# M

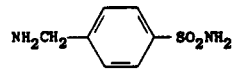
## MAFENIDE ACETATE

**Therapeutic Function:** Antibacterial

**Chemical Name:** α-Acetylamino-p-toluenesulfonamide

**Common Name:** –

**Structural Formula:**




(base)

**Chemical Abstracts Registry No.:** 13009-99-9; 138-39-6 (Base)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Sulfamylon | Winthrop | U.S. | 1949 |
| Napaltan | Winthrop | W. Germany | 1969 |
| Sulfamylon | Winthrop | U.K. | 1970 |
| Mafatate | Torii | Japan | 1980 |
| Mafylon | Winthrop | – | – |

**Raw Materials**

Acetylbenzylamine
Chlorosulfonic acid
Ammonia

**Manufacturing Process**

For the preparation of mafenide 50 g of acetylbenzylamine are introduced while stirring into 150 cc of chlorosulfonic acid, whereby the temperature is kept below 40°C by external cooling. After several hours' storing at ordinary temperature the mixture is heated for 1 hour in the boiling water-bath and after cooling, poured on to ice. Thereupon the 4-acetylaminoethyl-benzenesulfonic acid chloride precipitates at first in an oily form, but solidifies after short stirring to crystals. The product sucked off and washed with cold water is introduced into a 10% aqueous ammonia solution. Thereby dissolution takes place while heating and after a short time the 4-acetylaminomethyl-benzenesulfonic acid amide precipitates in a crystalline form. After heating to 70°C for 30 minutes the solution is cooled, filtered with suction and washed out. The product is obtained when recrystallized from water or dilute alcohol in colorless crystals melting at 177°C. It is readily soluble in warm water, extremely readily soluble in dilute sodium hydroxide solution.

**References**

Merck Index 5466
Kleeman & Engel p. 534
PDR p. 1929
OCDS Vol. 2 p. 114 (1980)

DOT 5 (4) 132 (1969)
I.N. p. 574
REM p. 1162
Klarer, J.; U.S. Patent 2,288,531; June 30, 1942; assigned to Winthrop Chemical Co., Inc.

# MAGALDRATE

**Therapeutic Function:** Antacid

**Chemical Name:** Tetrakis(hydroxymagnesium)decahydroxydialuminate dihydrate

**Common Name:** Magnesium aluminate hydrate; monalium hydrate

**Structural Formula:** $[Mg(OH)]_4[(HO)_4Al(OH)(HO)Al(OH)_4]\cdot 2H_2O$

**Chemical Abstracts Registry No.:** 1317-26-6

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Riopan | Ayerst | U.S. | 1960 |
| Riopan | Byk Gulden | W. Germany | 1981 |
| Dynese | Galen | U.K. | 1983 |
| Bismag-Lac | Much | W. Germany | — |

**Raw Materials**

Aluminum chloride
Sodium hydroxide
Magnesium sulfate

**Manufacturing Process**

1 kg aluminum chloride hydrate was dissolved in 2 kg water and reacted with a solution of 1.2 kg sodium hydroxide in 2.5 kg water, under constant stirring. The resultant sodium aluminate solution was cooled to about 20°C and, with thorough stirring, it was reacted with 3.5 kg of a magnesium sulfate solution produced by dissolving 1 kg of magnesium sulfate anhydride in 2.5 kg water. The magnesium sulfate solution was introduced in a plurality of thin jets through several shower heads to avoid localized differences of concentration as much as possible. After all the magnesium sulfate was added, stirring was continued for about ½ hour.

A colorless, colloidal precipitate was formed and stirred thoroughly for about 15 minutes, whereupon it was filtered by suction. The raw product thus obtained was washed with water until it contained only about ½% water-soluble salts. After drying for 12 hours in a vacuum apparatus at 60°C and under a pressure of 12 mm Hg, the product had the form of hard pieces. The pieces were comminuted to powder in a ball mill and the powder was passed through a sieve (3,600 meshes per $cm^2$). The small residue on the sieve was again pulverized and passed through the same sieve. The yield was 870 g, or 99% of theoretical, calculated on the assumed formula

$$[Mg(OH)]_4[(HO)_4Al(OH)(HO)Al(OH)_4]\cdot 2H_2O$$

with a molecular weight of 425.

**References**

Merck Index 5467

PDR p. 650
I.N. p. 574
REM p. 795
Hallmann, G.; U.S. Patent 2,923,660; February 2, 1960; assigned to Byk-Gulden Lomberg Chemische Fabrik GmbH, Germany

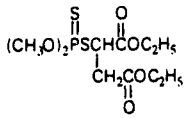
# MALATHION

**Therapeutic Function:** Pediculicide

**Chemical Name:** Diethyl(dimethoxyphosphinothioyl)thiobutanedioate

**Common Name:** Mercaptothion (South Africa), maldison (Australia and New Zealand), carbofos (U.S.S.R.)

**Structural Formula:**



**Chemical Abstracts Registry No.:** 121-75-5

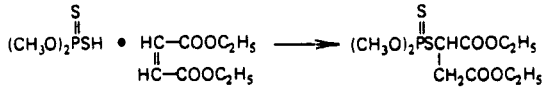
| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Prioderm | Purdue Fredrick | U.S. | 1982 |
| Organoderm | Mundipharma | W. Germany | 1982 |
| Derbac | Benque | U.K. | — |
| Lusap | Interdelta | Switz. | — |
| Taskil | Tasman Vaccine | U.K. | — |

**Raw Materials**

O,O-Dimethyl phosphorodithioic acid
Diethyl maleate

**Manufacturing Process**

The feed materials for malathion manufacture are O,O-dimethyl phosphorodithioic acid and diethyl maleate or fumarate which react according to the equation:



An antipolymerization agent such as hydroquinone may be added to the reaction mixture to inhibit the polymerization of the maleate or fumarate compound under the reaction conditions. This reaction is preferably carried out at a temperature within the range of 20°C to 150°C. This reaction is preferably carried out at atmospheric pressure. Reaction time of 16 to 24 hours have been specified for this reaction by J.T. Cassaday. The reaction is preferably carried out in a solvent such as the low molecular weight aliphatic monohydric alcohols, ketones, aliphatic esters, aromatic hydrocarbons or trialkyl phosphates.

The reaction may be accelerated by using an aliphatic tertiary amine catalyst, usually within the range of 0.2 to 2.0% based on the total weight of the reactants. A stirred, jacketed re-

actor of conventional design may be used. After cooling, the reaction mixture may be taken up in benzene. It is then washed with 10% $Na_2CO_3$ and with water. The organic layer is dried over anhydrous $Na_2SO_4$, filtered and concentrated in vacuo to give the final product as residue.

**References**

Merck Index 5522
I.N. p. 575
REM p. 1240
Cassaday, J.T.; U.S. Patent 2,578,652; December 18, 1951; assigned to American Cyanamid Co.
Backlund, G.R., Martino, J.F. and Divine, R.D.; U.S. Patent 3,463,841; August 26, 1969; assigned to American Cyanamid Co.
Usui, M.; U.S. Patent 2,962,521; November 29, 1960; assigned to Sumitomo Chemical Co.

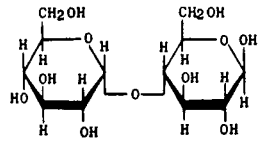
## MALTOSE

**Therapeutic Function:** Sugar supplement for diabetics

**Chemical Name:** 4-O-α-Glucopyranosyl-D-glucose

**Common Name:** –

**Structural Formula:**



**Chemical Abstracts Registry No.:** 69-79-4

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Maltos-10 | Otsuka | Japan | 1974 |

**Raw Materials**

Starch
Water

**Manufacturing Process**

The process of manufacturing a maltose product from a suitably purified starch source includes preparing an aqueous starchy suspension, adjusting the acidity thereof to from 4.6 to 6.0 pH, liquefying the suspension by heating in the presence of a diastatic agent, diastatically saccharifying the liquefied mixture, filtering, and concentrating the liquid to a syrup.

**References**

Merck Index 5536
DOT 10 (11) 308 (1974)
REM p. 1029
Gore, H.C.; U.S. Patent 1,657,079; January 24, 1928; assigned to The Fleischmann Co.

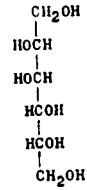
# MANNITOL

**Therapeutic Function:** Diuretic; diagnostic aid (kidney function)

**Chemical Name:** D-mannitol

**Common Name:** –

**Structural Formula:**



**Chemical Abstracts Registry No.:** 69-65-8

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Mannitol | MSD | U.S. | 1946 |
| Osmitrol | Travenol | U.S. | 1964 |
| Mannitol I.V. | Abbott | U.S. | 1968 |
| Eufusol | Knoll | W. Germany | – |
| Isotol | Baxter | Italy | – |
| Manit | Pliva | Yugoslavia | – |
| Mannidex | Pharmacia | Sweden | – |
| Osmofundin | Braun | W. Germany | – |
| Osmosol | Farmer Hill | Australia | – |
| Rectisol | McGaw | U.S. | – |

**Raw Materials**

Glucose
Hydrogen

**Manufacturing Process**

250 g of glucose is dissolved in distilled water to give a solution of 48% concentration. This solution is heated to 65°C and barium hydroxide added in quantity sufficient to make the concentration of the barium hydroxide 0.2 mol/liter. The solution is agitated and maintained at 65°C for 6 hours after the addition of the barium hydroxide. It is then cooled and neutralized to a pH of 6.8 with sulfuric acid. The precipitated barium sulfate is filtered out. A quantity of activated supported nickel catalyst containing 5 g of nickel is added.

The slurry is introduced into a 3-liter rocking autoclave, and hydrogen admitted to a pressure of 1,500 psi. The autoclave is heated to a temperature of 150°C in one hour and held at this temperature for 2½ hours more. Pressure rises to about 1,800 psi and then declines to about 1,600 during the hydrogenation. The autoclave is then cooled, emptied, and the catalyst filtered from the product. The filtrate is then concentrated under vacuum on a hot water bath to remove a part of the water.

The concentrate is taken up in warm aqueous methanol so adjusted that the composition of the solvent is 90% methanol/10% water, and the weight of the solvent is 3 times the weight of the solids in the concentrate. This solution is cooled to 20°C and held overnight. The mannitol which crystallizes is filtered out. The filtrate is concentrated on a water bath under vacuum to remove methanol and adjusted to a water percentage of 16%. The re-

sulting syrup is viscous, noncrystallizing and nongelling, and analysis shows a PN (Pyridine Number) of 32 and essentially no reducing sugar, according to U.S. Patent 2,749,371.

**References**

Merck Index 5569
I.N. p. 576
REM p. 935
Kasehagen, L.; U.S. Patent 2,642,462; June 16, 1953; assigned to Atlas Powder Company
Kasehagen, L.; U.S. Patent 2,749,371; June 5, 1956; assigned to Atlas Powder Company
Kasehagen, L. and Luskin, M.M.; U.S. Patent 2,759,024; August 14, 1956; assigned to Atlas Powder Company

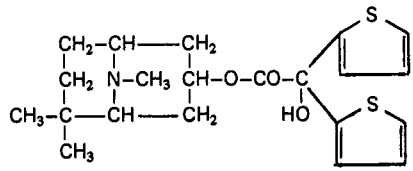
# MAZATICOL HYDROCHLORIDE

**Therapeutic Function:** Antiparkinsonian

**Chemical Name:** 6,6,9-Trimethyl-9-azabicyclo[3.3.1]non-3β-yl di-2-thienylglycolate hydrochloride

**Common Name:** –

**Structural Formula:**




(base)

**Chemical Abstracts Registry No.:** 38738-59-9; 42024-98-6 (Base)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Pentona | Tanabe | Japan | 1978 |

**Raw Materials**

6,6,9-Trimethyl-9-azabicyclo[3.3.1]nonan-3α-ol
Methyl α,α-di(2-thienyl)glycollate

**Manufacturing Process**

A mixture of 1.0 g of 6,6,9-trimethyl-9-azabicyclo[3.3.1]nonan-3β-ol, methyl α,α-di-(2-thienyl)-glycollate and 30 mg of metallic sodium is heated at 80°C to 90°C for about 2 hours under reduced pressure. After cooling, ether is added to the reaction mixture. The mixture is extracted with 10% hydrochloric acid. The aqueous layer is alkalified with sodium carbonate and reextracted with ethyl acetate. The extract is washed with water, dried and concentrated to dryness. The residue thus obtained is treated with hydrogen chloride by conventional manner. 2.0 g of the α,α-di-(2-thienyl)glycollate of 6,6,9-trimethyl-9-azabicyclo-[3.3.1]nonan-3β-ol hydrochloride are obtained. Yield 83%.

**References**

Kleeman & Engel p. 535
DOT 13 (2) 72 (1977)

I.N. p. 579
Yoneda, N., Ishihara, T., Kobayashi, T., Kondo, Y., Okumura, K., Kojima, M. and Nose, T.; U.S. Patent 3,673,195; June 27, 1972; assigned to Tanabe Swiyaku Co.

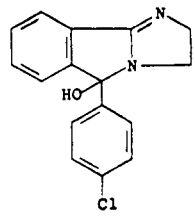
# MAZINDOL

**Therapeutic Function:** Antiobesity

**Chemical Name:** 5-(4-chlorophenyl)-2,5-dihydro-3H-imidazo[2,1-a] isoindol-5-ol

**Common Name:** –

**Structural Formula:**




**Chemical Abstracts Registry No.:** 22232-71-9

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Sanorex | Sandoz | U.S. | 1973 |
| Teronac | Wander | U.K. | 1974 |
| Teronac | Wander | W. Germany | 1976 |
| Mazildene | Farmochimica | Italy | 1979 |
| Mazanor | Wyeth | U.S. | 1980 |
| Degonan | Spofa | Czechoslovakia | – |
| Magrilan | Sintyal | Argentina | – |

**Raw Materials**

3-(p-Chlorophenyl)phthalimidine
Epichlorohydrin
Ethylene imine

**Manufacturing Process**

*Step 1: 1-(p-Chlorophenyl)-3-Ethoxy-1H-Isoindole* – Crystalline triethyloxonium borontetrafluoride (21 g) (prepared from 23 g of borontrifluoride etherate and 11 g of epichlorohydrin) is dissolved in 100 ml of absolute methylenechloride. 3-(p-Chlorophenyl) phthalimidine (21 g) is added and the reaction mixture is stirred overnight at room temperature. The resulting solution is poured onto 50 ml of saturated sodium carbonate, extracted with 500 ml of ether and dried. Upon evaporation of the solvent there is obtained crude material which is recrystallized from methylene chloride/hexane (1:1) to yield 1-(p-chlorophenyl)-3-ethoxy-1H-isoindole; MP 102° to 103°C.

*Step 2: 5-(p-Chlorophenyl)-5-Hydroxy-2,3-Dihydro-5H-Imidazo[2,1-a] Isoindole* – 1-(p-Chlorophenyl)-3-ethoxy-1H-isoindole (1 g), 2 g of ethyleneimine hydrotetrafluoroborate moistened with methylene chloride (containing approximately 0.66 g of dry salt) is refluxed in 25 ml of absolute toluene for 2 hours in an atmosphere of nitrogen. The result-

ing mixture is poured into 2 N sodium carbonate solution (25 ml) and extracted with ether. The ether solution is contacted with air for 6 days at room temperature to give the desired product. The crude material is recrystallized from acetone/hexane (1:1) to give 5-(p-chlorophenyl)-5-hydroxy-2,3-dihydro-5H-imidazo[2,1-a]isoindole; MP 198° to 199°C.

**References**

Merck Index 5585
Kleeman & Engel p. 535
PDR pp. 1595, 1958
OCDS Vol. 2 p. 462 (1980)
DOT 10 (1) 24 (1974)
I.N. p. 579
REM p. 892
Houlihan, W.J. and Eberle, M.K.; U.S. Patent 3,597,445; August 3, 1971; assigned to Sandoz-Wander, Inc.
Sulkowski, T.S.; U.S. Patent 3,763,178; October 2, 1973; assigned to American Home Products Corp.

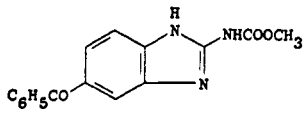
# MEBENDAZOLE

**Therapeutic Function:** Anthelmintic

**Chemical Name:** (5-benzoyl-1H-benzimidazol-2-yl)carbamic acid methyl ester

**Common Name:** Methyl-5-benzoyl-2-benzimidazole carbamate

**Structural Formula:**




**Chemical Abstracts Registry No.:** 31431-39-7

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Vermox | Ortho | U.S. | 1975 |
| Vermox | Janssen | U.K. | 1976 |
| Vermox | Janssen | W. Germany | 1976 |
| Vermox | Janssen | Italy | 1978 |
| Vermox | Janssen | Sweden | 1983 |
| Lomper | Esteve | Spain | — |
| Mebutar | Andromaco | Argentina | — |
| Panfugan | Byk Procienx | Brazil | — |
| Sirben | Andromaco | Brazil | — |
| Sufil | Cusi | Spain | — |
| Vermirax | Biosintetica | Brazil | — |
| Verpanil | Krka | Yugoslavia | — |

**Raw Materials**

4-Chloro-3-nitrobenzophenone
S-Methylisothiourea sulfate
Methyl chloroformate
Ammonia
Hydrogen

**Manufacturing Process**

A mixture of 5.2 parts of 4-chloro-3-nitrobenzophenone, 5 parts of ammonia, 72 parts of methanol and 13 parts of sulfolane is heated overnight at 125°C in a sealed tube. The reaction mixture is evaporated in vacuo. The semisolid residue is boiled in 100 parts of a diluted hydrochloric acid solution. After cooling, the precipitated product is filtered off and dissolved in chloroform. The chloroform phase is dried and evaporated. The residue is crystallized from toluene, yielding 4-amino-3-nitrobenzophenone; MP 141°C.

A mixture of 9.6 parts of 4-amino-3-nitrobenzophenone, 160 parts of methanol, 8 parts of concentrated hydrochloric acid and 1 part of palladium-on-charcoal catalyst 10% is hydrogenated at normal pressure and at room temperature. After the calculated amount of hydrogen is taken up, hydrogenation is stopped. The catalyst is filtered off and the solvent is evaporated. The solid residue is triturated in 2-propanol. The latter is partly evaporated and the solid product is filtered off, washed with 2-propanol and dried, yielding 3,4-diaminobenzophenone hydrochloride; MP 207°C.

7.8 parts of S-methylisothiourea sulfate are stirred in 10 parts of water in an ice bath and there are added 4.5 parts of methyl chloroformate. While keeping the temperature below 20°C, there are added dropwise, in the course of 10 minutes, 17 parts of sodium hydroxide solution 25% (pH 8±), followed by the addition of 5.6 parts of acetic acid (pH 5±). To this mixture is added at 20°C a suspension of 7 parts of 3,4-diaminobenzophenone hydrochloride in 100 parts of water, followed by the addition of 2.3 parts of sodium acetate.

The whole is slowly heated to 85°C and stirred at this temperature for 45 minutes. The reaction mixture is cooled and the precipitated product is filtered off. It is washed successively with water and ethanol, dried and crystallized from a mixture of acetic acid and methanol, yielding methyl N-[5(6)-benzoyl-2-benzimidazolyl] carbamate; MP 288.5°C.

**References**

Merck Index 5589
Kleeman & Engel p 536
PDR p. 960
OCDS Vol. 2 p. 353 (1980)
DOT 7 (5) 195 (1971); 9 (7) 299 (1973); 16 (10) 350 (1980) & 17 (6) 262 (1981)
I.N. p. 580
REM p. 1235
Van Gelder, J.L.H., Roevens, L.F.C. and Raeymaekers, A.H.M.; U.S. Patent 3,657,267; April 18, 1972; assigned to Janssen Pharmaceutica, NV, Belgium

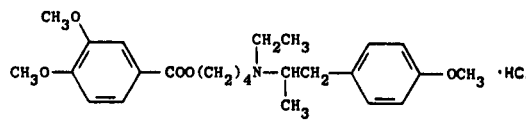
# MEBEVERINE HYDROCHLORIDE

**Therapeutic Function:** Antispasmodic

**Chemical Name:** 3,4-dimethoxybenzoic acid 4-[ethyl-[2-(4-methoxyphenyl)-1-methylethyl]-amino] butyl ester hydrochloride

**Common Name:** –

**Structural Formula:**



**Chemical Abstracts Registry No.:** 2753-45-9; 3625-06-7 (Base)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Duspatalin | Duphar | France | 1965 |
| Colofac | Duphar | U.K. | 1967 |
| Duspatal | I.S.M. | Italy | 1970 |
| Duspatal | Thomae | W. Germany | 1977 |
| Duspatalin | Duphar | Switz. | 1981 |

**Raw Materials**

3,4-Dimethoxybenzoic acid
Tetramethylene dichloride
p-Methoxyphenyl acetone
Ethylamine
Sodium
Ethanol
Sodium iodide
Hydrogen

**Manufacturing Process**

*(A) Sodium-3,4-Dimethoxybenzoate:* A solution of 91 g of 3,4-dimethoxybenzoic acid in 500 ml of boiling, absolute alcohol was added quickly to a solution of 11.5 g of sodium in 300 ml of absolute alcohol; after cooling to room temperature the resulting precipitate was filtered off and washed with 2 x 50 ml of absolute alcohol and 4 x 200 ml of ether and dried in air to constant weight; yield 92.5 g, MP about 265°C. The filtrate was bulked with the alcohol and ether washings, left to stand overnight, and a further precipitate then filtered off, washed with 3 x 100 ml of ether, and dried in air to constant weight. Yield 22.5 g, MP about 265°C. Total yield therefore 115 g (=113%).

*(B) 4'-Chlorobutyl-3,4-Dimethoxybenzoate:* 92 g of the sodium salt described under (A) (it contains at the most 81.5 g of sodium 3,4-dimethoxybenzoate) was boiled in 900 ml of tetramethylene dichloride for 90 hours; after cooling the mixture was filtered and the residue washed with 3 x 50 ml of ether. The filtrate was evaporated to dryness in vacuo and the residue (102 g) was distilled in vacuo. Fraction 1: 50° to 55°C/0.5 mm; 19 g (probably tetramethylene dichloride). Fraction 2: 175° to 184°C/0.5 mm; 77.5 g (=71%); Cl= 12.6% (calculated 13.0%). Remark: The second fraction partially solidified or became more viscous on standing, and even during the distillation.

*(C) 4'-Iodobutyl-3,4-Dimethoxybenzoate:* 32.5 g of 4'-chlorobutyl-3,4-dimethoxybenzoate and 19.5 g of sodium iodide (10% excess) were boiled in 150 ml of methyl ethyl ketone for 2.5 hours; after cooling and filtering off the sodium chloride produced, the reaction was found not to be entirely completed; boiling was then continued for another two hours; the reaction mixture was cooled, and the solid filtered off and washed with 2 x 100 ml of ether.

The filtrate was evaporated to dryness in vacuo and the residue was dissolved in 300 ml of ether and 100 ml of water; the layers were separated and the water layer was once again extracted with 100 ml of ether; then the ether layers were boiled and washed again with a solution of 3.5 g of sodium thiosulfate in 100 ml of water. The ether layer was dried over sodium sulfate. Finally the solution was filtered and the ether was evaporated; the residue was an almost colorless oil, which partially solidified or became more viscous after being left to stand for some time. Yield: 40 g (=92%), I=34.2% (calculated 34.9%).

*(D) 4'-[N-Ethyl-1''-Methyl-2''-(4'''-Methoxyphenyl)Ethylamino] Butyl-3,4-Dimethoxybenzoate Hydrochloride:* 10.3 g of 4'-iodobutyl-3,4-dimethoxybenzoate and 11.0 g of N-ethyl-p-methoxyphenylisopropylamine (obtained by catalytic reduction of an alcoholic solution of an excess quantity (60%) of p-methoxy-phenyl-acetone, to which was added a 33% (weight-for-weight) aqueous solution of ethylamine, with Pt as a catalyst), were boiled in 200 ml of methyl ethyl ketone for 20 hours, cooled and the iodine ion was determined; the reaction was found to be complete. Then the methyl ethyl ketone was evaporated in vacuo and the residue was dissolved in 300 ml of water and 30 ml of ether; the layers were separated and the water layer was extracted twice more with 20 ml portions of ether.

**References**

Merck Index 5590
Kleeman & Engel p. 537
OCDS Vol. 2 p. 54 (1980)
DOT 3 (4) 143 (1967)
I.N. p. 580
Phillips' Gloeilampenfabrieken; British Patent 1,009,082; November 3, 1965

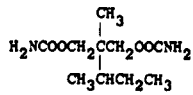
# MEBUTAMATE

**Therapeutic Function:** Antihypertensive

**Chemical Name:** 2-Methyl-2-(1-methylpropyl)-1,3-propandiol dicarbamate

**Common Name:** Dicamoylmethane

**Structural Formula:**



**Chemical Abstracts Registry No.:** 64-55-1

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Capla | Wallace | U.S. | 1961 |
| Axiten | Zambon | Italy | – |
| Butatensin | Benvegna | Italy | – |
| Carbuten | Kalopharma | Italy | – |
| Dormate | Wallace | U.S. | – |
| Ipotensivo | Vita | Italy | – |
| Mebutina | Formenti | Italy | – |
| No-Press | Janus | Italy | – |
| Prean | Chemil | Italy | – |
| Preminex | Dumex | Denmark | – |
| Sigmafon | Lafare | Italy | – |
| Vallene | Simes | Italy | – |

**Raw Materials**

Diethyl-sec-butyl methyl malonate
Lithium aluminum hydride
Ethyl urethane

**Manufacturing Process**

The following example illustrates the preparation of 2-methyl-2-sec-butyl-1,3-propanediol:

92 g of diethyl-sec-butyl methyl malonate were reduced in the usual manner using 22.8 g of lithium aluminum hydride in a suitable volume of anhydrous ethyl ether. The mixture was treated with 10% sulfuric acid and the ether soluble components extracted. The ether solution was dried, using a suitable drying agent, and the residue obtained by the removal of the ether was purified by distilling under reduced pressure. This material was further purified by redistillation. Approximately 46 g of 2-methyl-2-sec-butyl-1,3-propanediol were obtained as a clear colorless liquid, boiling point 92°C to 97°C (0.1 mm pressure).

The following example describes the preparation of 2-methyl-2-sec-butyl-1,3-propanediol dicarbamate using the urethane exchange method:

14.6 g of 2-methyl-2-sec-butyl-1,3-propanediol and 18.7 g ethyl urethane are dissolved in about 100 ml anhydrous toluene. 3 g of aluminum isopropylate are added and the mixture distilled to remove the ethyl alcohol formed in the condensation of ethyl urethane and the diol. The alcohol distills in the form of an azeotrope with toluene. Distillation is continued until the theoretical quantity of ethanol has been removed. The toluene is distilled from the mixture under reduced pressure and the residue dissolved in hot aqueous isopropanol solution. The hot solution is filtered and allowed to cool, whereupon approximately 14 g of product separates. The purified product represents a yield of about 60% of theoretical and melts at 77°C to 79°C.

**References**

Merck Index 5594
Kleeman & Engel p. 538
OCDS Vol. 1 p. 218 (1977)
I.N. p. 581
Berger, F.M. and Ludwig, B.J.; U.S. Patent 2,878,280; March 17, 1959; assigned to Carter Products, Inc.

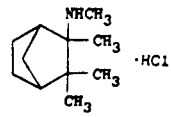
# MECAMYLAMINE HYDROCHLORIDE

**Therapeutic Function:** Antihypertensive

**Chemical Name:** N,2,3,3-Tetramethylbicyclo[2.2.1]heptan-2-amine hydrochloride

**Common Name:** Dimecamin hydrochloride

**Structural Formula:**




**Chemical Abstracts Registry No.:** 826-39-1; 60-40-2 (Base)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Inversine | MSD | U.S. | 1956 |
| Mevasine | MSD | W. Germany | — |
| Prexion | I.T.I. | Italy | — |

**Raw Materials**

dl-Camphene
Lithium aluminum hydride
Sodium cyanide
Sulfuric acid

**Manufacturing Process**

*Preparation of 2-(N-Formylamino)Isocamphane:* Into a 5-liter 3-necked round bottom flask equipped with stirrer, dropping funnel and thermometer, was added 325 ml of glacial acetic acid. Then, portionwise, a total of 133 g of sodium cyanide (granular, 2.6 mols) was added with stirring while holding the temperature at 15°C. To the thick white slurry was added dropwise a previously prepared cold mixture of 325 ml glacial acetic acid and 360 ml concentrated sulfuric acid.

After addition of a few milliliters at 15°C, the thick slurry thins slowly and the remainder of the sulfuric-glacial acetic acid mixture was added at 0° to 2°C. A total of about 2 hours was required for the addition. After addition, stirring was continued for 15 minutes. Then dropwise, over an hour, a solution of 178 g (1.3 mols) of dl-camphene in 50 ml of glacial acetic acid was added while keeping the temperature at about 0°C (±3°C).

Stirring was continued for two hours at 0°C during which time a slight pinkish-yellow color developed in the reaction mixture. The cooling bath was removed and the temperature allowed to rise to 15° to 20°C in about 2 to 3 hours. The ice bath was then replaced and while holding the temperature at about 20°C, the mixture was gradually diluted with 3 liters of water while stirring vigorously. After an hour or two of good agitation at room temperature, the oily product was extracted with 2 x 500 ml and 1 x 200 ml of chloroform and the combined extracts washed with 2 x 500 ml of water. The chloroform extract was then rendered neutral by stirring with 500 ml water and gradually adding solid sodium bicarbonate to the mixture until the aqueous phase had a pH of about 7; required, approximately 88 g of $NaHCO_3$.

After separation the chloroform layer was washed with 2 x 500 ml water, dried over calcium chloride, and after filtration the solvent was removed in vacuo on the steam bath. A solid somewhat sticky residue of 231.2 g was obtained. After removal of last traces of chloroform by repeated swishing with petroleum ether, the cake was finally refluxed with about 500 ml petroleum ether (BP 30° to 60°C) until a thick crystalline slurry was obtained. After refrigeration for a day, the white crystalline mass was filtered by suction, washed with petroleum ether (2 x 125 ml), then n-heptane (2 x 125 ml) and again with petroleum ether (2 x 125 ml). After air drying at room temperature to constant weight, 180.6 g of the dl-2-(N-formylamino)isocamphane melting at 160° to 165°C was obtained.

The combined petroleum ether and n-heptane washes were concentrated under diminished pressure and the residual oil dissolved in a minimum amount of hot petroleum ether (about 75 ml). The resulting solution was placed in the refrigerator for two days. The precipitated dl-2-(N-formylamino)isocamphane was then recovered by filtration and washed with petroleum ether and n-heptane as described above. Obtained, 12.6 g of product having a MP of 158° to 164°C.

The dl-2-(N-formylamino)isocamphane (193 g) was dissolved in 1.9 liters n-heptane by heating on a steam bath. After clarifying the solution by filtration, the clear filtrate was allowed to stand at room temperature until crystallization was complete. The crystalline product is filtered by suction, washed with a little cold n-heptane and air dried. The dl-2-(N-formylamino)isocamphane melted at 169° to 174°C.

*Preparation of 2-(N-Methylamino)Isocamphane:* To 4.23 liters of anhydrous ether in a 12-liter 3-necked flask fitted with a stirrer, reflux condenser and dropping funnel was quickly added 78 g (2.05 mols) of lithium aluminum hydride. The mixture was gently refluxed with stirring until all hydride had dissolved which required several hours.

A solution of 168 g (0.92 mol) of dl-2-(N-formylamino)isocamphane, prepared as described above, in 1.81 liters of anhydrous ether was then added during a period of about one hour with stirring. After addition, the mixture was refluxed for about 6 hours after which it was cooled slightly and 347 ml of water added with stirring, hydrogen gas being evolved during the addition. Stirring was continued until the precipitate changed to a powder, which was filtered by suction and washed with ether (a total of about 2 liters).

The combined filtrate and washes were concentrated to 1.6 liters and the concentrate containing the dl-2-(N-methylamino)isocamphane washed once with about 350 cc water, and then dried over anhydrous sodium sulfate. The dried ether concentrate was then cooled in an ice bath and with stirring a cold saturated ethereal-hydrogen chloride solution was added slowly until acid to Congo red; required, about 440 ml anhydrous ether saturated (at 0°C) with HCl gas. After precipitation was complete, the white crystalline dl-2-(N-methylamino)isocamphane hydrochloride was filtered, and washed with anhydrous ether

(about 1 liter) until the washes were neutral. The dl-2-(N-methylamino)isocamphane hydrochloride was air dried at room temperature. Obtained, 156.5 g of product melting with decomposition at 249°C.

**References**

Merck Index 5595
Kleeman & Engel p. 538
I.N. p. 581
REM p. 849
Pfister, K., III and Stein, G.A.; U.S. Patent 2,831,027; April 15, 1958; assigned to Merck & Co., Inc.

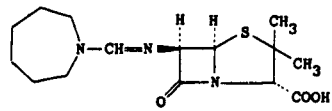
# MECILLINAM

**Therapeutic Function:** Antibacterial

**Chemical Name:** 6-[[(Hexahydro-1H-azepin-1-yl)methylene]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylic acid

**Common Name:** Amdinocillin

**Structural Formula:**




**Chemical Abstracts Registry No.:** 32887-01-7

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Selexidin | Leo | U.K. | 1979 |
| Celfuron | Roche | – | – |

**Raw Materials**

Hexamethylene imine
Trimethylsilyl 6-amino penicillinate
Chloral
Oxalyl chloride

**Manufacturing Process**

The starting material N-formylhexamethyleneimine was prepared from hexamethyleneimine and chloral.

12.7 g of N-formylhexamethyleneimine were dissolved in 250 ml of dry ether. While stirring and cooling, 8.5 ml of oxalyl chloride in 50 ml of dry ether were added dropwise, whereafter the mixture was stirred overnight at room temperature. The precipitated amide chloride was filtered off and washed with dry ether, and was placed in an exsiccator.

A solution of the amide chloride (4.6 g) in dry, alcohol-free chloroform (20 ml) was added slowly to a solution of trimethylsilyl 6-amino-penicillanate (7.2 g) and triethylamine (3.5 ml) in dry, alcohol-free chloroform (50 ml) with stirring and cooling to -70°C. The temperature was raised to 0°C during 1½ hours. The solution was evaporated to dryness *in vacuo* and the residue was triturated with dry ether (200 ml). The precipitate was filtered off and washed with dry ether. The filtrate was diluted with ether (200 ml). 2-Butanol (2.8 ml) was added dropwise with stirring and cooling to 0°C. The stirring was continued for ¼ hour at 0°C, whereupon the precipitate was filtered off, washed with ether and dried. It was a white, amorphous powder, soluble in water.

**References**

Merck Index 390
Kleeman & Engel p. 539
OCDS Vol. 3 p. 208 (1984)
DOT 11 (11), 489 (1975) and 16 (6) 193 (1980)
I.N. p. 582
REM p. 1201
Lund, F.J.; British Patent 1,293,590; October 18, 1972; and U.S. Patent 3,957,764; May 18, 1976; both assigned to Lovens Kemiske Fabrik Produktionsakties Lab (Denmark)

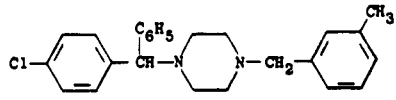
# MECLIZINE HYDROCHLORIDE

**Therapeutic Function:** Antinauseant

**Chemical Name:** 1-[(4-Chlorophenyl)phenylmethyl]-4-[(3-methylphenyl)methyl] piperazine hydrochloride

**Common Name:** Meclozin; histamethizine

**Structural Formula:**




(base)

**Chemical Abstracts Registry No.:** 1104-22-9; 569-65-3

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Antivert | Roerig | U.S. | 1957 |
| Ru-Vert M | Reid Provident | U.S. | 1983 |
| Ancolan | Duncan Flockhart | U.K. | – |
| Bonamine | Pfizer | W. Germany | – |
| Calmonal | Heyden | W. Germany | – |
| Chiclida | Torpens | Spain | – |
| Diadril | Pliva | Yugoslavia | – |
| Duremesan | Streuli | Switz. | – |
| Itinerol | Galenica | Switz. | – |
| Mecazine | Barlow Cote | Canada | – |
| Navicalur | Delagrange | France | – |
| Peremesin | Heyden | W. Germany | – |
| Postafen | U.C.B. | W. Germany | – |
| Supermesin | M.P.Q. | Spain | – |
| Suprimal | A.C.F. | Neth. | – |
| Taizer | Pfizer Taito | Japan | – |
| V-Cline | Vangard | U.S. | – |
| Veritab | Vista | U.S. | – |
| Vertizine | Merchant | U.S. | – |

**Raw Materials**

1-p-Chlorobenzhydryl-4-benzyl-piperazine
Hydrogen
Sodium amide
m-Methyl benzyl chloride

**Manufacturing Process**

32.3 g of 1-p-chlorobenzhydryl-4-benzyl-piperazine, dissolved in 300 $cm^3$ of alcohol are heated in an autoclave vessel, in the presence of Raney nickel, under a pressure of 100 kg $H_2$ at about 150°C for 6 hours. The catalyst is filtered, the solvent is evaporated and the residue is fractionated under a high vacuum. p-Chlorobenzylhydryl-piperazine (BP 180° to 185°C/1 mm Hg) is isolated with a yield of 75%. Then finely ground $NaNH_2$ is added. The mixture is heated under reflux for 1 hour, the mass is cooled and a molar equivalent of m-methyl benzyl chloride is added.

The solvent is evaporated and the residue is dissolved in chloroform. This solution is washed with a saturated solution of $K_2CO_3$ and dried on $K_2CO_3$. The solvent is evaporated and the residue is distilled under high vacuum. The product of the condensation distills near 230°C at 2 mm Hg pressure and the corresponding dihydrochloride melts at 217° to 224°C.

**References**

Merck Index 5598
Kleeman & Engel p. 540
PDR pp. 993, 1403, 1449, 1520, 1606, 1999
OCDS Vol. 1 p. 59 (1977)
I.N. p. 583
REM p. 808
Morren, H.; U.S. Patent 2,709,169; May 24, 1955; assigned to Union Chimique Belge Societe' Anonyme, Belgium

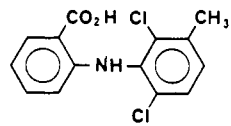
# MECLOFENAMIC ACID

**Therapeutic Function:** Antiinflammatory

**Chemical Name:** N-(2,6-Dichloro-3-methylphenyl)anthranilic acid

**Common Name:** –

**Structural Formula:**




**Chemical Abstracts Registry No.:** 644-62-2; 6385-02-0 (Sodium Salt)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Meclomen | Warner Lambert | U.S. | 1980 |
| Meclomen | Parke Davis | Switz. | 1982 |
| Arquel | Parke Davis | – | – |

**Raw Materials**

Potassium o-bromobenzoate
2,6-Dichloro-3-methylaniline
N-ethylmorpholine

**Manufacturing Process**

A mixture consisting of 22.7 g potassium o-bromobenzoate, 16.6 g 2,6-dichloro-3-methylaniline, 12 ml N-ethylmorpholine, 60 ml diethylene glycol dimethyl ether, and 1.0 g anhydrous cupric bromide is heated in a nitrogen atmosphere at 145°C to 155°C for 2 hours. The reaction mixture is diluted with 60 ml diethylene glycol dimethyl ether and acidified with 25 ml concentrated hydrochloric acid. The acidic mixture is diluted with 100 ml of water and the liquid phase decanted from the insoluble oil. The insoluble oil is stirred with methanol and the crystalline N-(2,6-dichloro-3-methylphenyl)anthranilic acid which separates is collected and washed with methanol. The product, after recrystallization from acetone-water mixture, melts at 248°C to 250°C.

**References**

Merck Index 5600
DFU 3 (4) 307 (1978)
Kleeman & Engel p. 539
PDR p. 1366
OCDS Vol. 1 p. 110 (1977) & 2, 88 (1980)
DOT 17 (6) 250 (1981)
I.N. p. 31
REM p. 1118
Scherrer, R.A. and Short, F.W.; U.S. Patent 3,313,848; April 11, 1967; assigned to Parke-Davis & Co.

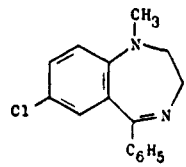
# MEDAZEPAM

Therapeutic Function: Tranquilizer

Chemical Name: 7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepine

Common Name: –

Structural Formula:




**Chemical Abstracts Registry No.:** 2898-12-6

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Nobrium | Roche | Italy | 1969 |
| Nobrium | Roche | W. Germany | 1969 |
| Nobrium | Roche | France | 1970 |
| Lesmit | Shionogi | Japan | 1971 |
| Nobrium | Roche | Japan | 1971 |
| Nobrium | Roche | U.K. | 1971 |
| Azepamid | Taiyo | Japan | – |
| Becamedic | Nemi | Argentina | – |
| Benson | Farber-R.E.F. | Italy | – |
| Cerase | Torii | Japan | – |
| Diepin | Biosintetica | Brazil | – |
| Enobrin | I.E. Kimya Evi | Turkey | – |

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Esmail | Richter | Mexico | – |
| Glorium | Teva | Israel | – |
| Kobazepam | Nihon Yakuhin | Japan | – |
| Lerisum | Poli | Italy | – |
| Medaurin | Isis | Yugoslavia | – |
| Megasedan | Andrew | Spain | – |
| Metonas | Kanto | Japan | – |
| Mezepan | Hosbon | Brazil | – |
| Narsis | Sumitomo | Japan | – |
| Nivelton | Lemonier | Argentina | – |
| Nobraskin | Fako | Turkey | – |
| Nobral | Nobel | Turkey | – |
| Pazital | Andromaco | Spain | – |
| Psiquium | Sintofarma | Brazil | – |
| Rudotel | Arzneimittelwerk Dresden | E. Germany | – |
| Sedepam | Sawai | Japan | – |
| Serenium | Richter | Brazil | – |
| Tranqulax | Hokuriku | Japan | – |
| Vegatar | Orion | Finland | – |

**Raw Materials**

5-Chloro-N-methylanthranilic acid
Bromoethylamine hydrobromide
Calcium carbonate
Sodium hydroxide
Phosphorus oxychloride
Oxalic acid
Acetic anhydride
Bromobenzene
Magnesium

**Manufacturing Process**

*(A) Preparation of 4-Acetyl-7-Chloro-1,2,3,4-Tetrahydro-1-Methyl-5H-1,4-Benzodiazepin-5-one:* A mixture of 68.5 g (0.37 mol) of 5-chloro-N-methylanthranilic acid, 51 g (0.51 mol) of calcium carbonate, 76 g (0.37 mol) of bromoethylamine hydrobromide and 2.5 liters of water was stirred and heated under reflux for 3 hours. A solution of 23.4 g (0.26 mol) of anhydrous oxalic acid in 250 ml of water was slowly added to the refluxing mixture. The precipitated calcium oxalate was filtered off, and the filtrate adjusted to pH 7 with concentrated ammonium hydroxide. The filtrate was then concentrated to dryness in vacuo and the residue heated on the steam bath with 400 ml of 6 N ethanolic hydrogen chloride until the residue was crystalline. Filtration gave 122 g of N-(aminoethyl)-5-chloro-N-methylanthranilic acid hydrochloride as a solid.

A mixture of 100 g of this solid and 1 liter of acetic anhydride was stirred and heated under reflux for 1.5 hours and then allowed to stand for 18 hours at room temperature. The excess acetic anhydride was removed in vacuo, and the residue was treated with one liter of water and ice and sufficient sodium bicarbonate to make neutral. The solid was collected, sucked dry on the filter, and triturated with hot ethanol. The ethanol solution on cooling gave 30.8 g of 4-acetyl-7-chloro-1,2,3,4-tetrahydro-1-methyl-5H-1,4-benzodiazepin-5-one.

*(B) Preparation of 7-Chloro-1,2,3,4-Tetrahydro-1-Methyl-5H-1,4-Benzodiazepin-5-one:* A mixture of 25.25 g (0.1 mol) of 4-acetyl-7-chloro-1,2,3,4-tetrahydro-1-methyl-5H-1,4-benzodiazepin-5-one, 33.3 ml (0.1 mol) of 3 N sodium hydroxide and 350 ml of ethanol was heated under reflux for 15 minutes and then concentrated to dryness in vacuo. The residue was treated with 500 ml of water, collected and washed with ethanol to give 20.2 g of 7-chloro-1,2,3,4-tetrahydro-1-methyl-5H-1,4-benzodiazepin-5-one.

*(C) Preparation of 7-Chloro-2,3-Dihydro-1-Methyl-5-Phenyl-1H-1,4-Benzodiazepine:* A mixture of 4.7 g (22.6 mol) of 7-chloro-1,2,3,4-tetrahydro-1-methyl-5H-1,4-benzodiazepin-5-one and 100 ml of phosphorus oxychloride was heated in an oil bath at 100°C for 15 minutes. The solution was concentrated to dryness in vacuo. The residue was partitioned

between methylene chloride and cold saturated sodium bicarbonate solution. The methylene chloride phase was dried over sodium sulfate and sodium bicarbonate, filtered, diluted with benzene and concentrated in vacuo to produce crude 5,7-dichloro-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine.

The residue was dissolved in 75 ml of tetrahydrofuran, treated with charcoal, and sodium sulfate and filtered. This solution was added to a solution in 250 ml of tetrahydrofuran of phenyl magnesium bromide prepared from 17.7 ml (0.17 mol) of bromobenzene. This mixture was stirred and heated under reflux for 1 hour. It was then cooled and diluted with 400 ml of ether and sufficient 3 N hydrochloric acid to make it acidic. The aqueous phase was separated, adjusted to pH 8 with 3 N sodium hydroxide and extracted 3 times with 200 ml of ether. The ether extracts were combined, washed with water and dried over sodium sulfate. The residue left on removal of the ether in vacuo was crystallized from petroleum ether to give 3.3 g of 7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepine, according to U.S. Patent 3,624,703.

A variety of alternative routes are outlined by Kleeman & Engel.

**References**

Merck Index 5609
Kleeman & Engel p. 542
OCDS Vol. 1 p. 368 (1977)
DOT 5 (4) 150 (1969) & 9 (6) 238 (1973)
I.N. p. 584
Reeder, E. and Sternbach, L.H.; U.S. Patent 3,109,843; November 5, 1963; assigned to Hoffmann-LaRoche Inc.
Archer, G.A. and Sternbach, L.H.; U.S. Patent 3,131,178; April 28, 1964; assigned to Hoffmann-LaRoche Inc.
Reeder, E. and Sternbach, L.H.; U.S. Patent 3,141,890; July 21, 1964; assigned to Hoffmann-LaRoche Inc.
Reeder, E. and Sternbach, L.H.; U.S. Patent 3,144,439; August 11, 1964; assigned to Hoffmann-LaRoche Inc.
Field, G.F., Sternbach, L.H. and Zally, W.J.; U.S. Patent 3,624,073; November 30, 1971; assigned to Hoffmann-LaRoche Inc.

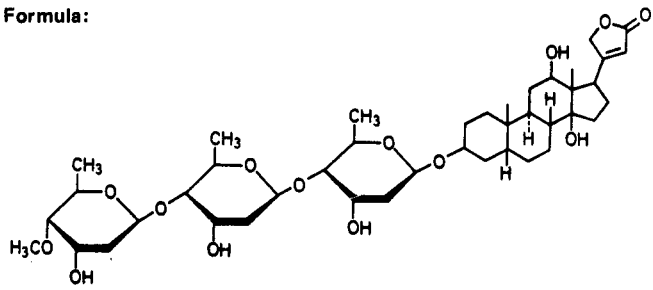
## MEDIGOXIN

**Therapeutic Function:** Cardiotonic

**Chemical Name:** 3β,12β,14β-Trihydroxy-5β-card-20(22)-enolide-3-(4'''-o-methyltridigitoxoside)

**Common Name:** β-Methyldigoxin

**Structural Formula:**



**Chemical Abstracts Registry No.:** 30685-43-9

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Lanitop | Boehr-Mann. | W. Germany | 1972 |
| Lanitop | Boehr-Mann. | Italy | 1973 |
| Lanitop | Roussel | U.K. | 1976 |
| Lanirapid | Yamanouchi | Japan | 1979 |
| Cardiolan | Tosi-Novara | Italy | – |
| Digicor | Lek | Yugoslavia | – |
| Intensain-Lanitop | Boehr-Mann. | W. Germany | – |

**Raw Materials**

Digoxin
Methyl mesylate

**Manufacturing Process**

Digoxin (10 g) is dissolved in a mixture of dimethylformamide (80 ml) and dioxane (80 ml) and then strontium hydroxide (3.5 g) and aluminum oxide (10 g, activity 1-2 according to Brockmann) are added. To this suspension methyl mesylate (9.3 g), dissolved in dioxane (80 ml) is added dropwise within one hour in the presence of an inert gas and under stirring. After the addition of the methylating agent is completed, the reaction mixture is stirred for further 5 hours, then chloroform (160 ml) is added, the precipitate is filtered off, washed with chloroform (100 ml), pyridine (40 ml) is added to the filtrate, which is then concentrated in vacuo to an oily residue. The latter is diluted with chloroform (300 ml) and extracted four times with distilled water (40 ml portions). The combined chloroform extracts are dried with anhydrous sodium sulfate and then concentrated in vacuo to a dry residue. Therefrom β-methyldigoxin is eluted on a $SiO_2$ column with a chloroform/ethanol mixture (93:7). After recrystallization from ethyl acetate, saturated with water, the yield of β-methyldigoxin is 6.7 g; MP 225°C to 229°C. IR spectrum is identical with the spectrum of standard methyldigoxin.

**References**

Merck Index 3148
Kleeman & Engel p. 544
DOT 12 (8) 319, 323 (1976)
I.N. p. 627
Pelan, B., Milohnoja, M. and Pezdirc, M.; U.S. Patent 4,145,528; March 20, 1979; assigned to L.E.K. Tovarna Farmacevtskih in Kemicnih Izdelkov (Yugoslavia)

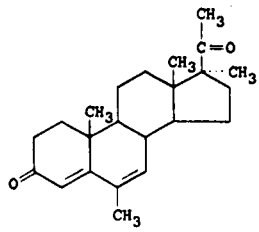
# MEDROGESTONE

Therapeutic Function: Progestin

Chemical Name: 6,17-dimethylpregna-4,6-diene-3,20-dione

Common Name: 6,17α-dimethyl-6-dehydroprogesterone

Structural Formula:



**Chemical Abstracts Registry No.:** 977-79-7

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Colpro | Ayerst | Italy | 1970 |
| Colprone | Auclair | France | 1972 |
| Prothil | Kali-Chemie | W. Germany | 1975 |
| Colpron | Arcana | Austria | — |

**Raw Materials**

17α-Methyl-17β-carbomethoxyandrost-5-ene-3β-ol
Hydrogen peroxide
N-Bromosuccimide
Acetic anhydride
Methyl magnesium bromide
Chromic acid

**Manufacturing Process**

The manufacturing process as described in U.S. Patent 3,170,936 uses the readily available methyl 3β-hydroxy-17α-methyl-$\Delta^5$-etienate (I), described by Plattner in *Helv. Chim. Acta,* vol. 31, p 603 (1948), as the starting material. The etienic acid ester (I) may also be called 17α-methyl-17β-carbomethoxyandrost-5-ene-3β-ol.

*3β,5α,6β-Trihydroxy-17α-Methyl-17β-Carbomethoxyandrostane (II):* 5 g of 17α-Methyl-17β-carbomethoxyandrost-5-ene-3β-ol (I) is dissolved in formic acid (50 ml) and heated on the steam bath for 10 minutes. The solution is cooled to room temperature and a crystalline solid precipitates. This is stirred, 30% hydrogen peroxide (5 ml) is added, and the reaction mixture is left at room temperature for 2 hours. The clear solution is poured into water (300 ml) and the solid which precipitates is filtered.

It is dissolved in hot methanol and heated on the steam bath with 10% methanolic potassium hydroxide solution (15.8 ml) for 10 minutes. Then more potassium hydroxide solution (2 ml) is added, the solution is cooled and on dilution with water a solid (II), MP 245° to 255°C, is obtained. A second crop is obtained from the mother liquors. Several recrystallizations from acetone yield an analytical sample, MP 262° to 265°C, $[\alpha]_D^{24}$ is -2.1°.

*3β-Acetoxy-5α-Hydroxy-17α-Methyl-17β-Carbomethoxyandrostane-6-one (IIIb):* 3β,5α,6β-Trihydroxy-17α-methyl-17β-carbomethoxyandrostane (II, 5.2 g) is dissolved in methanol (105 ml) to which ether (105 ml) and water (84 ml) are added. Then N-bromosuccinimide (5.2 g) is added with stirring and the clear solution is left in the refrigerator for 3 hours. The ether is removed under reduced pressure at room temperature and a crystalline solid (IIIa) separates, MP 268° to 272°C.

The above substance is dissolved in pyridine (15 ml) and acetic anhydride (7.5 ml), and heated on the steam bath for ½ hour. The product (IIIb) crystallizes from aqueous ethanol in leaflets, MP 237° to 239°C. An analytical sample has MP 241° to 243°C.

*3β,5α,6β-Trihydroxy-6α,17α-Dimethyl-17β-Carbomethoxyandrostane (IV):* 3β-Acetoxy-5α-hydroxy-17α-methyl-17β-carbomethoxyandrostan-6-one (III, 1.004 g) is dissolved in dry benzene (25 ml) and methyl magnesium bromide solution in ether (3 M, 10 ml) is added. The reaction mixture is diluted with dry tetrahydrofuran (25 ml) and allowed to stand at room temperature for 20 hours. Excess Grignard reagent is quenched by adding a saturated solution of ammonium chloride. The organic layer is separated and the aqueous layer is extracted with ethyl acetate.

After washing the combined extracts with ammonium chloride solution and water and working up in the usual way a white solid (IV) is obtained which after one recrystallization from aqueous methanol has MP 242° to 243°C. The infrared spectrum of this compound indi-

cates the presence of a carbomethoxy group (1,730 $cm^{-1}$) and disappearance of the 6-keto group together with the presence of an ester group (1,727 $cm^{-1}$). This substance is used without further purification for the next step.

*3β,5α,6β-Trihydroxy-6α,17α-Dimethylpregnan-20-one (V):* Crude 3β,5α,6β-trihydroxy-6α,-17α-dimethyl-17β-carbomethoxyandrostane (IV, 773 mg) is dissolved in dry benzene (25 ml) and tetrahydrofuran (freshly distilled over lithium aluminum hydride, 25 ml). To the stirred solution under dry $N_2$ there is added methyl magnesium bromide solution in ether (3 M, 10 ml) over a period of 10 minutes. Then the ether and tetrahydrofuran are almost all distilled and the resulting solution is refluxed for 3 hours (solid precipitates during the reaction). The reaction mixture is cooled and worked up in the same way as in the previous experiment leaving a white solid (V) with an infrared spectrum which indicates the presence of a 20-ketone group (1,690 $cm^{-1}$), a sample of which is recrystallized to MP 238° to 240°C.

Analysis confirmed the empirical formula $C_{23}H_{38}O_4 \cdot H_2O$: Required: C, 69.60%; H, 10.17%. Found: C, 69.90%; H, 10.15%.

Alternatively, 25.0 g of either 3β,5α-dihydroxy-17α-methyl-17β-carbomethoxyandrostan-6-one (IIIa) or 25.0 g of its 3β-acetate (IIIb), are dissolved in dry tetrahydrofuran (1,250 ml, freshly distilled over lithium aluminum hydride) and dry benzene (2,000 ml) is added. Methyl magnesium bromide in ether solution (3 M, 750 ml) is added to the stirred solution and the resulting mixture is stirred at room temperature for 16 hours. An additional quantity of methyl magnesium bromide solution in ether (2 M, 375 ml) is added, and 1,250 ml of the solvent mixture are distilled off. The resulting mixture is refluxed for 5 hours and worked up as described above, yielding compound (V) as a colorless oil.

*5α,6β-Dihydroxy-6α,17α-Dimethylpregnane-3,20-dione (VI):* Crude 3β,5α,6β-trihydroxy-6α,17α-dimethylpregnan-20-one (V, 650 mg) is dissolved in acetone (freshly distilled over potassium permanganate, 150 ml) and cooled in an ice-water bath with stirring. Then excess chromic acid solution (8 N) is added and stirring is continued at room temperature for 4 minutes. The reaction mixture is poured into water and extracted with ethyl acetate. The combined extracts are washed with dilute sodium bicarbonate solution and water and then dried over magnesium sulfate. Removal of the solvent leaves a white solid (VI). This crude product is used for the next step. Its IR spectrum shows a strong band at 1,705 $cm^{-1}$. A sample is recrystallized to MP 243° to 245°C (dec.).

*6,17α-Dimethyl-4,6-Pregnadiene-3,20-dione (VII):* 5α,6β-Dihydroxy-6α,17α-dimethylpregnane-3,20-dione (VI, 553 mg) is dissolved in absolute ethanol (60 ml) and two drops of concentrated hydrochloric acid are added. This solution is heated on a steam bath for 45 minutes, cooled, diluted with water and extracted with ether. The combined extracts are washed with dilute sodium bicarbonate solution and water and subsequently dried over magnesium sulfate. After the solvent has been removed a syrup remains and the UV spectrum of this substance indicates the presence of a $\Delta^{4,6}$-ketone. Elution of this material over alumina (Woelm, Grade III, 25 g) with 1:1 hexane-benzene gives a crystalline substance, MP 138° to 141°C which, after one recrystallization from ether, has an infrared spectrum identical to that of an authentic sample of 6,17α-dimethyl-4,6-pregnadiene-3,20-dione (VII).

**References**

Merck Index 5613
Kleeman & Engel p. 545
OCDS Vol. 1 p. 182 (1977)
I.N. p. 586
Deghenghi, R.; U.S. Patent 3,133,913; May 19, 1964; assigned to American Home Products Corporation
Morand, P.F. and Deghenghi, R.; U.S. Patent 3,170,936; February 23, 1965; assigned to American Home Products Corporation
Deghenghi, R.; U.S. Patent 3,210,387; October 5, 1965; assigned to American Home Products Corporation