.	1982
Brevicon	Syntex	U.S.	–
Norlutin-A	Parke Davis	U.K.	–
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-acetate, 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.; U.S. Patent 2,964,537; Dec. 13, 1960; assigned to Schering AG, Germany

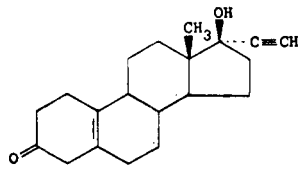
NORETHYNODREL

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	U.S.	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 U.S. Patent 2,655,518, according to U.S. 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-1,4,6,7,8,9,11,12,13,14,16,17-dodecahydro-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.; U.S. Patent 2,691,028; October 5, 1954; assigned to G.D. Searle & Co.
Colton, F.B.; U.S. Patent 2,725,389; November 29, 1955; assigned to G.D. Searle & Co.

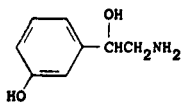
NORFENEFRINE

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)

Trade Name	Manufacturer	Country	Year Introduced
Zordel	Grelan	Japan	1970
Coritat	Green Cross	Japan	—
Esbufon	Schaper & Brummer	W. Germany	—
Euro-Cir	Virgiliano	Italy	—

Trade Name	Manufacturer	Country	Year Introduced
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

m-Acetoxyacetophenone
Sodium iodide
Hydrogen
Bromine
Hexamethylene tetramine

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.; U.S. Patent 2,312,916; March 2, 1943; assigned to Ciba Pharmaceutical Products Inc.

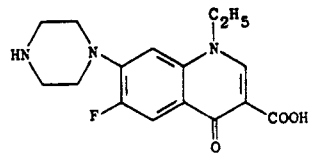
NORFLOXACIN

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

Trade Name	Manufacturer	Country	Year Introduced
Sebercim	I.S.F.	Italy	1983
Primoxin	Sharp & 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 cm^3 of 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.; U.S. Patent 4,292,317; September 29, 1981; assigned to Laboratorie Roger Bellon (France) and Dainippon Pharmaceutical (Japan)

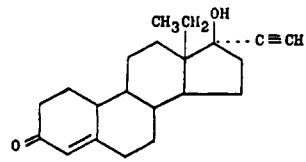
NORGESTREL

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	U.S.	1968
Eugynon	Schering	Italy	1969
Neogest	Schering	U.K.	1974
Microlut	Schering	W. Germany	1974
Planovar	Wyeth	Japan	1979
Duoluton	Schering	Japan	1979
Prempak	Ayerst	U.K.	–

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

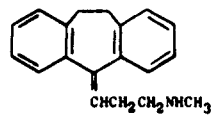
NORTRIPTYLINE

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)

Trade Name	Manufacturer	Country	Year Introduced
Aventyl	Lilly	U.K.	1963
Nortrilen	Tropon	W. Germany	1964
Aventyl	Lilly	U.S.	1965
Psychostyl	Lilly	France	1966
Vividyl	Lilly	Italy	1967
Noritren	Dainippon	Japan	1971
Altilev	Squibb	France	1976
Pamelor	Sandoz	U.S.	1977
Allegron	Dista	U.K.	—
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.; U.S. Patent 3,281,469; October 25, 1966; assigned to Eli Lilly & Co.

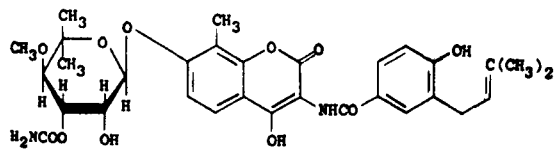
NOVOBIOCIN

Therapeutic Function: Antibiotic

Chemical Name: N-[7-[[3-O-(aminocarbonyl)-5,5-di-C-methyl-4-O-methyl-α-L-lyxo-pyranosyl] 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	U.S.	1956
Cathomycin	MSD	U.S.	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 U.S. 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 U.S. Patent 3,049,534.

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

References

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

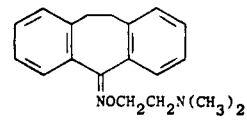
NOXIPTILIN

Therapeutic Function: Psychostimulant

Chemical Name: 10,11-dihydro-5H-dibenzo[α,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)

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
Hydroxyamine 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.; U.S. Patent 3,505,321; April 7, 1970; assigned to Farbenfabriken Bayer A.G.

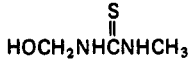
NOXYTIOLIN

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	U.K.	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.

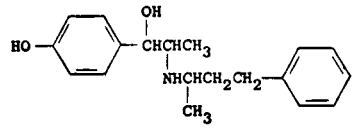
NYLIDRIN

Therapeutic Function: Peripheral 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; 849-55-8 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Arlidin	U.S.V.	U.S.	1955
Arlibide	U.S.V.	Argentina	–
Bufedon	Cosmopharma	Neth.	–
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 & Nephew	U.K.	–
Pervadil	I.C.N.	Canada	–
Pharmadil	Pharmacia	Sweden	–
Rudilin	Darby	U.S.	–
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 U.S. 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
Schöpf, C. and Kunz, K.J.; U.S. Patent 2,661,372; December 1, 1953; assigned to Troponwerke Dinklage & Co., Germany
Külz, F. and Schöpf, C.; U.S. Patent 2,661,373; December 1, 1953

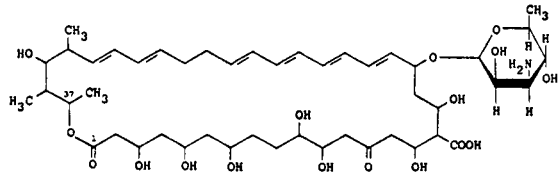
NYSTATIN

Therapeutic Function: Antifungal

Chemical Name: See structural formula

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 1400-61-9

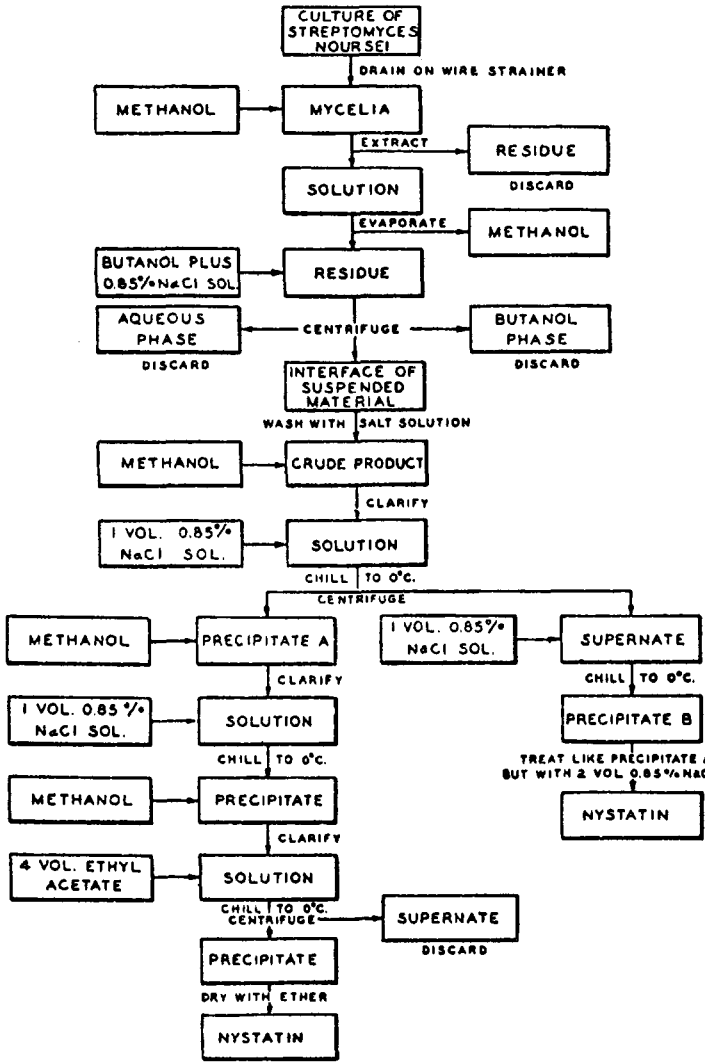
Trade Name	Manufacturer	Country	Year Introduced
Mycostatin	Squibb	U.S.	1954
Mycostatine	Squibb	France	1956
Nysta-Dome	Dome	U.S.	1964
Nilstat	Lederle	U.S.	1970
Nysert	Norwich-Eaton	U.S.	1979
Multilind	F.A.I.R.	U.K.	1979
Nystex	Savage	U.S.	1983
Biofanal	Pfleger	W. Germany	–
Candex	Dome	U.S.	–
Candio-Hermal	Hermal	W. Germany	–
Herniocid	Mayrhofer	Austria	–
Korostatin	Holland-Rantos	U.S.	–
Mycolog	Squibb	U.S.	–
Myco-Triacet	Lemmon	U.S.	–
Mytrex	Savage	U.S.	–
Nadostine	Nadeau	Canada	–
Nyaderm	K-Line	Canada	–
Nystacid	Farmos	Finland	–
Nyst-olone	Schein	U.S.	–
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 U.S. 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.; U.S. Patent 2,786,781; March 26, 1957; assigned to Olin Mathieson Chemical Corporation
Hazen, E.L. and Brown, R.F.; U.S. Patent 2,797,183; June 15, 1957; assigned to Research Corporation
Vandeputte, J.; U.S. Patent 2,832,719; April 29, 1958; assigned to Olin Mathieson Chemical Corporation
Renella, J.G.; U.S. Patent 3,517,100; June 23, 1970; assigned to American Cyanamid Co.