**References**

Merck Index 6033
Kleeman & Engel p. 597
PDR pp. 830, 872, 876, 993, 1034, 1305, 1605, 1670, 1723, 1999
OCDS Vol. 1 p. 240 (1977)
DOT 13 (4) 147 (1977) & 17 (1) 34 (1981)
I.N. p. 632
REM p. 1222
Jacob, R.M., Regnier, G.L. and Crisan, C.; U.S. Patent 2,944,061; July 5, 1960; assigned to Societe des Usines Chimiques Rhone-Poulenc, France

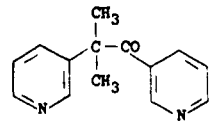
# METYRAPONE

**Therapeutic Function:** Diagnostic aid (pituitary function)

**Chemical Name:** 2-methyl-1,2-di-3-pyridyl-1-propanone

**Common Name:** –

**Structural Formula:**




**Chemical Abstracts Registry No.:** 54-36-4

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Metopirone | Ciba | U.S. | 1961 |
| Metopirone | Ciba | U.K. | 1961 |
| Metyrapone | Ciba | Switz. | 1964 |
| Metopiron | Ciba | W. Germany | 1966 |

**Raw Materials**

3-Acetylpyridine
Sulfuric acid
Hydrogen
Hydroxylamine sulfate

**Manufacturing Process**

According to U.S. Patent 2,966,493, the 2,3-bis-(3-pyridyl)-2,3-butanediol used as the starting material may be prepared as follows. A solution of 1,430 g of 3-acetyl-pyridine in 7,042 ml of a 1 N aqueous solution of potassium hydroxide is placed into a cathode chamber containing a mercury cathode with a surface of 353 $cm^2$ and is separated from an anode chamber by an Alundum membrane. As anode a platinum wire is used and the anolyte consists of a 1 N solution of aqueous potassium hydroxide which is replenished from time to time.

The electrolysis is carried out at a reference potential of -2.4 volts vs a standard calomel electrode. An initial current density of 0.0403 amp/$cm^2$ is obtained which drops to 0.0195 amp/$cm^2$ at the end of the reduction, which is carried on over a period of 1,682 minutes at 15° to 20°C. The catholyte is filtered, the solid material is washed with water and dried. 430 g of the 2,3-bis-(3-pyridyl)-butane-2,3-diol is recrystallized from water, MP 244° to 245°C.

A mixture of 3.43 g of 2,3-bis-(3-pyridyl)-2,3-butane-diol and 25 ml of concentrated sulfuric acid is heated to 76°C and kept at that temperature for 7½ hours. It is then poured on ice, neutralized with 50% aqueous solution of sodium hydroxide and the pH is adjusted to 8 with solid sodium carbonate. The aqueous solution is three times extracted with ethyl acetate, the separated organic layer dried over sodium sulfate and evaporated to dryness. The residue is distilled and 1.86 g of viscous, colorless oil is obtained which is purified by distillation. BP 140° to 160°C/0.07 mm. The infrared spectrum shows the presence of a mixture of two compounds, one containing a conjugated, the other one an unconjugated carbonyl group, without the presence of a compound containing a hydroxyl group; thus the rearrangement has taken place.

The resulting mixture does not crystalize and is converted into a mixture of oximes by treatment of a solution of the mixture in 20 ml of ethanol with a solution of 1.8 g of hydroxylamine sulfate in 3 ml of water. 1.8 g of sodium acetate in 5 ml of water is added, and the mixture is refluxed for 5 hours, then extracted with ethyl acetate, and the ethyl acetate solution is washed with a saturated aqueous sodium chloride solution and dried over sodium sulfate. After evaporating the solvent, the residue is triturated with warm ether and 1.1 g of a crystalline oxime is obtained, MP 168° to 171°C.

0.1 g of the resulting oxime is dissolved in 5 ml of 2 N aqueous sulfuric acid and the mixture is refluxed for 3 hours and allowed to stand overnight. After being rendered basic by adding a concentrated aqueous solution of sodium hydroxide and adjusted to a pH of 8 with sodium carbonate, the mixture is extracted 3 times with ethyl acetate; the organic layer is washed with water, dried and evaporated. Upon distillation of the residue an oily product is obtained, BP 130° to 160°C/0.3 mm. Infrared analysis shows the presence of a uniform compound, containing a conjugated carbonyl group. The 2-methyl-1,2-bis-(3-pyridyl)-propane-1-one crystallizes upon standing at room temperature or by covering the oily distillate with pentane and cooling to -80°C and filtering the oily crystals. It melts after recrystallization from a mixture of ether, hexane and petroleum ether at 48° to 50°C.

**References**

Merck Index 6036
Kleeman & Engel p. 598
PDR p. 803
I.N. p. 633
REM p. 1276
Bencze, W.L. and Allen, M.J.; U.S. Patent 2,923,710; February 2, 1960; assigned to Ciba Pharmaceutical Products, Inc.
Allen, M.J. and Bencze, W.L.; U.S. Patent 2,966,493; December 27, 1960; assigned to Ciba Pharmaceutical Products, Inc.

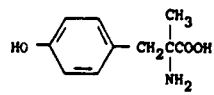
## METYROSINE

**Therapeutic Function:** Tyrosine hydroxylase inhibitor

**Chemical Name:** α-Methyl-L-tyrosine

**Common Name:** Metirosine

**Structural Formula:**




**Chemical Abstract Registry No.:** 672-87-7

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Demser | MSD | U.S. | 1979 |

**Raw Materials**

α-Methyl-N-dichloroacetyl-p-nitrophenylalanine
Hydrogen
Sodium nitrite
Sulfuric acid
Hydrogen chloride

**Manufacturing Process**

50 g of α-methyl-N-dichloroacetyl-p-nitrophenylalanine was dissolved in 500 ml methanol, 300 mg of platinum oxide were added and the mixture reduced at 41 pounds of pressure; within an hour 14.5 pounds were used up (theory 12.4 pounds). After filtration of the catalyst, the red clear filtrate was concentrated in vacuo and the residual syrup flushed several times with ether. The crystalline residue thus obtained, after air drying, weighed 45.3 g (99.5%), MP unsharp at about 104°C to 108°C with decomposition. After two precipitations with ether from an alcoholic solution, the somewhat hygroscopic amine was dried over sulfuric acid for analysis.

10 g of the amine prepared above was dissolved in 5 ml of 50% sulfuric acid at room temperature; the viscous solution was then cooled in ice and a solution of sodium nitrite (2.4 g) in 10 ml water gradually added with agitation. A flocculent precipitate formed. After all the nitrite had been added, the mixture was aged in ice for an hour, after which it was allowed to warm up to room temperature. Nitrogen came off and the precipitate changed to a sticky oil. After heating on the steam bath until evolution of nitrogen ceased, the oil was extracted with ethyl acetate. After removal of the solvent in vacuo, 9.4 g of colored solid residue was obtained, which was refluxed with 150 ml hydrochloric acid (1:1) for 17 hours. The resulting dark solution; after Norite treatment and extraction with ethyl acetate, was concentrated in vacuo to dryness and the tan colored residue (7.4 g) sweetened with ethanol. Dissolution of the residue in minimum amount of ethanol and neutralization with diethylamine of the clarified solution, precipitated the α-methyl tyrosine, which was filtered, washed with ethanol (until free of chlorides) and ether. The crude amino acid melted at 309°C with decomposition. For further purification, it was dissolved in 250 ml of a saturated sulfur dioxide-water solution, and the solution, after Noriting, concentrated to about 80 ml, the tan colored solid filtered washed with ethanol and ether. Obtained 1.5 g of α-methyl tyrosine, MP 320°C dec.

**References**

Merck Index 6038
PDR p. 1167
DOT 16 (10) 346 (1980)
I.N. p. 628
REM p. 909
Pfister, K. III and Stein, G.A.; U.S. Patent 2,868,818; January 13, 1959; assigned to Merck & Co., Inc.

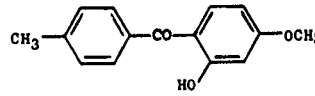
# MEXENONE

**Therapeutic Function:** Sunscreen agent

**Chemical Name:** (2-hydroxy-4-methoxyphenyl)(4-methylphenyl)methanone

**Common Name:** 2-hydroxy-4-methoxy-4'-methylbenzophenone

**Structural Formula:**



**Chemical Abstracts Registry No.:** 1641-17-4

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Uvistat-L | Ward Blenkinsop | U.K. | 1960 |

**Raw Materials**

p-Toluyl chloride
1,3-Dimethoxybenzene
Hydrogen chloride
Sodium hydroxide

**Manufacturing Process**

p-Toluyl chloride is the starting material. To this is added chlorobenzene and 1,3-dimethoxybenzene. The reaction mixture is cooled to 12°C in an ice bath and aluminum chloride is added gradually, keeping the reaction below 30°C. The reaction is then gradually heated to 115°C with the evolution of hydrogen chloride gas. As the temperature increases, the reaction mixture becomes thicker. At 105°C, dimethyl formamide is added slowly. The reaction is heated at 115°C for a short time and is then poured into concentrated hydrochloric acid. The reaction mixture pours very easily and very cleanly. The acid mixture is heated with steam to dissolve all the material which had not hydrolyzed and the mixture is filtered. The red chlorobenzene layer is separated and washed twice with hot water.

To the chlorobenzene solution is then added sodium hydroxide dissolved in water and the chlorobenzene is removed by a steam distillation. After all of the chlorobenzene is removed, the precipitate which forms during the distillation is removed by filtration and discarded. The solution is cooled and acidified with hydrochloric acid, precipitating a tan solid. This is removed by filtration and washed acid-free. It is then treated with sodium bicarbonate solution to remove any acid present and is then washed with water to remove all traces of bicarbonate. After drying approximately a 75% yield of mexenone is obtained.

**References**

Merck Index 6045
Kleeman & Engel p. 598
OCDS Vol. 2 p. 175 (1980)
I.N. p. 633
Hardy, W.B. and Forster, W.S.; U.S. Patent 2,773,903; December 11, 1956; assigned to American Cyanamid Company

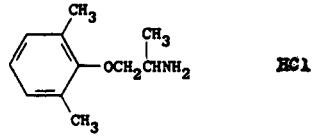
## MEXILETINE HCl

**Therapeutic Function:** Antiarrhythmic

**Chemical Name:** 1-(2,6-Dimethylphenoxy)-2-propanamine hydrochloride

**Common Name:** –

**Structural Formula:**



**Chemical Abstracts Registry No.:** 5370-01-4; 31828-71-4 (Base)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Mexitil | Boehr. Ingel. | U.S. | 1976 |
| Mexitil | Boehr. Ingel. | Switz. | 1978 |
| Mexitil | Boehr. Ingel. | W. Germany | 1979 |
| Mexitil | Boehr. Ingel. | France | 1981 |
| Mexitil | Boehr. Ingel. | Italy | 1982 |

**Raw Materials**

Dimethyl phenol
Chloroacetone
Hydrogen
Sodium hydroxide
Hydroxylamine

**Manufacturing Process**

The sodium salt of dimethyl phenol was reacted with chloroacetone and this product with hydroxylamine to give the starting material.

245 g of this 1-(2',6'-dimethyl-phenoxy)-propanone-(2)-oxime were dissolved in 1,300 cc of methanol, and the solution was hydrogenated at 5 atmospheres gauge and 60°C in the presence of Raney nickel. After the calculated amount of hydrogen had been absorbed, the catalyst was filtered off, the methanol was distilled out of the filtrate, and the residue, raw 1-(2',6'-dimethyl-phenoxy)-2-amino-propane, was dissolved in ethanol. The resulting solution was acidified with ethereal hydrochloric acid, the acidic solution was allowed to cool, and the precipitate formed thereby was collected by vacuum filtration. The filter cake was dissolved in ethanol and recystallized therefrom by addition of ether. 140.5 g (51.5% of theory) of a substance having a melting point of 203°C to 205°C were obtained, which was identified to be 1-(2',6'-dimethyl-phenoxy)-2-amino-propane hydrochloride.

**References**

Merck Index 6047
DFU 1 (4) 180 (1976)
Kleeman & Engel p. 598
DOT 12 (9) 361 (1976)
I.N. p. 633
REM p. 861
Koppe, H., Zeile, K., Kummer, W., Stahle, H. and Dannenberg, P.; U.S. Patent 3,659,019; April 25, 1972; assigned to Boehringer Ingelheim G.m.b.H. (W. Germany)

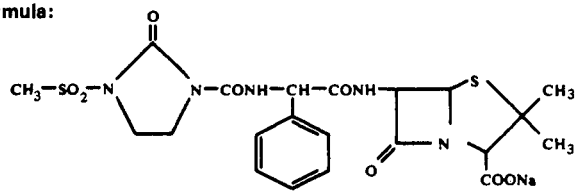
# MEZLOCILLIN

**Therapeutic Function:** Antibiotic

**Chemical Name:** Sodium D(-)-α-[(3-methylsulfonyl-imidazolidin-2-on-1-yl)-carbonyl-amino] benzylpenicillin

**Common Name:** –

**Structural Formula:**



**Chemical Abstracts Registry No.:** 51481-65-3

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Baypen | Bayer | W. Germany | 1977 |
| Baypen | Bayer | U.K. | 1980 |
| Baypen | Bayer | Switz. | 1980 |
| Baypen | Bayer | Italy | 1981 |
| Mezlin | Miles | U.S. | 1981 |
| Baypen | Bayer Yakuhin | Japan | 1982 |
| Baypen | Bayer | France | 1983 |
| Baypen | Bayer | Sweden | 1983 |
| Baycipen | Bayer | – | – |
| Optocillin | Bayer | W. Germany | – |

**Raw Materials**

Ampicillin
Methane sulfonyl chloride
2-Imidazolidone
Phosgene

**Manufacturing Process**

9.3 parts by weight of ampicillin were suspended in 80% strength aqueous tetrahydrofuran (140 parts by volume) and sufficient triethylamine (approximately 6.3 parts by volume) was added dropwise while stirring at 20°C, just to produce a clear solution and to give a pH value of between 7.5 and 8.2 (glass electrode). The mixture was cooled to 0°C and 5.1 parts by weight of 3-methyl-sulfonyl-imidazolidin-2-one-1-carbonyl chloride were added gradually in portions over the course of 30 minutes, while the mixture was stirred and kept at a pH value of between 7 and 8 by simultaneous addition of triethylamine.

The carbonyl chloride reactant was prepared by reacting 2-imidazolidone with methane sulfonyl chloride then that product with phosgene. The mixture was stirred for 10 minutes at 0°C and subsequently further stirred at room temperature until no further addition of triethylamine was necessary to maintain a pH value of 7 to 8. 150 parts by volume of water were added and the tetrahydrofuran was largely removed in a rotary evaporator at room temperature.

The residual aqueous solution was extracted once by shaking with ethyl acetate, covered with 250 parts by volume of fresh ethyl acetate and acidified to pH 1.5 to 2.0 with dilute hydrochloric acid while being cooled with ice. The organic phase was separated off, washed twice with 50 parts by volume of water at a time and dried for 1 hour over anhydrous $MgSO_4$ in a refrigerator. After filtration, about 45 parts by volume of a 1 molar solution of sodium 2-ethyl hexanoate in ether containing methanol were added to the solution of the penicillin. The mixture was concentrated on a rotary evaporator until it had an oily consistency and was dissolved in a sufficient amount of methanol by vigorous shaking, and the solution was rapidly added dropwise, with vigorous stirring, to 500 parts by volume of ether which contained 10% of methanol.

The precipitate was allowed to settle for 30 minutes, the solution was decanted from the pre-

cipitate, and the latter was again suspended in ether, filtered off and washed with anhydrous ether. After drying over $P_2O_5$ in a vacuum desiccator, the sodium salt of the mezlocillin was obtained in the form of a white solid substance.

**References**

Merck Index 6049
DFU 2 (9) 200 (1977)
Kleeman & Engel p. 599
PDR p. 1254
OCDS Vol. 3 p. 206 (1984)
DOT 11 (11) 444 (1975) & 15 (2) 54 (1979)
I.N. p. 633
REM p. 1196
Konig, H.B., Schrock, W. and Metzger, K.G.; U.S. Patents 3,972,869; August 3, 1976; 3,972,870; August 3, 1976; 3,974,141; August 10, 1976; 3,974,142; August 10, 1976; 3,975,375; August 17, 1976; 3,978,056; August 31, 1976; 3,983,105; September 28, 1976; and 4,009,272; February 22, 1977; all assigned to Bayer AG

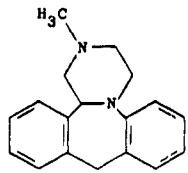
# MIANSERIN

**Therapeutic Function:** Serotonin inhibitor; antihistaminic

**Chemical Name:** 1,2,3,4,10,14b-hexahydro-2-methyldibenzo[c] pyrazino[1,2-a] azepine

**Common Name:** 2-methyl-1,2,3,4,10,14b-hexahydro-2H-pyrazino-[1,2-f] morphanthridine

**Structural Formula:**




**Chemical Abstracts Registry No.:** 24219-97-4; 21535-47-7 (Hydrochloride)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Tolvin | Organon | W. Germany | 1975 |
| Bolvidon | Organon | U.K. | 1976 |
| Norval | Bencard | U.K. | 1976 |
| Lantanon | Ravasini | Italy | 1976 |
| Athymil | Organon | France | 1979 |
| Athmyl | Organon | Switz. | 1980 |
| Tetramide | Sankyo | Japan | 1983 |

**Raw Materials**

2-Benzylaniline
Polyphosphoric acid
Diethyloxalate
Diborane
Chloroacetyl chloride
Methylamine
Lithium aluminum hydride

**Manufacturing Process**

(A) 25 g of 2-benzylaniline dissolved in 150 ml of benzene are cooled down in an ice bath to 8°C. To this solution are added 15 ml of pyridine and after that a solution of 15 ml of

chloroacetyl chloride in 25 ml of benzene, maintaining the temperature of the reaction mixture at 10° to 15°C. After stirring for 1 hour at room temperature 25 ml of water are added and the mixture is shaken for 30 minutes. Next the mixture is sucked off and the benzene layer separated. Then the benzene layer is washed successively with 2 N HCl, a sodium carbonate solution and water. The extract dried on sodium sulfate is evaporated and the residue crystallized together with the crystals obtained already from benzene. Yield 18 g; MP 130° to 133°C.

(B) 40 g of N-chloroacetyl-2-benzylaniline are heated for 2 hours at 120°C together with 50 ml of phosphorus oxychloride and 320 g of polyphosphoric acid. Next the reaction mixture is poured on ice and extracted with benzene. The extract is washed and dried on sodium sulfate and the benzene distilled off. The product obtained (31 g) yields after recrystallization 24 g of 6-chloromethyl-morphanthridine of MP 136° to 137°C.

(C) 10 g of 6-chloromethyl-morphanthridine are passed into 150 ml of a solution of methylamine in benzene (10%). After storage of the solution for 20 hours at 0° to 5°C the methylamine hydrochloride formed is sucked off and the filtrate evaporated to dryness. There remains as residue 11 g of crude 6-methylaminomethyl-morphanthridine.

(D) 11 g of crude 6-methylaminomethyl-morphanthridine are dissolved in 50 ml of absolute ether. While cooling in ice 2.7 g of lithium aluminumhydride, dissolved in 100 ml of absolute ether, are added. After boiling for 1 hour and cooling down in ice 11 ml of water are added slowly dropwise while stirring. After stirring for another 30 minutes at room temperature the mixture is sucked off and the filtrate evaporated to obtain 11 g of crude 5,6-dihydro-6-methylaminomethyl-morphanthridine in the form of a light yellow oil.

(E) 10 g of 5,6-dihydro-6-methylaminomethyl-morphanthridine are heated slowly, in 30 minutes, from 100° to 160°C with 7 g of pure diethyloxalate and after that from 160° to 180°C in 45 minutes. After cooling down the reaction mixture is stirred with benzene. The crystals are sucked off and yield after crystallization from dimethylformamide 9 g of 1,2-diketo-3(N)-methyl-2,3,4,4a-tetrahydro-1H-pyrazino-[1,2-f]-morphanthridine of MP 245° to 247°C.

(F) 9 g of the diketo-pyrazino-morphanthridine compound obtained above are reduced with diborane to give mianserin.

**References**

Merck Index 6050
Kleeman & Engel p. 599
OCDS Vol. 2 p. 451 (1980)
DOT 12 (1) 31 (1976)
I.N. p. 634
van der Burg, W.J. and Delobelle, J.; U.S. Patent 3,534,041; October 13, 1970; assigned to Organon Inc.

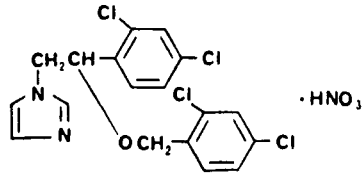
## MICONAZOLE NITRATE

**Therapeutic Function:** Antifungal

**Chemical Name:** 1-[2,4-Dichloro-β-[(2,4-dichlorobenzyl)oxy] phenethyl] imidazole mononitrate

**Common Name:** –

**Structural Formula:**



**Chemical Abstracts Registry No.:** 22832-87-7; 22916-47-8 (Base)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Daktarin | Janssen | Italy | 1974 |
| Daktarin | Janssen | U.K. | 1974 |
| Daktar | Janssen | W. Germany | 1974 |
| Dermonistat | Ortho | U.K. | 1974 |
| Monistat | Ortho | U.S. | 1974 |
| Daktarin | Le Brun | France | 1975 |
| Micatin | Johnson & Johnson | U.S. | 1976 |
| Minostate | Janssen | U.S. | 1978 |
| Andergin | Isom | Italy | 1980 |
| Frolid P | Mochida | Japan | 1981 |
| Aflorix | Gerardo Ramon | Argentina | — |
| Conofite | Pitman-Moore | U.S. | — |
| Dektarin | Janssen | Italy | — |
| Deralbine | Andromaco | Argentina | — |
| Epi-Monistat | Cilag | W. Germany | — |
| Florid | Mochida | Japan | — |
| Fungisdin | Esteve | Spain | — |
| Gyno-Daktarin | Le Brun | France | — |
| Gyno-Monistat | Cilag | W. Germany | — |
| Micatin | McNeil | U.S. | — |
| Miconal | Ecobi | Italy | — |
| Micotef | Italfarmaco | Italy | — |
| Vodol | Andromaco | Brazil | — |

**Raw Materials**

Imidazole
ω-Bromo-2,4-dichloroacetophenone
2,4-Dichlorobenzyl chloride
Sodium borohydride
Sodium hydride
Nitric acid

**Manufacturing Process**

Imidazole is reacted with ω-bromo-2,4-dichloroacetophenone and that product reduced with sodium borohydride.

A suspension of 10.3 parts of the α-(2,4-dichlorophenyl)imidazole-1-ethanol thus obtained and 2.1 parts of sodium hydride in 50 parts of dry tetrahydrofuran is stirred and refluxed for 2 hours. After this reaction time, the evolution of hydrogen is ceased. Then there are added successively 60 parts dimethylformamide and 8 parts of 2,4-dichlorobenzyl chloride and stirring and refluxing are continued for another 2 hours. The tetrahydrofuran is removed at atmospheric pressure. The dimethylformamide solution is poured onto water.

The product, 1-[2,4-dichloro-β-(2,4-dichlorobenzyloxy)phenethyl] imidazole, is extracted with benzene. The extract is washed with water, dried, filtered and evaporated in vacuo. From the residual oily free base, the nitrate salt is prepared in the usual manner in 2-propanol by treatment with concentrated nitric acid, yielding, after recrystallization of the crude solid salt from a mixture of 2-propanol, methanol and diisopropyl ether, 1-[2,4-dichloro-β-dichlorobenzyloxy)phenethyl] imidazole nitrate; melting point 170.5°C.

**References**

Merck Index 6053
Kleeman & Engel p. 601
PDR pp. 956, 1293
OCDS Vol. 2 p. 249 (1980)
DOT 7 ( ) 192 (1971) & 8 (6) 229 (1972)
I.N. p. 634
REM p. 1229
Godefroi, E.F. and Heeres, J.; U.S. Patent 3,717,655; February 20, 1973; assigned to Janssen Pharmaceutica NV
Godefroi, E.F. and Heeres, J.; U.S. Patent 3,839,574; October 1, 1974; assigned to Janssen Pharmaceutica NV

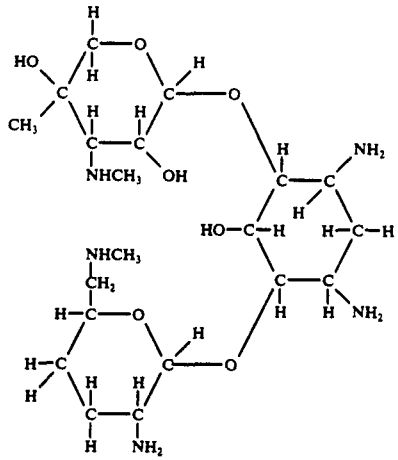
# MICRONOMICIN

**Therapeutic Function:** Antibiotic

**Chemical Name:** O-2-amino-2,3,4,6-tetradeoxy-6-(methylamino)-α-D-erythrohexopyranosyl-(1→4)-O-[3-deoxy-4-C-methyl-3-(methylamino)-β-L-arabinopyranosyl-(1→6)-2-deoxy-D-streptamine

**Common Name:** 6'-N-Methylgentamicin; sagamicin

**Structural Formula:**



**Chemical Abstracts Registry No.:** –

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Sagamicin | Kyowa Hakko | Japan | 1982 |

**Raw Materials**

Bacterium *Micromonospora sagamiensis*
Dextrin
Soybean meal

**Manufacturing Process**

*A. Culturing of MK-65:* In this example, *Micromonospora sagamiensis* MK-65 ATCC 21826 (FERM-P No. 1530) is used as the seed strain. One loopful of the seed strain is inoculated into 30 ml of a first seed medium in a 250 ml-Erlenmeyer flask. The first seed medium has the following composition:

| | Percent |
|---|---|
| Dextrin | 1 |
| Glucose | 1 |
| Peptone | 0.5 |
| Yeast xtract | 0.5 |
| $CaCO_3$ | 0.1 |
| (pH: 7.2 before sterilization) | |

Culturing is carried out with shaking at 30°C for 5 days. 30 ml of the seed culture is then inoculated into 300 ml of a second seed medium, of the same composition as the first seed medium, in a 2 liter-Erlenmeyer flask provided with baffles. The second seed culturing is carried out with shaking at 30°C for 2 days. Then 1.5 liters of the second seed culture (corresponding to the content of 5 flasks) is inoculated into 15 liters of a third seed medium of the same composition as set forth above, in a 30 liter-glass jar fermenter. Culturing in the jar fermenter is carried out with aeration (15 liters/minute) and stirring (350 rpm) at 30°C for 2 days. Then, 15 liters of the third seed culture is inoculated into 60 liters of a fourth seed medium of the same composition as set forth above, in a 300 liter-fermenter. Culturing in the fermenter is carried out with aeration (60 liters/minute) and stirring (150 rpm) at 30°C for 2 days. Finally, 60 liters of the fourth seed culture is inoculated into 600 liters of a fermentation medium having the following composition in a 1,000 liter-fermenter.

| | Percent |
|---|---|
| Dextrin | 5 |
| Soybean meal | 4 |
| $CaCO_3$ | 0.7 |
| (pH: 7.2 before sterilization) | |

Culturing in the fermenter is carried out with aeration (600 liters/minute) and stirring 150 rpm) at 35°C for 5 days.

*B. Isolation of crude antibiotic:* After the completion of fermentation, the culture liquor is adjusted to a pH of 2.0 with 12 N sulfuric acid and stirred for 30 minutes. Then, about 10 kg of a filter aid, Radiolite No. 600 (product of Showa Kagaku Kogyo Co., Ltd., Japan) is added thereto and the microbial cells are removed by filtration. The filtrate is adjusted to a pH of 8.0 with 6 N sodium hydroxide and passed through a column packed with about 50 liters of a cation exchange resin, Amberlite IRC-50 (ammonia form). The active substance is adsorbed on the resin and the eluate is discarded. After washing the resin with water, the active substance is eluted out with 1 N aqueous ammonia. The eluate is obtained in fractions and the activity of each of the fractions is determined against *Bacillus subtilis* No. 10707 by a paper disk method using an agar plate.

Active fractions are combined and concentrated in vacuo to about 5 liters. The concentrate is then adjusted to a pH of 8.0 with 6 N sulfuric acid and passed through a column packed with 1 liter of an anion exchange resin, Dowex 1X2 ($OH^-$ form). The column is washed with about 5 liters of water and the effluent and the washings containing active substance are combined and are concentrated to 1/15 by volume. The concentrate is adjusted to a pH of 10.5 with 6 N sodium hydroxide and 5 volumes of acetone is added thereto. The resultant precipitate is removed by filtration and the filtrate is concentrated to 500 ml. The concentrate is adjusted to a pH of 4.5 with 6 N sulfuric acid and 2.5 liters of methanol is added thereto. After cooling, a white precipitate is obtained. The precipitate is separated by filtration and washed with methanol. After drying in vacuo, about 300 g of white powder is obtained.

The white powder is a mixture of the sulfate of gentamicin $C_{1a}$ and the sulfate of XK-62-2, and exhibits an activity of 620 units/mg (the activity of 1 mg of pure product corresponds to 1,000 units).

*C. Isolation and purification of XK-62-2:* 100 g of the white powder obtained in the above step B are placed to form a thin, uniform layer on the upper part of a 5 cm$\phi$ X 150 cm column packed with about 3 kg of silica gel advancely suspended in a solvent of chloroform, isopropanol and 17% aqueous ammonia (2:1:1 by volume). Thereafter, elution is carried out with the same solvent at a flow rate of about 250 ml/hour. The eluate is separated in 100 ml portions. The active fraction is subjected to paper chromatography to examine the components eluted. XK-62-2 is eluted in fraction Nos. 53–75 and gentamicin $C_{1a}$ is eluted in fraction Nos. 85–120. The fraction Nos. 53–75 are combined and concentrated under reduced pressure to sufficiently remove the solvent. The concentrate is then dissolved in a small amount of water. After freeze-drying the solution, about 38 g of a purified preparate of XK-62-2 (free base) is obtained. The preparate has an activity of 950 units/mg. Likewise, fraction Nos. 85–120 are combined and concentrated under reduced pressure to sufficiently remove the solvent. The concentrate is then dissolved in a small amount of water. After freeze-drying the solution, about 50 g of a purified preparate of gentamicin $C_{1a}$ (free base) is obtained. The activity of the preparate is about 980 units/mg.

**References**

Merck Index A-9
DFU 4 (5) 360 (1979) (as sagamicin) & 6 (5) 332 (1980)
DOT 19 (4) 211 (1983)
I.N. p. 635
Nara, T., Takasawa, S., Okachi, R., Kawamoto, I., Yamamoto, M., Sato, S., Sato, T. and Morikawa, A.; U.S. Patent 4,045,298; August 30, 1977; assigned to Abbott Laboratories

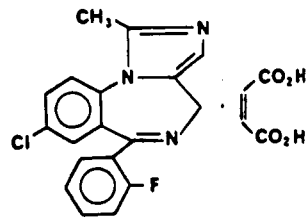
# MIDAZOLAM MALEATE

**Therapeutic Function:** Anaesthetic

**Chemical Name:** 8-Chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo-[1,5-a] [1,4]-benzodiazepine maleate

**Common Name:** —

**Structural Formula:**




**Chemical Abstracts Registry No.:** 59467-70-8 (Base)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Dormicum | Roche | Switz. | 1982 |
| Dormonid | Roche | — | — |

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Hypnovel | Roche | U.K. | – |
| Sorenor | Roche | – | – |

**Raw Materials**

2-Aminomethyl-7-chloro-2,3-dihydro-5-(2-fluorophenyl)-1H-1,4-benzodiazepine
Acetic anhydride
Polyphosphoric acid
Manganese dioxide
Maleic acid

**Manufacturing Process**

Acetic anhydride (7 ml) was added to a solution of 6.16 g of crude 2-aminomethyl-7-chloro-2,3-dihydro-5-(2-fluorophenyl)-1H-1,4-benzodiazepine in 200 ml of methylene chloride. The solution was added to 200 ml of saturated aqueous sodium bicarbonate and the mixture was stirred for 20 minutes. The organic layer was separated, washed with sodium bicarbonate, dried over sodium sulfate and evaporated to leave resinous 2-acetylaminomethyl-7-chloro-2,3-dihydro-5-(2-fluorophenyl)-1H-1,4-benzodiazepine. This material was heated with 40 g of polyphosphoric acid at 150°C for 10 minutes. The cooled reaction mixture was dissolved in water, made alkaline with ammonia and ice and extracted with methylene chloride. The extracts were dried and evaporated and the residue was chromatographed over 120 g of silica gel using 20% methanol in methylene chloride. The clean fractions were combined and evaporated to yield resinous 8-chloro-3a,4-dihydro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]-benzodiazepine.

A mixture of this material with 500 ml of toluene and 30 g of manganese dioxide was heated to reflux for 1½ hours. The manganese dioxide was separated by filtration over Celite. The filtrate was evaporated and the residue was crystallized from ether to yield 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]-benzodiazepine, melting point 152°C to 154°C. The analytical sample was recrystallized from methylene chloride/hexane.

A warm solution of 6.5 g (0.02 mol) of 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo-[1,5-a][1,4]-benzodiazepine in 30 ml of ethanol was combined with a warm solution of 2.6 g (0.022 mol) of maleic acid in 20 ml of ethanol. The mixture was diluted with 150 ml of ether and heated on the steam bath for 3 minutes. After cooling, the crystals were collected, washed with ether and dried in vacuo to yield 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]-benzodiazepine maleate, melting point 148°C to 151°C.

**References**

Merck Index 6056
DFU 3 (11) 822 (1978)
OCDS Vol. 3 p. 197 (1984)
DOT 19 (2) 113; (4) 221 & (7) 378 (1983)
I.N. p. 635
F. Hoffmann-La Roche & Co.; British Patent 1,527,131; October 4, 1978

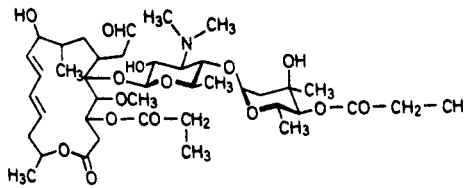
# MIDECAMYCIN

**Therapeutic Function:** Antibacterial

**Chemical Name:** Kleeman, p. 601

**Common Name:** Espinomycin

**Structural Formula:**



**Chemical Abstracts Registry No.:** 35457-80-8

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Medemycin | Meiji Seika | Japan | 1974 |
| Midecacine | Clin Midy | France | 1978 |
| Midecacine | Clin Midy | Switz. | 1980 |
| Midicacin | Midy | Italy | 1981 |
| Aboren | Promeco | Argentina | — |
| Macro-Dil | Roussel | — | — |

**Raw Materials**

Bacterium *Streptomyces mycarofaciens*
Starch
Vegetable protein

**Manufacturing Process**

The SF-837 strain, namely *Streptomyces mycarofaciens* identified as ATCC No. 21454 was inoculated to 60 liters of a liquid culture medium containing 2.5% saccharified starch, 4% soluble vegetable protein, 0.3% potassium chloride and 0.3% calcium carbonate at pH 7.0, and then stir-cultured in a jar-fermenter at 28°C for 35 hours under aeration. The resulting culture was filtered directly and the filter cake comprising the mycelium cake was washed with dilute hydrochloric acid.

The culture filtrate combined with the washing liquid was obtained at a total volume of 50 liters (potency 150 mcg/ml). The filtrate (pH 8) was then extracted with 25 liters of ethyl acetate and 22 liters of the ethyl acetate phase was concentrated to approximately 3 liters under reduced pressure. The concentrate was diluted with 1.5 liters of water, adjusted to pH 2.0 by addition of 5 N hydrochloric acid and then shaken thoroughly. The aqueous phase was separated from the organic phase and this aqueous solution was adjusted to pH 8 by addition of 3 N sodium hydroxide and then extracted with 800 ml of ethyl acetate. The resulting ethyl acetate extract was then shaken similarly together with 500 ml of aqueous hydrochloric acid to transfer the active substances into the latter which was again extracted with 400 ml of ethyl ether at pH 8. The ether extract was dried with anhydrous sodium sulfate and concentrated under reduced pressure to give 16.5 g of light yellow colored powder.

12 g of this crude powder were dissolved in 200 ml of ethyl acetate and the solution was passed through a column of 600 ml of pulverized carbon which had been impregnated with ethyl acetate. The development was carried out using ethyl acetate as the solvent and the active fractions of eluate were collected to a total volume of 2,500 ml, which was then evaporated to dryness under reduced pressure to yield 5 g of a white colored powder. This powder was dissolved in 10 ml of benzene and the insoluble matters were filtered out. The filtered solution in benzene was then subjected to chromatographic isolation by passing through a column of 700 ml of silica gel which had been impregnated with benzene. The development of the active substances adsorbed on the silica gel was effected using a solvent system consisting of benzene-acetone (4:1), and the eluate was collected in fractions of each 20 ml. The active fractions No. 90-380 which gave a single spot in alumina thin layer chromatography and which could be recognized as containing the SF-837 substance purely in view of

the Rf-value of the single spot were combined together to a total volume of 4,000 ml, and then concentrated under reduced pressure to yield 1.5 g of white colored powder of a melting point of 122°C to 124°C which was found by analysis to be the pure SF-837 substance free base.

**References**

Merck Index 6057
Kleeman & Engel p. 601
DOT 10 (2) 62 (1974)
I.N. p. 635
Tsuruoka, T., Shomura, T., Ezaki, N., Akita, E., Inoue, S., Fukatsu, S., Amano, S., Watanabe, H. and Niida, T.; U.S. Patent 3,761,588; September 25, 1973; assigned to Meiji Seika Kaisha, Ltd. (Japan)

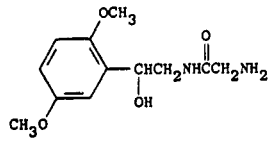
# MIDODRINE

**Therapeutic Function:** Peripheral vasotonic; antihypotensive

**Chemical Name:** 2-Amino-N-[2-(2,5-dimethoxyphenyl)-2-hydroxyethyl]-acetamide

**Common Name:** –

**Structural Formula:**




**Chemical Abstracts Registry No.:** 42794-76-3; 3092-17-9 (Hydrochloride)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Gutron | Hormon-Chemie | W. Germany | 1977 |
| Gutron | Chemie Linz | Italy | 1981 |
| Alphamine | Centerchem | U.S. | – |

**Raw Materials**

Carbobenzoxyglycine
Isovaleric acid chloride
1-(2',5'-Dimethoxyphenyl)-2-aminoethanol-(1)
Hydrogen

**Manufacturing Process**

19.5 parts of carbobenzoxyglycine, 7.1 parts of triethylamine and 162 parts of dry toluene are mixed with 11.2 parts of isovaleric acid chloride at 0°C to form the mixed anhydride and the mixture is agitated for two hours at 0°C. 32.4 parts of 1-(2',5'-dimethoxyphenyl)-2-aminoethanol-(1) are then added, the mixture is agitated for four hours at a temperature between 0°C and +10°C and then left to stand overnight at that temperature. A thick crystal paste forms. The reaction product is dissolved in 450 parts of ethyl acetate and 200 parts of water. The ethyl acetate solution is separated, washed with hydrochloric acid, sodium bicarbonate solution and water, dried over sodium sulfate and inspissated. The inspissation residue is digested with 342 parts of xylene, the required product crystallizing out. 34.9 parts of 1-(2',5'-dimethoxyphenyl)-2-(N-carbobenzoxyglycineamido)-ethanol -(1) are obtained.

66.2 parts of 1-(2',5'-dimethoxyphenyl)-2-(N-carbobenzoxyglycineamido)-ethanol-(1) are hydrogenated in the presence of 6.6 parts of palladium carbon (10%) in 2,000 parts of glacial acetic acid. When no more hydrogen is absorbed (3 mols of hydrogen are used), hydrogenation stops. The catalyst is removed by suction and the equivalent quantity of hydrochloric acid in ethanol is added to the filtrate with agitation. During further agitation at room temperature 28.6 parts of crude 1-(2',5'-dimethoxyphenyl)-2-glycineamidoethanol-(1)-hydrochloride crystallize, and are isolated and recrystallized from water-methanol for purification. 22.1 parts of pure product are obtained with a melting point of 192°C to 193°C.

An alternative synthesis route is described by Kleeman & Engel.

**References**

Merck Index 6058
Kleeman & Engel p. 602
DOT 18 (10 530 (1982)
I.N. p. 636
Wismayr, K., Schmid, O., Kilches, R. and Zolss, G.; U.S. Patent 3,340,298; September 5, 1967; assigned to Oesterreichische Stickstoffwerke A.G. (Austria)

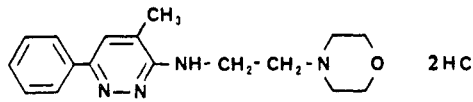
# MINAPRINE

**Therapeutic Function:** Antidepressant

**Chemical Name:** 3-(2-Morpholinoethylamino)-4-methyl-6-phenylpyridazine dihydrochloride

**Common Name:** —

**Structural Formula:**




**Chemical Abstracts Registry No.:** 25905-77-5; 25953-17-7 (Dihydrochloride)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Cantor | Clin Midy | France | 1979 |
| Kantor | Gador | Argentina | 1983 |

**Raw Materials**

3-Chloro-4-methyl-6-phenylpyridazine
N-(2-Aminoethyl)morpholine
Hydrogen chloride

**Manufacturing Process**

*(a) Preparation of the free base:* A mixture comprising 0.1 mol (20.4 g) of 3-chloro-4-methyl-6-phenylpyridazine and 0.2 mol (26.2 g) of N-(2-aminoethyl)-morpholine in 100 ml of n-butanol, with a pinch of copper powder, was heated under reflux for 12 hours. At the end of this time, the hot solution was poured into 200 ml of cold water. The resulting mixture was filtered through a sintered glass filter and the precipitate washed with ether. The filtrate and the ether washings were placed in a separating funnel and extracted with two 150 ml portions of ether. The ethereal layer was then extracted with about 250 ml of N sulfuric acid.

The acid solution was made alkaline with a 10% aqueous solution of sodium carbonate, and left to crystallize overnight.

The solution was filtered, yielding the colorless needles which were recrystallized from isopropanol. The yield was 15 g (53%).

*(b) Preparation of the hydrochloride:* The base was dissolved in the smallest amount possible of anhydrous acetone. Double that volume of anhydrous ether was added, and a stream of hydrogen chloride gas was passed through the solution. The hydrochloride salt obtained was recrystallized from absolute alcohol. The yield after recrystallization was 17 g (90%).

**References**

Merck Index 6066
DFU 2 (12) 811 (1977)
Kleeman & Engel p. 602
I.N. p. 637
Laborit, H.; British Patent 1,345,880; Feb. 6, 1974; and U.S. Patent 4,169,158; Sept. 25, 1979; both assigned to Centre D'Etudes Experimentales et Cliniques de Physiobiologie de Pharmacologie et D'Eutonologie (C.E.P.B.E.P.E.)

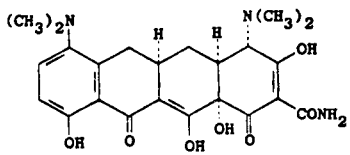
# MINOCYCLINE

Therapeutic Function: Antibiotic

Chemical Name: 4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

Common Name: 7-dimethylamino-6-demethyl-6-deoxytetracycline

Structural Formula:




**Chemical Abstracts Registry No.:** 10118-90-8; 13614-98-7 (Hydrochloride)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Minocin | Lederle | U.S. | 1971 |
| Minomycin | Lederle | Japan | 1971 |
| Klinomycin | Lederle | W. Germany | 1972 |
| Minocin | Lederle | Italy | 1972 |
| Minomycin | Takeda | Japan | 1972 |
| Vectrin | Parke Davis | U.S. | 1973 |
| Minocin | Lederle | U.K. | 1973 |
| Mynocine | Lederle | France | 1973 |
| Ultramycin | Parke Davis | — | — |

**Raw Materials**

6-Demethyltetracycline
Dibenzyl azodicarboxylate
Hydrogen

**Manufacturing Process**

*Preparation of 7-(N,N'-Dicarbobenzyloxyhydrazino)-6-Demethyltetracycline:* A 1.0 g portion of 6-demethyltetracycline was dissolved in a mixture of 9.6 ml of tetrahydrofuran and 10.4 ml of methanesulfonic acid at -10°C. The mixture was allowed to warm to 0°C. A solution of 0.86 g of dibenzyl azodicarboxylate in 0.5 ml of tetrahydrofuran was added dropwise and the mixture was stirred for 2 hours while the temperature was maintained at 0°C. The reaction mixture was added to ether. The product was filtered off, washed with ether and then dried. The 7-(N,N'-dicarbobenzyloxyhydrazino)-6-demethyltetracycline was identified by paper chromatography.

*Reductive Methylation of 7-(N,N'-Dicarbobenzyloxyhydrazino)-6-Demethyl-6-Deoxytetracycline to 7-Dimethylamino-6-Demethyl-6-Deoxytetracycline:* A solution of 100 mg of 7-(N,N'-dicarbobenzyloxyhydrazino)-6-demethyl-6-deoxytetracycline in 2.6 ml of methanol, 0.4 ml of 40% aqueous formaldehyde solution and 50 mg of 5% palladium on carbon catalyst was hydrogenated at room temperature and two atmospheres pressure. Uptake of the hydrogen was complete in 3 hours. The catalyst was filtered off and the solution was taken to dryness under reduced pressure. The residue was triturated with ether and then identified as 7-dimethylamino-6-demethyl-6-deoxytetracycline by comparison with an authentic sample, according to U.S. Patent 3,483,251.

**References**

Merck Index 6068
Kleeman & Engel p. 603
PDR p. 1018
OCDS Vol. 1 p. 214 (1977) & 2, 288 (1980)
DOT 5 (2) 75 (1969); 7 (5) 188 (1971) & 8 (3) 93 (1972)
I.N. p. 637
REM p. 1206
Boothe, J.H. and Petisi, J.; U.S. Patent 3,148,212; September 8, 1964; assigned to American Cyanamid Company
Petisi, J. and Boothe, J.H.; U.S. Patent 3,226,436; December 28, 1965; assigned to American Cyanamid Company
Winterbottom, R., Bitha, P. and Kissman, H.M.; U.S. Patent 3,345,410; October 3, 1967; assigned to American Cyanamid Company
Zambrano, R.T.; U.S. Patent 3,403,179; September 24, 1968; assigned to American Cyanamid Company
Zambrano, R.T.; U.S. Patent 3,483,251; December 9, 1969; assigned to American Cyanamid Company

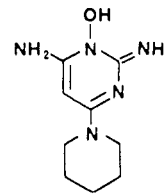
# MINOXIDIL

**Therapeutic Function:** Antihypertensive

**Chemical Name:** 6-Amino-1,2-dihydro-1-hydroxy-2-imino-4-piperidinopyrimidine

**Common Name:** –

**Structural Formula:**



**Chemical Abstracts Registry No.:** 38304-91-5

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Loniten | Upjohn | U.S. | 1979 |
| Loniten | Upjohn | U.K. | 1980 |
| Loniten | Upjohn | Switz. | 1981 |
| Lonolox | Upjohn | W. Germany | 1982 |
| Loniten | Upjohn | Italy | 1983 |
| Prexidil | Bioindustria | Italy | 1983 |

**Raw Materials**

Barbituric acid
2,4,6-Trichloropyrimidine
m-Chloroperbenzoic acid
Phosphorus oxychloride
Ammonia
Piperidine

**Manufacturing Process**

Barbituric acid is reacted with phosphorus oxychloride then with 2,4,6-trichloropyrimidine and that product with ammonia to give 4-chloro-2,6-diaminopyrimidine

A 30 g (0.15 mol) quantity of 4-chloro-2,6-diaminopyrimidine is dissolved in 600 ml of hot 3A alcohol, the solution cooled to 0°C to 10°C and 41.8 g (0.24 mol) of m-chloroperbenzoic acid is added. The mixture is held at 0°C to 10°C for 4 hours and filtered. The solid is shaken for 2 hours in 0.24 mol of 10% sodium hydroxide and filtered. The solid is washed with water and dried to yield 19.3 g of crude product. This product is extracted for 1 hour with 900 ml of boiling acetonitrile to yield 14.8 g (44.7% yield) of 6-amino-4-chloro-1,2-dihydro-1-hydroxy-2-iminopyrimidine, melting point 193°C.

A mixture of 3.0 g (0.019 mol) of 6-amino-4-chloro-1,2-dihydro-1-hydroxy-2-iminopyrimidine and 35 ml of piperidine is refluxed for 1.5 hours, cooled and filtered. The solid is shaken for 20 minutes in a solution of 0.8 g of sodium hydroxide in 30 ml of water and filtered. The solid is washed with water and extracted with 800 ml of boiling acetonitrile and filtered to yield 3.5 g (89%) yield of 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-piperidinopyrimidine, melting point 248°C, decomposition at 259°C to 261°C.

**References**

Merck Index 6069
DFU 2 (6) 383 (1977)
Kleeman & Engel p. 604
PDR p. 1848
OCDS Vol. 1 p. 262 (1977)
DOT 8 (7) 277 (1972) & 16 (9) 298 (1980)
I.N. p. 638
REM p. 848
Anthony, W.C. and Ursprung, J.J.; U.S. Patents 3,382,247; May 7, 1968 and 3,382,248; May 7, 1968; both assigned to The Upjohn Co.
Anthony, W.C.; U.S. Patent 3,644,364; February 22, 1972; assigned to The Upjohn Co.

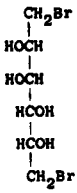
# MITOBRONITOL

**Therapeutic Function:** Cancer chemotherapy

**Chemical Name:** 1,6-dibromo-1,6-dideoxy-D-mannitol

**Common Name:** —

**Structural Formula:**



**Chemical Abstracts Registry No.:** 488-41-5

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Myelobromol | Hormon Chemie | W. Germany | 1967 |
| Myelobromol | Berk | U.K. | 1970 |
| Myebrol | Kyorin | Japan | 1978 |

**Raw Materials**

D-Mannitol
Hydrogen bromide

**Manufacturing Process**

750 g D-mannitol are dissolved in 4,000 ml of a 48% aqueous hydrogen bromide solution, whereupon the solution thus obtained is saturated at 0°C with gaseous hydrogen bromide until a HBr content of 69 to 70% is achieved. The reaction mixture is heated for 6 hours at 60°C in an autoclave, is then decolorized with charcoal, extracted with 1 liter chloroform twice and diluted with 7 liters of water. The pH value of the solution is adjusted by means of sodium bicarbonate to 1 to 2. The crystals precipitated after cooling for a day are filtered and washed with water until free from acid. 250 g crude 1,6-dibromo-1,6-didesoxy-D-mannitol are obtained. MP 176° to 178°C. Analysis: Br % = 52 (calc.: 51.9).

250 g of the crude DBM are dissolved in 2.5 liters of hot methanol and on decolorizing and filtration 2.5 liters of dichloroethane are added. 220 g of crystalline DBM are obtained. MP 178°C. Br % = 51.9.

**References**

Merck Index 6076
Kleeman & Engel p. 604
I.N. p. 639
REM p. 1156
Chinoin Gyogyszer-es Vegyeszeti Termekek Gyarart; British Patent 959,407; June 3, 1964

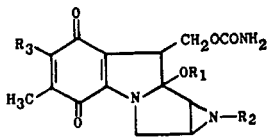
## MITOMYCIN

**Therapeutic Function:** Cancer chemotherapy

**Chemical Name:** See structural formula

**Common Name:** —

**Structural Formula:**



**Chemical Abstracts Registry No.:** 50-07-7

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Mitomycin | Medac | W. Germany | 1960 |
| Mitomycin C | Kyowa | Italy | 1961 |
| Ametycine | Choay | France | 1970 |
| Mutamycin | Bristol | U.S. | 1974 |
| Mytomycin C | Kyowa | Japan | 1980 |
| Mutamycin | Bristol | Sweden | 1983 |
| Mitomycin C | Syntex | Switz. | 1983 |

**Raw Materials**

Bacterium *Streptomyces caespitosus*
Nutrient broth

**Manufacturing Process**

The commercial production of mitomycin involves the preparation of mitomycin-containing broths by culturing a mitomycin-producing organism, e.g. *Streptomyces caespitosus*, in suitable media as described at length in the literature. At the end of the fermentation cycle the whole broth is usually centrifuged, filtered or otherwise treated to separate the solids (mycelia) from the supernatant which contains substantially all of the antibiotic activity.

In commercial processes there is usually a period of time intervening between the end of the fermentation cycle and the time at which the mycelia is actually removed from the broth; such a period may range from several minutes to several hours in length and may be due to a number of factors, e.g., the time necessary to conduct the actual centrifugation or filtration of large quantities of broth, or the time involved in waiting for equipment to become available for use. In the commercial preparation of mitomycin, the mitomycin-containing whole broths decrease rapidly in potency during the time following the completion of the fermentation cycle and prior to the removal of the mycelia. It has been observed that a whole broth will lose substantially all of its mitomycin activity within about 6 hours at room temperature and within about 24 hours at 10°C. It has, however, been discovered, as described in U.S. Patent 3,042,582, that in the process for the recovery of mitomycin C from mitomycin C-containing whole broth, the step of adding about 0.1 wt % with whole broth of sodium lauryl sulfate to the whole broth at the completion of the fermentation cycle substantially eliminates such destruction of mitomycin C by mitase.

**References**

Merck Index 6079
Kleeman & Engel p. 604
PDR p. 724
I.N. p. 640
REM p. 1156
Gourevitch, A., Chertow, B. and Lein, J.; U.S. Patent 3,042,582; July 3, 1962; assigned to Bristol-Myers Company

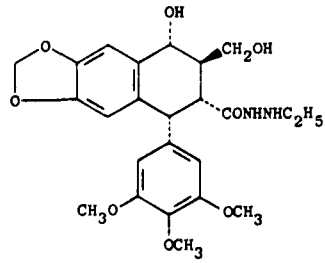
# MITOPODOZIDE

**Therapeutic Function:** Antineoplastic

**Chemical Name:** 5,6,7,8-Tetrahydro-8-hydroxy-7-(hydroxymethyl)-5-(3,4,5-trimethoxyphenyl)naphtho[2,3,d] -1,3-dioxole-6-carboxylic acid-2-ethylhydrazide

**Common Name:** Podophyllinic acid 2-ethylhydrazide

**Structural Formula:**




**Chemical Abstracts Registry No.:** 1508-45-8

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Proresid | Sandoz | W. Germany | 1966 |
| Proresid | Sankyo | Japan | 1969 |

**Raw Materials**

Podophyllinic acid hydrazide
Acetaldehyde
Hydrogen

**Manufacturing Process**

500 g of podophyllinic acid hydrazide are heated together with 150 cc of acetaldehyde with 2,200 cc of methanol to 40°C. The solution obtained is filtered and then cooled. The product which crystallizes out is filtered off with suction and washed with methanol. Together with a second fraction obtained after concentration of the mother liquors there are produced 450 g of podophyllinic acid ethylidene hydrazide, having a melting point of 222°C to 224°C and a specific rotation of $[\alpha]_D = -285°$ (c. = 0.5 in ethanol).

The product is hydrogenated in 4,000 cc of ethanol at room temperature and under normal atmospheric pressure with a catalyst prepared in the usual manner from 400 g of Raney nickel alloy. The calculated amount of hydrogen is taken up in approximately 75 hours. After filtration and evaporation to a small volume, the residue is distributed between 1,000 cc of chloroform and water each. The chloroform solution is then dried over sodium sulfate and evaporated to a small volume. Precipitation of the hydrogenation product with petroleum ether yields an amorphous white powder which is filtered by suction, washed with petroleum ether and dried at 50°C in a high vacuum. 1-ethyl-2-podophyllinic acid hydrazide is obtained in a practically quantitative yield.

**References**

Merck Index 7414
Kleeman & Engel p. 605
I.N. p. 640
Rutschmann, J.; U.S. Patent 3,054,802; September 18, 1962; assigned to Sandoz Ltd. (Switzerland)

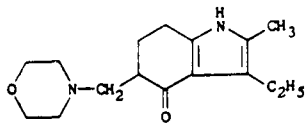
## MOLINDONE

**Therapeutic Function:** Antipsychotic

**Chemical Name:** 3-Ethyl-1,5,6,7-tetrahydro-2-methyl-5-(4-morpholinylmethyl)-4H-indol-4-one

**Common Name:** –

**Structural Formula:**



**Chemical Abstracts Registry No.:** 7416-34-4; 15622-65-8 (Hydrochloride)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Moban | Endo | U.S. | 1974 |
| Lidone | Abbott | U.S. | 1977 |

**Raw Materials**

Diethyl ketone
Cyclohexan-1,3-dione
Paraformaldehyde
Methyl nitrite
Morpholine hydrochloride

**Manufacturing Process**

Diethyl ketone may be reacted with methyl nitrite and that product in turn reacted with cyclohexan-1,3-dione to give 3-ethyl-4,5,6,7-tetrahydro-2-methyl-4-oxoindole.

3-ethyl-4,5,6,7-tetrahydro-2-methyl-4-oxoindole 14.1 g (0.08 mol), 14.8 g morpholine hydrochloride (0.12 mol), and 3.6 g paraformaldehyde (0.12 mol) were refluxed in 200 ml ethanol for 40 hours. The solution was evaporated to dryness in vacuo on a steam bath and the residue digested with a mixture of 150 ml water and 10 ml 2N HCl. An insoluble residue of unreacted starting material was filtered off. To the acid solution, ammonia water was added dropwise with stirring and the amine crystallized out. It was purified by dissolving in 1 N HCl and addition of ammonia, then by 2 crystallizations from benzene followed by 2 crystallizations from isopropanol, to yield 3-ethyl-4,5,6,7-tetrahydro-2-methyl-5-morpholino-methyl-4-oxoindole, melting point 180°C to 181°C.

**References**

Merck Index 6086
Kleeman & Engel p. 606
PDR p. 856
OCDS Vol. 2 p. 455 (1980)
DOT 5 (1) 34 (1969); 9 (6) 233 (1973) & 11 (2) 60 (1975)
I.N. p. 642
REM p. 1092
Pachter, I.J. and Schoen, K.; U.S. Patent 3,491,093; January 20, 1970; assigned to Endo Laboratories, Inc.

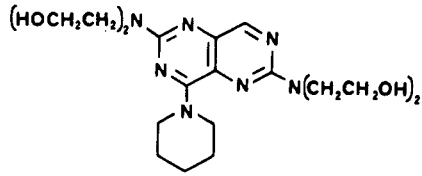
## MOPIDAMOL

**Therapeutic Function:** Blood platelet aggregation inhibitor

**Chemical Name:** 2,6-Bis(diethanolamino)-8-(N-piperidino)pyrimido[5,4-d] pyrimidine

**Common Name:** –

**Structural Formula:**



**Chemical Abstracts Registry No.:** 13665-88-8

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Rapenton | Thomae | W. Germany | 1980 |

**Raw Materials**

Dipyridamole
Iodine
Zinc
Formic acid

**Manufacturing Process**

3.9 g (0.06 mol) of zinc powder were introduced into a solution of 5.0 g (0.01 mol) of 2,6-bis-(diethanolamino)-4,8-dipiperidino-pyrimido-[5,4-d] -pyrimidine (dipyridamole; see entry under that name for its synthesis) in 120 cc of aqueous 10% formic acid. The resulting mixture was heated on a water bath, while occasionally stirring, until the intense yellow color of the starting compound disappeared, which occurred after about 30 to 40 minutes. Thereafter, the unconsumed zinc powder was separated by vacuum filtration, the virtually colorless filtrate was essentially an aqueous solution of 2,6-bis-(diethanolamino)-8-piperidino-1,2,3,4-tetrahydropyrimido-[5,4-d] pyrimidine.

The filtrate was adjusted to a pH of 9 by adding concentrated ammonia, and then a 1 N aqueous iodine-potassium iodide solution was added dropwise, whereby the tetrahydro-pyrimido-[5,4-d] pyrimidine obtained by hydrogenation with zinc in formic acid was converted by oxidation into 2,6-bis-(diethanolamino)-8-piperidino-pyrimido-[5,4-d] -pyrimidine. The completion of the oxidation was checked by means of a starch solution. The major amount of the oxidation product already separated out as a deep yellow crystalline precipitate during the addition of the iodine solution. After the oxidation reaction was complete, the reaction mixture was allowed to stand for a short period of time, and then the precipitate was separated by vacuum filtration, washed with water and dried. It had a melting point of 157°C to 158°C. The yield was 8.0 g, which corresponds to 95% theory.

**References**

Merck Index 6115
DFU 5 (11) 550 (1980)
Kleeman & Engel p. 608
DOT 17 (3) 89 (1981)
I.N. p. 644
Roch, J. and Scheffler, H.; U.S. Patent 3,322,755; May 30, 1967; assigned to Boehringer Ingelheim GmbH

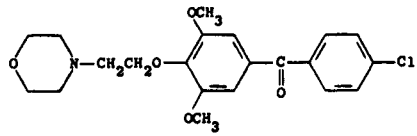
## MORCLOFONE

**Therapeutic Function:** Antitussive

**Chemical Name:** (4-Chlorophenyl)[3,6-dimethoxy-4-[2-(4-morpholinyl)-ethoxy] phenyl]-methanone

**Common Name:** Dimeclophenone

**Structural Formula:**



**Chemical Abstracts Registry No.:** 31848-01-8; 31848-02-9 (Hydrochloride)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Plausitin | Carlo Erba | Italy | 1975 |
| Nitux | Inpharzam | Switz. | 1981 |
| Medicil | Medici | Italy | – |
| Novotussil | Inpharzam | Belgium | – |

**Raw Materials**

3,5-Dimethoxy-4'-chloro-4-hydroxybenzophenone
Sodium methoxide
β-Morpholinoethyl chloride

**Manufacturing Process**

Sodium methoxide (1.2 g) in dimethylformamide (150 ml) was stirred with 3,5-dimethoxy-4'-chloro-4-hydroxybenzophenone (6 g) in dimethylformamide (50 ml), for 2 hours at 120°C. The reaction mixture was then treated with β-morpholinoethyl chloride (3.4 g) and heated for 1 hour at 140°C, then evaporated to dryness, and treated with water to give a solid material. The mixture was filtered, washed and crystallized from cyclohexane to give 3,5-dimethoxy-4'-chloro-4-(β-morpholinoethoxy)-benzophenone (6.5 g), MP 91°C to 92°C. The product was then reacted at about 0°C with gaseous hydrogen chloride in ether to give, after crystallization from isopropanol, the corresponding hydrochloride which had a MP of 187.9°C.

**References**

Merck Index 6120
Kleeman & Engel p. 609
DOT 12 (7) 269 (1976)
I.N. p. 645
Lauria, F., Vecchietti, V. and Logemann, W.; U.S. Patent 3,708,482; January 2, 1973; assigned to Carlo Erba SpA (Italy)

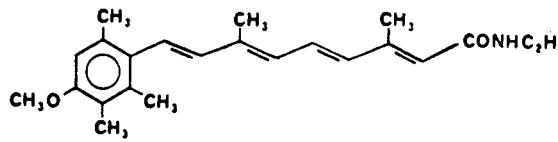
## MOTRETINIDE

**Therapeutic Function:** Antipsoriasis

**Chemical Name:** N-Ethyl-9-(4-methoxy-2,3,6-trimethylphenyl-3,7-dimethyl-2,4,6,8-nonatetraenamide

**Common Name:** –

**Structural Formula:**




**Chemical Abstracts Registry No.:** 56281-36-8

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Tasmaderm | Roche | Switz. | 1981 |

**Raw Materials**

5-(4-Methoxy-2,3,6-trimethylphenyl)-3-methylpenta-2,4-diene-1-triphenylphosphonium bromide
Sodium hydride
3-Formylcrotonic acid butyl ester
Sodium hydroxide
Phosphorus trichloride
Ethylamine

**Manufacturing Process**

228 g of 5-(4-methoxy-2,3,6-trimethyl-phenyl)-3-methyl-penta-2,4-diene-1-triphenylphosphonium bromide are introduced under nitrogen gassing into 910 ml of dimethylformamide and treated with cooling at 5°C to 10°C within 20 minutes with 17.5 g of a suspension of sodium hydride (about 50% by weight) in mineral oil. The mixture is stirred for 1 hour at about 10°C, then treated at 5°C to 8°C dropwise with 61.8 g of 3-formylcrotonic acid butyl ester, heated for 2 hours at 65°C, subsequently introduced into 8 liters of ice-water and, after the addition of 300 g of sodium chloride, thoroughly extracted with a total of 18 liters of hexane. The extract is washed 5 times with 1 liter of methanol/water (6:4 parts by volume) each time and 2 times with 1.5 liters of water each time, dried over sodium sulfate and evaporated under reduced pressure to leave 9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester, MP 80°C to 81°C as the residue.

125.8 g of 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester are introduced into 2,000 ml of absolute ethanol and treated with a solution of 125.8 g of potassium hydroxide in 195 ml of water. The mixture is heated to boiling under nitrogen gassing for 30 minutes, then cooled, introduced into 10 liters of ice-water and, after the addition of about 240 ml of concentrated hydrochloric acid (pH 2–4), thoroughly extracted with a total of 9 liters of methylene chloride. The extract is washed with about 6 liters of water to neutrality, dried over calcium chloride and evaporated under reduced pressure. The residue is taken up in 700 ml of hexane. The precipitated 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid melts at 228°C to 230°C.

28.6 g of 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid are introduced into 300 ml of benzene and treated under nitrogen gassing with 12 g of phosphorus trichloride. The benzene is subsequently distilled off under reduced pressure. The remaining 9-(4-methoxy-2,4,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid chloride is dissolved in 1,200 ml of diethyl ether. The solution is added dropwise at -33°C into 500 ml of ethylamine and stirred for 3 hours. The reaction mixture is then diluted with 500 ml of diethyl ether and stirred without cooling for a further 12 hours, the ammonia evaporating. The residue is dissolved in 10 liters of methylene chloride. The solution is washed 2 times with 3 liters of water, dried over sodium sulfate and evaporated under reduced pressure. The remaining N-ethyl-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid amide melts, after recrystallization from ethanol, at 179°C to 180°C.

**References**

Merck Index 6142
DFU 3 (2) 126 (1978)
OCDS Vol. 3 p. 12 (1984)
DOT 18 (12) 653 (1982)
I.N. p. 647
Bollag, W., Ruegg, R. and Ryser, G.; U.S. Patents 4,105,681; August 8, 1978; and 4,215,215; July 29, 1980; both assigned to Hoffmann-LaRoche, Inc.

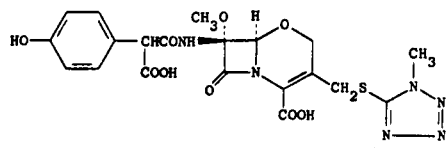
# MOXALACTAM DISODIUM

**Therapeutic Function:** Antiinfective

**Chemical Name:** 7-[[[Carboxy(4-hydroxyphenyl)acetyl]amino]7-methoxy-3-[[[(1-methyl-1H-tetrazol-5-yl)thio]-methyl]-8-oxo-5-oxa-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid disodium salt

**Common Name:** Lamoxactam; latamoxef

**Structural Formula:**




(base)

**Chemical Abstracts Registry No.:** 64952-97-2 (Base)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Moxam | Lilly | U.S. | 1981 |
| Moxalactam | Lilly | W. Germany | 1981 |
| Festamoxin | Shionogi | W. Germany | 1981 |
| Moxalactam | Lilly | France | 1981 |
| Moxalactam | Lilly | U.K. | 1982 |
| Shiomalin | Shionogi | Japan | 1982 |

**Raw Materials**

p-(p-Methoxybenzyloxy)-phenylmalonic acid
Diphenylmethyl 7β-amino-7α-methoxy-3-(1-methyltetrazol-5-yl)-thiomethyl-1-oxa-dethia-3-cephem-4-carboxylate
Aluminum chloride
Sodium-2-ethylhexanoate

**Manufacturing Process**

To a stirred suspension of p-(p-methoxybenzyloxy)-phenylmalonic acid (125 mg) in methylene chloride (3 ml) are added triethylamine (55 μl) and oxalyl chloride (26 μl) at -15°C, and the suspension is stirred for 40 minutes at 0°C. The mixture is added to a solution of diphenylmethyl 7β-amino-7α-methoxy-3-(1-methyltetrazol-5-yl)thiomethyl-1-oxadethia-3-cephem-4-carboxylate (100 mg) in methylene chloride (3 ml) and pyridine (63 μl), and the mixture is stirred for 30 minutes at 0°C. The reaction mixture is diluted with ethyl acetate, washed with aqueous 2N-hydrochloric acid and water, dried over sodium sulfate, and concentrated to give crude product (212 mg), which is chromatographed on silica gel (20 g) and

eluted with a mixture of ethyl acetate and acetic acid (99:1) to give diphenylmethyl-7β-[α-p-(p-methoxybenzyloxy)phenyl-α-carboxyacetamido]-7α-methoxy-3-(1-methyltetrazol-5-yl)thiomethyl-1-oxadethia-3-cephem-4-carboxylate as foam (71 mg). Yield: 45%.

To a solution of diphenylmethyl 7β-[α-p-(p-methoxybenzyl)-oxy-phenyl-α-p-methoxybenzyl-oxycarbonyl-acetamido]-7α-methoxy-3-(1-methyltetrazol-5-yl)thiomethyl-1-oxadethia-3-cephem-4-carboxylate (1.20 g) in methylene chloride (24 ml) are added anisole (2.4 ml) and a solution of aluminum chloride (2.58 g) in nitromethane (12 ml) at 0°C under nitrogen. After stirring for 15 minutes at 0°C, the mixture is poured into cold 5% sodium hydrogen carbonate aqueous solution (100 ml) and filtered to remove the formed precipitate. The filtate is washed twice with methylene chloride (2 X 100 ml), acidified with 2N-hydrochloric acid to pH 2.60, and poured in a column of high porous polymer HP-20 (60 ml) sold by Mitsubishi Chemical Industries Ltd. The column is washed with water (300 ml) and eluted with methanol. The eluate is concentrated under reduced pressure at room temperature. The residue is dissolved in methanol, treated with active carbon, and concentrated under reduced pressure to give 7β-(α-p-hydroxyphenyl-α-carboxyacetamido)-7β-methoxy-3-(1-methyl-tetrazol-5-yl)thiomethyl-1-oxadethia-3-cephem-4-carboxylic acid as powder (595 mg) decomposing at 125°C to 132°C. Yield: 88.5%.

To a solution of 7β-(α-p-hydroxyphenyl-α-carboxyacetamido-7α-methoxy-3-(1-methyl-tetrazol-5-yl)thiomethyl-1-oxadethia-3-cephem-4-carboxylic acid (359 mg) in methanol (7 ml) is added a solution of sodium 2-ethylhexanoate in methanol (2 mols/liter; 1.73 ml) at room temperature. After stirring for 10 minutes, the reaction mixture is diluted with ethyl acetate, stirred for 5 minutes, and filtered to collect separated solid, which is washed with ethyl acetate, and dried to give disodium salt of 7β-(α-p-hydroxyphenyl-α-carboxyacetamido)-7α-methoxy-3-(1-methyl-tetrazol-5-yl)thiomethyl-1-oxadethia-3-cephem-4-carboxylic acid (342 mg). Yield: 88.8%. Colorless powder. MP decomposition from 170°C.

**References**

Merck Index 6143
DFU 5 (9) 467 (1980)
PDR p. 1064
OCDS Vol. 3 p. 218 (1984)
DOT 18 (3) 132 (1982)
I.N. p. 550
Narisada, M. and Nagata, W.; U.S. Patent 4,138,486; February 6, 1979; assigned to Shionogi & Co., Ltd. (Japan)

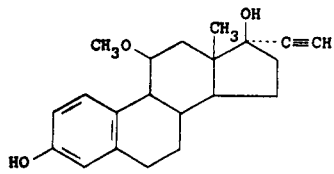
## MOXESTROL

Therapeutic Function: Estrogen

Chemical Name: 11β-methoxy-19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol

Common Name: 11β-methoxy-17α-ethynylestradiol

Structural Formula:



**Chemical Abstracts Registry No.:** 34816-55-2

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Surestryl | Roussel | France | 1974 |

**Raw Materials**

$\Delta^{4,9}$-Estradiene-11$\beta$-ol-3,17-dione
Palladium hydroxide
Acetylene
Methanol
Potassium

**Manufacturing Process**

*(A) Preparation of 11β-Methoxy-$\Delta^{4,9}$-Estradiene-3,17-Dione:* 0.5 g of $\Delta^{4,9}$-estradiene-11$\beta$-ol-3,17-dione were dissolved at room temperature in 25 cc of methylene chloride containing 2% of methanol and after 5 mg of p-toluene-sulfonic acid were added, the reaction mixture was agitated for several minutes. Then the reaction mixture was poured into ice water, washed with water until the wash waters were neutral, and distilled to dryness under vacuum. The resulting residue was crystallized from ethyl ether to obtain 0.46 g of 11$\beta$-methoxy-$\Delta^{4,9}$-estradiene-3,17-dione having a MP of 140°C.

*(B) Preparation of 11β-Methoxy-$\Delta^{1,3,5(10)}$-Estratriene-3-ol-17-one:* 12.3 g of 11$\beta$-methoxy-$\Delta^{4,9}$-estradiene-3,17-dione were dissolved in 1,230 cc of methanol and then, under an atmosphere of nitrogen, 7.38 g of palladium hydroxide were added and the mixture was held at reflux for one hour under agitation and a nitrogen atmosphere. Then the reaction mixture was cooled to 30°C, filtered, vacuum filtered and washed with methanol. The methanolic solutions were concentrated to about 50 cc, allowed to stand overnight at room temperature and filtered. The precipitate formed was triturated in methanol and dried at 80°C to obtain 10.74 g (yield = 87.5%) of 11$\beta$-methoxy-$\Delta^{1,3,5(10)}$-estratriene-3-ol-17-one having a MP of 264°C.

*(C) Preparation of 11β-Methoxy-17α-Ethynyl-$\Delta^{1,3,5(10)}$-Estratriene-3,17β-Diol:* Under agitation and an atmosphere of nitrogen, 12 g of potassium were heated at 80°C in 180 cc of tertiary-amyl alcohol. The mixture was agitated for 30 minutes, cooled to 20°C and after 60 cc of dioxane were added thereto, a stream of acetylene was allowed to bubble through the mixture for one hour and fifteen minutes. Then a solution of 3 g of 11$\beta$-methoxy-$\Delta^{1,3,5(10)}$-estratriene-3-ol-17-one in 50 cc of dioxane was added and the mixture was agitated for 4 hours while continuing the passage of acetylene at room temperature. Thereafter, 50 cc of a 50% aqueous acetic acid solution was added and the mixture was poured into water and extracted with ether. The organic phases were washed first with an aqueous solution containing 10% of neutral sodium carbonate, then with water until the wash waters were neutral, dried over sodium sulfate and concentrated under vacuum until crystallization started. The reaction mixture was iced for one hour, vacuum filtered and the precipitate dried under vacuum to obtain 3.8 g of the raw 17$\alpha$-ethynyl derivative, which was purified by dissolution in ethyl acetate at reflux and by icing to obtain 2.33 g (yield = 77%) of 11$\beta$-methoxy-17$\alpha$-ethynyl-$\Delta^{1,3,5(10)}$-estratriene-3,17$\beta$-diol, having a MP of 280°C.

**References**

Merck Index 6145
Kleeman & Engel p. 611
DOT 11 (4) 149 (1975)
I.N. p. 647
Bertin, D. and Pierdet, A.; U.S. Patent 3,579,545; May 18, 1971; assigned to Roussel-UCLAF, France

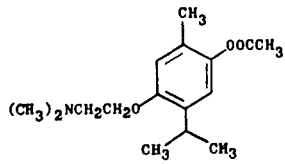
# MOXISYLYTE

**Therapeutic Function:** Peripheral vasodilator

**Chemical Name:** 4-[2-(Dimethylamino)ethoxy] 2-methyl-5-(1-methylethyl)-phenol acetate (ester)

**Common Name:** Thymoxamine

**Structural Formula:**



**Chemical Abstracts Registry No.:** 54-32-0

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Carlytene | Dedieu | France | 1962 |
| Vasoklin | Godecke | W. Germany | 1973 |
| Opilon | Parke Davis | Italy | 1975 |
| Apifor | Substancia | Spain | — |
| Arlitene | Chinoin | Italy | — |
| Sympal | VEB Berlin-Chemie | E. Germany | — |
| Valyten | Landerlan | Spain | — |

**Raw Materials**

Thymol
Hydrogen sulfide
Sodium
Dimethylaminoethyl chloride
Sulfuric acid
Sodium nitrite
Acetic anhydride
Ethanol
Hydrogen chloride

**Manufacturing Process**

A hydrochloric acid solution of 100 g of thymol in alcohol is reacted with 72 g of sodium nitrite, the nitrosothymol (*Organic Syntheses* 6, New York, 1926, p. 92) thus obtained is introduced into ammonia, and is reduced by the introduction of hydrogen sulfide to 4-aminothymol (*Organic Syntheses Coll.* Vol. 1, New York, 1932, p. 458). 133.3 g of this 4-aminothymol are mixed with 67 g of sodium acetate, 107 g of glacial acetic acid and 80 g of acetic acid anhydride to form 4-acetaminothymol (Plancher, *Gazzetta Chimica Italiana* 25, II, p. 388). 156 parts by weight of this last formed substance dissolved in 600 cc of alcohol are added to a solution of 17.6 parts by weight of sodium in 600 cc of alcohol, the mixture being boiled under reflux for some time with 82 g of dimethylaminoethyl chloride. The reaction product is treated with water, and neutralized with hydrochloric acid using acid Congo reagent indicator, and the alcohol is distilled off in vacuo. The base liberated by alkali is dissolved in ether. By evaporating the ether solution the dimethylaminoethyl ether of the 4-acetaminothymol is obtained as a brownish-yellow oil. After some time this oil solidifies in a crystalline state.

100 g of this base are dissolved in a mixture of 300 cc of concentrated hydrochloric acid (density 1.19) and 400 cc of water, and the solution is boiled for one hour under a reflux condenser. Thereupon it is made alkaline, extracted with ether, and the ether is distilled off. 23.6 g of the 4-aminothymoxyethyldimethylamine thus obtained are diazotized in the presence of sulfuric acid at a temperature not exceeding 0°C using a solution of 7.2 g of sodium nitrite in 70 cc of water, and the diazo compound is heated to boiling point after the addition of 1 g of copper sulfate, until no further gas is evolved. It is then made alkaline, and carbon dioxide is introduced. The base is precipitated first in an oily state, and soon becomes crystalline. The 4-oxythymoxyethyldimethylamine forms a neutral hydrochloride which is readily soluble in water, and has a melting point of 174°C to 175.5°C.

36.8 g of 4-oxythymoxyethyldimethylamine are boiled for one hour on a water bath with 160 cc of acetic anhydride and 17.5 cc of pyridine. After this period, the solution is diluted with water, made alkaline, and the base is extracted with ether and the ether distilled off. With acids, the base obtained forms crystalline salts which are readily soluble in water. The hydrochloride melts between 208°C and 210°C.

**References**

Merck Index 6146
Kleeman & Engel p. 612
OCDS Vol. 1 p. 116 (1977)
I.N. p. 647
Veritas Drug Co., Ltd; British Patent 745,070; February 22, 1956

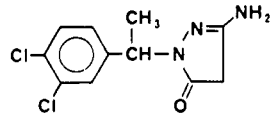
# MUZOLIMINE

**Therapeutic Function:** Diuretic

**Chemical Name:** (3-Amino-1-(α-methyl-3,4-dichlorobenzyl)pyrazol-5-one

**Common Name:** –

**Structural Formula:**




**Chemical Abstracts Registry No.:** 55294-15-0

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Edrul | Bayer | Italy | 1982 |

**Raw Materials**

α-Methyl-3,4-dichlorobenzylhydrazine
β-Amino-β-ethoxyacrylic acid ethyl ester

**Manufacturing Process**

41 g of α-methyl-3,4-dichlorobenzylhydrazine, dissolved in absolute ethanol, were added dropwise to a solution of 31.8 g of β-amino-β-ethoxyacrylic acid ethyl ester and 1.5 g of p-toluenesulfonic acid in 150 ml of ethanol at room temperature under nitrogen gas. After stirring for 2 hours and standing overnight, the reaction solution was concentrated as far as possible on a rotary evaporator. The residue which remained was dissolved in 2N sodium hydroxide solution. Any unconverted starting products or by-products were extracted with ether. The aqueous phase was then brought to pH 5 with acetic acid. The oil thereby produced was taken up in methylene chloride and the organic phase was dried over $Na_2SO_4$. After evaporating off the solvent, the reaction product crystallized out. It was recrystallized from methanol; melting point 127°C to 129°C; yield 21 g (38.5% of theory).

**References**

Merck Index 6165
DFU 2 (6) 387 (1977)
OCDS Vol. 3 p. 137 (1984)

DOT 18 (10) 555 (1982) & 19 (5) 267 (1983)
I.N. p. 649
Moller, E., Meng, K., Wehinger, E. and Horstmann, H.; British Patent 1,429,141; March 24, 1976; assigned to Bayer AG
Moller, E., Meng, K., Wehinger, E. and Horstmann, H.; U.S. Patent 4,018,890; April 19, 1977; assigned to Bayer AG