M

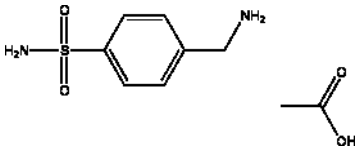
MAFENIDE ACETATE

Therapeutic Function: Antibacterial

Chemical Name: α-Acetylamino-p-toluenesulfonamide

Common Name: -

Structural Formula:



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

Trade Name	Manufacturer	Country	Year Introduced
Sulfamylon	Winthrop	US	1949
Napaltan	Winthrop	W. Germany	1969
Sulfamylon	Winthrop	UK	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%. It is readily soluble in warm water, extremely readily soluble in dilute sodium hydroxide solution.

References

Merck Index 5466
Kleeman and 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.; US 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: $[Mg(OH)]_4[(OH)_4Al(OH)(HO)Al(OH)_4]2H_2O$

Trade Name	Manufacturer	Country	Year Introduced
Riopan	Ayerst	US	1960
Riopan	Byk Gulden	W. Germany	1981
Dynese	Galen	UK	1983
Bismag-Lac	Much	W. Germany	-

Chemical Abstracts Registry No.: 1317-26-6

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 0.5% 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.; US Patent 2,923,660; February 2,1960; assigned to Byk-Gulden Lomberg Chemische Fabrik GmbH, Germany

MALATHION

Therapeutic Function: Pediculicide

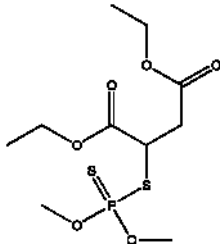
Chemical Name: Diethyl(dimethoxyphosphinothioyl)thiobutanedioate

Common Name: Mercaptothion (South Africa); Maldison (Australia and New Zealand); Carbofos (USSR)

Chemical Abstracts Registry No.: 121-75-5

Trade Name	Manufacturer	Country	Year Introduced
Prioderm	Purdue Frederick	US	1982
Organoderm	Mundipharma	W. Germany	1982
Derbac	Benque	UK	-
Lusap	Interdelta	Switz.	-
Taskil	Tasman Vaccine	UK	-

Structural Formula:



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 reactor 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.; US Patent 2,578,652; December 18, 1951; assigned to American Cyanamid Co.
Backlund, G.R., Martino, J.F. and Divine, R.D.; US Patent 3,463,841; August 26, 1969; assigned to American Cyanamid Co.
Usui, M.; US Patent 2,962,521; November 29, 1960; assigned to Sumitomo Chemical Co.

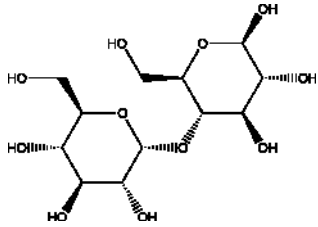
MALTOSE

Therapeutic Function: Sugar supplement

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.; US Patent 1,657,079; January 24, 1928; assigned to The Fleischmann Co.

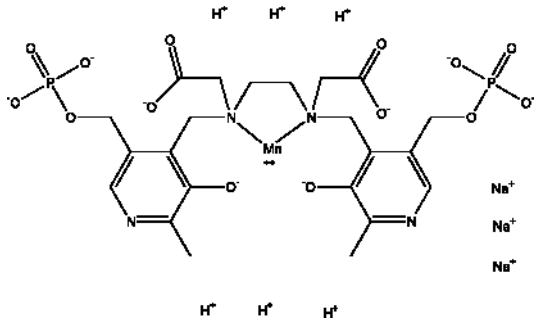
MANGAFODIPIR TRISODIUM

Therapeutic Function: Diagnostic aid

Chemical Name: Manganate(6-), ((N,N'-1,2-ethanediylbis(N-((3-hydroxy-2-methyl-5-((phosphonooxy)-methyl)-4-pyridinyl)methyl)glycinato)) (8-))-, trisodium trihydrogen, (OC-6-13)-

Common Name: Mangafodipir trisodium

Structural Formula:



Chemical Abstracts Registry No.: 140678-14-4

Trade Name	Manufacturer	Country	Year Introduced
Teslascan	Nycomed Amersham Health Inc.	-	-

Raw Materials

Pyridoxal-5-phosphate
Platinum on carbon
Sodium hydroxide
Manganese dichloride tetrahydrate
1,2-Diaminoethane
Hydrogen
Bromoacetic acid

Manufacturing Process

Sodium N,N'-bis(pyridoxal-5-phosphate)ethylenediimine

A 265.2 g (1 mole) of pyridoxal-5-phosphate was slurried in 1 L of methanol, and 400 mL of 5 M NaOH was added. When the solution was homogeneous, 34.2 mL of 1,2-diaminoethane was added rapidly with vigorous stirring. The imine product sodium N,N'-bis(pyridoxal-5-phosphate)ethylenediimine or sodium 5-(N-(3-hydroxy-2-methyl-5-phosphonomethyl-4-pyridyl) methylideneaminoethyleneiminomethyl)-2-hydroxy-3-methyl-5-pyridylmethylphosphate was stirred for 1 hr, 400 mL of diethyl ether was added, and the slurry was filtered. The filtrate was washed with 600 mL of

ethanol and dried at 60°C in vacuo. A 290 g of the bis-imine with a melting point of 215-220°C (decomp.) was isolated (90% yield, based on the tetra-sodium salt).

N,N'-bis(Pyridoxal-5-phosphate)ethylenediamine

To the diimine obtained was added 1.5 L of deionized water and 1.5 L of methanol. The yellow solution formed was stirred while sparging with nitrogen. Then 13 g of 5% Pt on carbon was added, and the apparatus was purged with hydrogen. The reaction was allowed to proceed for 5 hr with continuous addition of hydrogen. HPLC analysis showed complete reduction to the amine. The reaction mixture was sparged with nitrogen for 15 min and then filtered through Celite. The filtrate was concentrated in vacuo at 60°C to about 500 mL. The solution, containing N,N'-bis(pyridoxal-5-phosphate) ethylenediamine or 5-(N-(3-hydroxy-2-methyl-5-phosphonomethyl-4-pyridyl)methylaminoethyleneaminomethyl)-2-hydroxy-3-methyl-5-pyridylmethylphosphoric acid salt was used directly for the next step. If desired the diamine can be isolated as off-white crystals by the addition of 200 ml of 97% formic acid and allowing the product to crystallize at room temperature overnight. The diamine is isolated by filtration and washed with 150 mL of cold deionized water.

N,N'-Bis-(pyridoxal-5-phosphate)ethylenediamine-N,N'-diacetic acid synthesis

The diamine obtained was dissolved in a 100 g (2.5 mole) of NaOH, and 130 g (0.9 mole) of bromoacetic acid was dissolved in 180 mL of deionized water. Each solution was charged to an addition funnel. NaOH solution was added to the diamine solution to bring the pH to 11. The temperature was raised to 42°C, and bromoacetic acid and NaOH solution were added concurrently to maintain the pH at 11. The progress of the reaction was checked by HPLC. A 675 g of cation exchange resin (AMBERLITE IRC-50) was added, and the mixture was placed in a refrigerator for 14 hr. The pH had dropped to 6.5. The resin was removed by filtration, and the filtrate treated with 260 g of cation exchange resin (DOWEX 50W-X8). The pH dropped to about 4. The resin was removed by filtration, and the solution was concentrated in vacuo at 60°C to a viscous oil. The oil was dried in vacuo for 48 hr to yield a resinous solid containing N,N'-bis-(pyridoxal-5-phosphate)ethylenediamine-N,N'-diacetic acid or N,N'-bis(3-hydroxy-2-methyl-5-phosphonomethyl-4-pyridylmethyl) ethylenediamine-N,N'-diacetic acid (DPDP). The resinous solid obtained was dissolved in 600 mL of 88% formic acid, then 1.5 L of methanol and 2.2 L of ethanol was added, and the mixture was cooled to 0°C for 2 hr. The solvent mixture was decanted from the resulting gum. The gum was dissolved in 800 mL of deionized water which was then concentrated in vacuo to about 600-650 mL. Seed crystals were added, and the solution was allowed to stand overnight. The product was isolated by filtration, washed with 400 mL of cold water, 250 mL of ethanol, and then dried in vacuo to yield 65 g of DPDP in 85-90% purity by HPLC.

The 65 g of product was then dissolved in 75 mL of 88% formic acid containing 5 mL of deionized water with heating to 60°C. Cold water was added to a total volume of 1 L, and the solution was allowed to stand at 25°C for 16 hr to crystallize. The product was isolated by filtration, washed with 200 mL cold water, and dried in vacuo at 60°C to yield 55 g of DPDP in 93-95% purity by HPLC. A second recrystallization, using the same procedure

yields 50 g of DPDP in 96-98% purity by HPLC, melting point 174-180°C (decomp.).

Sodium salt of Mn(DPDP)

A 4.16 g (6.25 mmole) portion of DPDP was dissolved in 15 mL of rigorously degassed water by the addition of 1.0 g (25 mmoles) of NaOH. A 1.25 g (6.25 mmole) quantity of manganese dichloride tetrahydrate was added, and the solution immediately turned yellow. After stirring for 30 min, 0.25 g (6.25 mmole) of solid NaOH was added to bring the pH up to 6.5. Then degassed water was added to bring the volume of the solution to 25 mL. The clear yellow solution was sterilized by being filtered through a 0.2 micron filter to yield the sodium salt of a manganese chelate complex of N,N'-bis-(pyridoxal-5-phosphate)ethylenediamine-N,N'-diacetic acid or N,N'-bis(3-hydroxy-2-methyl-5-phosphonomethyl-4-pyridylmethyl)ethylenediamine-N,N'-diacetic acid.

References

Rocklage S.M., Quay S.C.; US Patent No. 4,933,456; Jun. 12, 1990; Assigned to Salutar, Inc.
Rocklage S.M., Quay S.C.; US Patent No. 4,935,518; Jun. 19, 1990; Assigned to Salutar, Inc.
Towart R. et al.; US Patent No. 6,258,828; Jul 10. 2001; Assigned to Nycomed Imaging AS (Oslo, NO)

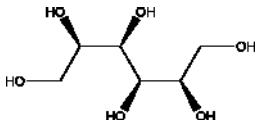
MANNITOL

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	US	1946
Osmitrol	Travenol	US	1964
Mannitol I.V.	Abbott	US	1968
Eufusol	Knoll	W. Germany	-

Trade Name	Manufacturer	Country	Year Introduced
Isotol	Baxter	Italy	-
Manit	Pliva	Yugoslavia	-
Mannidex	Pharmacia	Sweden	-
Osmofundin	Braun	W. Germany	-
Osmosol	Farmer Hill	Australia	-
Rectisol	McGaw	US	-

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

References

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

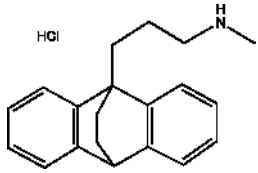
MAPROTILINE HYDROCHLORIDE

Therapeutic Function: Antidepressant

Chemical Name: 9,10-Ethanoanthracene-9(10H)-propylamine, N-methyl-, hydrochloride

Common Name: Maprotiline hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 10347-81-6; 10262-69-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Maprotiline hydrochloride	Mylan	-	-
Ludiomil	Novartis AE (ex. CIBA-GEIGY)	-	-
Retinyl	Kleva	-	-

Raw Materials

Thionyl chloride
Methylamine
Ethylene
3-(9-Anthryl)propionic acid
Lithium aluminum hydride

Manufacturing Process

9-(3-Hydroxypropyl)anthracene was prepared by reduction of 3-(9-anthryl) propionic acid with $LiAlH_4$. By action of thionylchloride and then methylamine the 9-(3-hydroxypropyl)anthracene was converted to 9-(3-methylaminopropyl) anthracene. By addition of ethylene to 9-(3-methylaminopropyl)anthracene (at 150°C, a pressure of ethylene 50 atm, 24 hours) was obtained 3-(9,10-dihydro-9,10-ethanoanthracene-9-yl)-N-methylpropylamine. Hydrochloride 3-(9,10-dihydro-9,10-ethanoanthracene-9-yl)-N-methylpropylamine may be prepared by action hydrochloric acid.

References

Merck Index, Monograph number: 5792, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Rev.: Scoginis, Clin. Chem. 1980, 26, 805-815

Boissier et al.; "Synthesis and Pharmacological Properties of New 9,10-Dihydro-9,10-ethanoanthracene Derivatives", J. Med. Chem. 10:86-91 (Jan. 1967)

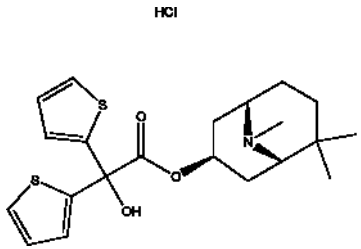
MAZATICOL HYDROCHLORIDE

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:



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)glycolate

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)-glycolate 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)glycolate of 6,6,9-trimethyl-9-azabicyclo[3.3.1]nonan-3β-ol hydrochloride are obtained. Yield 83%.

References

Kleeman and 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.; US Patent 3,673,195; June 27, 1972; assigned to Tanabe Swiyaku Co.

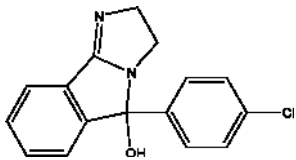
MAZINDOL

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	US	1973
Teronac	Wander	UK	1974
Teronac	Wander	W. Germany	1976
Mazildene	Farmochimica	Italy	1979
Mazanor	Wyeth	US	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-11H-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 resulting 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 and 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.; US Patent 3,597,445; August 3, 1971; assigned to Sandoz-Wander, Inc.
Sulkowski, T.S.; US Patent 3,763,178; October 2, 1973; assigned to American Home Products Corp.

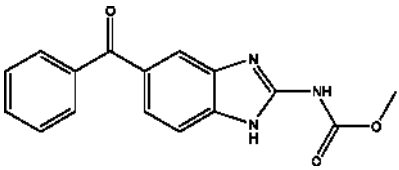
MEBENDAZOLE

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	US	1975
Vermox	Janssen	UK	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

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

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 and 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) and 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.; US Patent 3,657,267; April 18, 1972; assigned to Januen Pharmaceutica, NV, Belgium

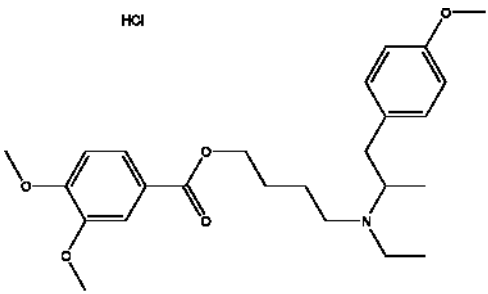
MEBEVERINE HYDROCHLORIDE

Therapeutic Function: Spasmolytic

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	UK	1967
Duspatal	I.S.M.	Italy	1970
Duspatal	Thomae	W. Germany	1977
Duspatalin	Duphar	Switz.	1981

Raw Materials

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

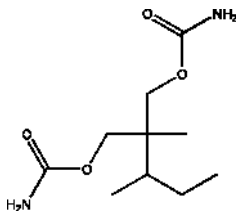
MEBUTAMATE

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	US	1961
Axiten	Zambon	Italy	-
Butatensin	Benvegna	Italy	-
Carbuten	Kalopharma	Italy	-
Dormate	Wallace	US	-
Ipotensivo	Vita	Italy	-
Mebutina	Formenti	Italy	-
No-Press	Janus	Italy	-
Prean	Chemil	Italy	-
Preminex	Dumex	Denmark	-

Trade Name	Manufacturer	Country	Year Introduced
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 and Engel p. 538
OCDS Vol. 1 p. 218 (1977)
I.N. p. 581
Berger, F.M. and Ludwig, B.J.; US Patent 2,878,280; March 17, 1959; assigned to Carter Products, Inc.

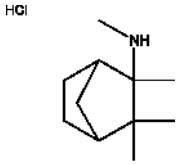
MECAMYLAMINE HYDROCHLORIDE

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	US	1956
Mevasine	MSD	W. Germany	-
Prexion	I.T.I.	Italy	-

Raw Materials

dl-Camphene
Sodium cyanide
Lithium aluminum hydride
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 mold 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 re placed 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 and Engal p. 538
I.N. p. 581
REM p.849
Pfister, K., Ill and Stein, G.A.; US Patent 2,831,027; April 15, 1958; assigned to Merck and Co., Inc.

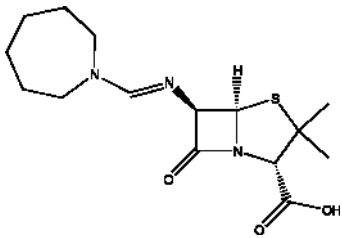
MECILLINAM

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	UK	1979
Celfuron	Roche	-	-

Raw Materials

Chloral
Hexamethyleneimine

Oxalyl chloride
Trimethylsilyl 6-aminopenicillinate

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 1.5 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 1/4 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 and 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 US Patent 3,957,764; May 18, 1976; both assigned to Lovens Kemiske Fabrik Produktionsakties Lab (Denmark)

MECLIZINE HYDROCHLORIDE

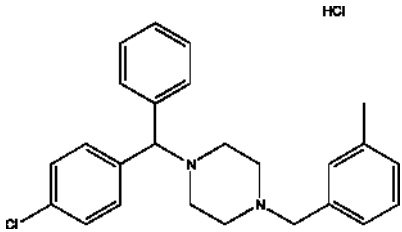
Therapeutic Function: Antinauseant

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

Common Name: Meclozin; Histamethizine

Chemical Abstracts Registry No.: 1104-22-9; 569-65-3 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Antivert	Roerig	US	1957
Ru-Vert M	Reid-Provident	US	1983
Ancolan	Duncan Flockhart	UK	-
Bonamine	Pfizer	W. Germany	-
Calmonal	Heyden	W. Germany	-
Chiclida	Torpens	Spain	-
Diadril	Pliva	Yugoslavia	-
Duremesan	Streuli	Switz.	-
Itinerol	Galenika	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.	Netherlands	-
Taizer	Pfizer Taito	Japan	-
V-Cline	Vangard	US	-
Veritab	Vista	US	-
Vertizine	Merchant	US	-

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 cm3 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 and 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.; US Patent 2,709,169; May 24, 1955; assigned to Union Chimique Belge Societe Anonyme, Belgium

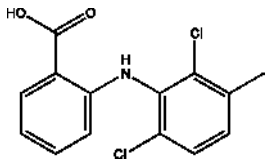
MECLOFENAMIC ACID

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

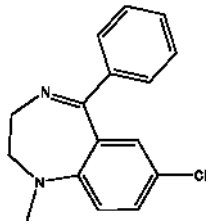
MEDAZEPAM

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	UK	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	-
Esmail	Richter	Mexico	-
Glorium	Teva	Israel	-
Kobazepam	Nihon Yakuhin	Japan	-
Lerisum	Poli	Italy	-
Medaurin	Isis	Yugoslavia	-
Megasedan	Andreu	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

Calcium carbonate	5-Chloro-N-methylanthranilic acid
Sodium hydroxide	Bromoethylamine hydrobromide
Oxalic acid	Phosphorus oxychloride
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 US Patent 3,624,703.

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

References

Merck Index 5609
Kleeman and Engel p. 542
OCDS Vol. 1 p. 368 (1977)
DOT 5 (4) 150 (1969) and 9 (6) 238 (1973)
I.N. p. 584

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Archer, G.A. and Sternbach, L.H.; US Patent 3,131,178; April 28, 1964; assigned to Hoffmann-LaRoche Inc.
Reeder, E. and Sternbach, L.H.; US Patent 3,141,890; July 21, 1964; assigned to Hoffmann-LaRoche Inc.
Reeder, E. and Sternbach, L.H.; US Patent 3,144,439; August 11, 1964; assigned to Hoffmann-LaRoche Inc.
Field, G.F., Sternbach, L.H. and Zally, W.J.; US Patent 3,624,073; November 30, 1971; assigned to Hoffmann-LaRoche Inc.

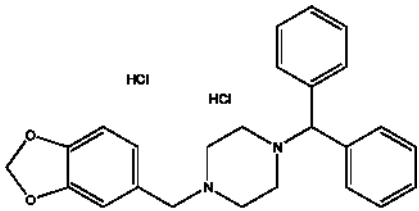
MEDIBAZINE DIHYDROCHLORIDE

Therapeutic Function: Coronary vasodilator

Chemical Name: Piperazine, 1-(1,3-benzodioxol-5-ylmethyl)-4-(diphenylmethyl)-, dihydrochloride

Common Name: Medibazine dihydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 96588-03-3; 53-31-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Vialibran	Servier	-	-

Raw Materials

Piperonyl-1-piperazine
Benzhydryl chloride
Methanesulfonic acid

Manufacturing Process

To a solution of 32 g piperonyl piperazine in 100 ml anhydrous toluene, 10 g sodium carbonate are added and 35.2 g benzhydryl chloride are added dropwise. The mixture is then heated to reflux for 7 hours with vigorous agitation. Then the mixture is cooled, the salt that has formed is filtered out and 100 ml water is added. The organic layer is extracted with several batches of 10% methane sulfonic acid. The acid extracts are combined and

washed with ether then alkalized with sodium carbonate. The mixture is extracted with several batches of chloroform and the combined chloroform solutions are washed several times with water. After drying and solvent evaporation, the crude base of 1-diphenylmethyl-4-piperonyl-piperazineis isolated and the hydrochloride thereof is formed in acetone. After recrystallization 22.5 g of the dihydrochloride are finally obtained. M.P.: 228°C, from methanol.

References

Regnier G. et al.; US Patent No. 3,119,826; Jan. 28, 1964; Assigned to Societe en nom collectif dite: Science Union et Compagnie-Societe Francaise de Recherche Medicale, Suresnes, Seine, France, a French society

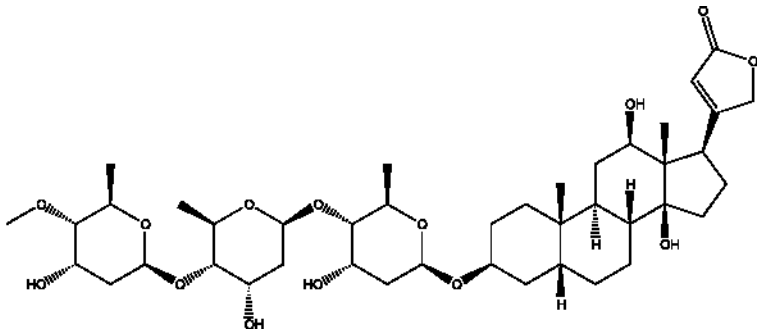
MEDIGOXIN

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	Boehringer Mannheim	W. Germany	1972
Lanitop	Boehringer Mannheim	Italy	1973
Lanitop	Roussel	UK	1976
Lanirapid	Yamanouchi	Japan	1979
Cardiolan	Tosi-Novara	Italy	-
Digicor	Lek	Yugoslavia	-
Intensain-Lanitop	Boehringer Mannheim	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 chloroformlethanol 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 and Engel p. 544
DOT 12 (8) 319, 323 (1976)
I.N.p.627
Pelan, E., Milohnoja, M. and Pezdirc, M.; US Patent 4,145,528; March 20, 1979; assigned to L.E.K. Tovarna Farmacevtskih in Kemicnih Izdelkov (Yugoslavia)

MEDROGESTONE

Therapeutic Function: Progestin

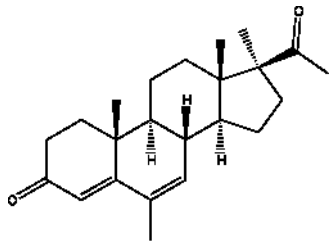
Chemical Name: 6,17-Dimethylpregna-4,6-diene-3,20-dione

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

Chemical Abstracts Registry No.: 977-79-7

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

Structural Formula:



Raw Materials

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

Manufacturing Process

The manufacturing process as described in US Patent 3,170,936 uses the readily available methyl 3β-hydroxy-17α-methyl-δ^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 1300 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,6βp-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 indicates 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 $C_{23}H_{38}O_4H_2O$: Required: C, 69.60%; H, 10.17%. Found: C, 69.90%; H, 10.15%.

Alternatively, 25.0 g of either 3β,5α-dihydroxy-17α-methy-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 and Engel p. 545
OCDS Vol. 1 p. 182 (1977)
I.N. p. 586
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Morand, P.F. and Deghenghi, R.; US Patent 3,170,936; February 23, 1965; assigned to American Home Products Corporation
Deghenghi, R.; US Patent 3,210,387; October 5, 1965; assigned to American Home Products Corporation

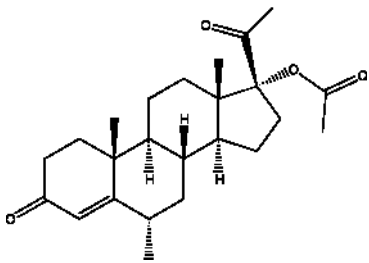
MEDROXYPROGESTERONE ACETATE

Therapeutic Function: Progestin

Chemical Name: 17-Acetoxy-6α-methyl-pregn-4-ene-3,20-dione

Common Name: 6α-Methyl-17α-acetoxyprogesterone

Structural Formula:



Chemical Abstracts Registry No.: 71-58-9; 520-85-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Provera	Upjohn	US	1959
Farlutal	Carlo Erba	France	1962
Provest	Upjohn	US	1964
Amen	Carnrick	US	1975
Unison	Reid-Provident	US	1978
Mepred	Savage	US	1978
Curretab	Reid-Provident	US	1979
Farlutal	Carlo Erba	UK	1982
Depcorlutin	O'Neal, Jones and Feldman	US	-
Depo-Clinovir	Upjohn	W. Germany	-
Depo-Progevera	Alter	Spain	-
Depo-Provera	Upjohn	US	-
Gestapuran	Lovens	Denmark	-
Hysron	Kyowa	Japan	-
Luteocrin	Richter	Italy	-
Luteodione	Panther-Osfa	Italy	-
Luteos	Ion	Italy	-
Lutopolar	Farmos	Finland	-
Lutoral	Midy	Italy	-
Metilgestene	Farmila	Italy	-
Nadigest	Streuli	Switz.	-
Oragest	Ikapharm	Israel	-
Petogen	Petersen	S. Africa	-
P-Medrate	Tutag	US	-
Progevera	Alter	Spain	-
Sodelut G	Sodex	Switz.	-

Raw Materials

Sulfuric acid
Ethylene glycol
Peracetic acid
17α-Hydroxyprogesterone
Methyl magnesium bromide
Acetic anhydride

Manufacturing Process

Preparation of 17α-Hydroxyprogesterone 3,20-Bis-(Ethylene Ketal): A solution was prepared containing 50.0 g of 17α-hydroxyprogesterone in 1,000 ml of benzene, 100 ml of ethylene glycol and 2.5 g of p-toluenesulfonic acid monohydrate. This mixture was refluxed for a period of 17 hours using a calcium carbide water-trap to remove the water formed in the reaction. After this period of reflux 6.5 ml of pyridine was added to the solution, and the mixture cooled to room temperature.

The lower glycol layer was separated and washed with benzene. The benzene layer and the benzene washings were combined and the combined solution was divided into two equal portions, one of which was used for the isolation of 17α-hydroxyprogesterone 3,20-bis-(ethylene ketal) as follows. The benzene solution was washed with 5% sodium carbonate solution, water and saturated

sodium chloride solution. After being dried over anhydrous magnesium sulfate the solution was concentrated to dryness at reduced pressure, The residue was recrystallized by taking up in hot methylene chloride, adding acetone and boiling to remove the methylene chloride until a final volume of about 200 ml was reached.

The solution was then refrigerated overnight and 17.8 g of crystals were removed by filtration. A second crop was obtained yielding 3.7 g of compound. The total yield of 17α-hydroxyprogesterone 3,20-bis-(ethylene ketal) was 20.3 g (64.3% of theory). Recrystallization of the crude 17α-hydroxyprogesterone 3,20-bis-(ethylene ketal) from methanol gave the pure bisketal of MP 209° to 211°C.

Preparation of 5α,6α-Oxido-17α-Hydroxyallopregnane-3,20-dione 3,20-Bis-(Ethylene Ketal): A solution was prepared by heating 19.96 g (0.0477 mol) of 17α-hydroxyprogesterone 3,20-bis-(ethylene ketal) and 500 ml of benzene. After the solution was effected the flask was cooled to 5°C and a mixture of 3.68 g (0.0449 mol) of sodium acetate and 174 ml of 40% peracetic acid was added with stirring. The reaction mixture was stirred in the ice bath for 3 hours. The lower peracid layer was separated, diluted with water and extracted twice with benzene.

The upper layer was neutralized by the addition of cold 10% sodium hydroxide solution while stirring in an ice bath. The rate of addition of the sodium hydroxide was regulated to keep the temperature below 10°C. The benzene extracts from the peracid layer were combined and washed with cold 10% sodium hydroxide solution and with saturated sodium chloride solution. All the aqueous layers were washed again with the same portion of benzene. The combined benzene layers were dried over anhydrous magnesium sulfate and concentrated to dryness at reduced pressure.

The residue was recrystallized from acetone using methylene chloride to aid in solution. The crystalline material was removed by filtration and was recrystallized from methylene chloride-acetone to yield a total of 8 g of 5α,6α-oxido-17α-hydroxyallopregnane-3,20-dione 3,20-bis-(ethylene ketal) of MP 211° to 215°C. For analytical purposes, another recrystallization from methylene chloride-acetone gave pure 5α,6α-oxido-17α-hydroxyallopregnane-3,20-dione 3,20-bis-(ethylene ketal) of MP 216° to 218.5°C.

Preparation of 5α,17α-Dihydroxy-6β-Methylallopregnane-3,20-dione 3,20-bis-(Ethylene Ketal): To a solution of 91.6 g of 5α,6α-oxido-17α-hydroxyallopregnane-3,20-dione 3,20-bis-(ethylene ketal) in 3,500 ml of freshly distilled tetrahydrofuran was added 1,170 ml of commercial 3 molar methyl magnesium bromide in ether solution. The reaction mixture was boiled to remove 1,800 ml of solvent by distillation and thereafter 1,000 ml of freshly distilled tetrahydrofuran was added.

Boiling was continued under reflux for a period of 16 hours. The solution was then concentrated to about one-half its original volume by distillation and was poured slowly with vigorous stirring into a large volume of ice water containing 340 g of ammonium chloride. The aqueous solution was saturated with sodium chloride and extracted with benzene. The benzene extract was washed with saturated brine, and both aqueous layers were washed again with the same portions of benzene.

The combined benzene layers were dried over anhydrous sodium carbonate and the solvent was removed at reduced pressure to give 90.5 g of crude crystalline 5α,17α-dihydroxy-6β-methylallopregnane-3,20-dione 3,20-bis-(ethylene ketal). Half of the residue, 45.2 g, was recrystallized from acetone and some methylene chloride to give 34.4 g of 5α,17α-dihydroxy-6β-methylallopregnane-3,20-dione 3,20-bis-(ethylene ketal). A sample recrystallized from acetone and methylene chloride for analysis melted at 160° to 163°C.

Preparation of 5α,17α-Dihydroxy-6β-Methylallopregnane-3,20-dione: A solution was prepared containing 38.9 g of 5α,7α-dihydroxy-6β-methylallopregnane-3,20-dione 3,20-bis-(ethylene ketal) in 389 ml of boiling acetone. Thereto was added 39 ml of 1 N sulfuric acid in portions under swirling and seeding with product. Boiling was continued for a period of 2 minutes and the mixture was allowed to stand at room temperature. Thereafter the mixture was diluted with 1,500 ml of water, chilled and filtered.

The precipitate was washed with water, dilute ammonium hydroxide and water, and dried in a vacuum oven overnight. The yield was 31.2 g which was recrystallized by dissolving in 1,200 ml of dimethylformamide, heating to 150°C, cooling slightly, and adding 12 ml of hot water. The recrystallized 5α,17α-dihydroxy-6β-methylallopregnane-3,20-dione thus obtained was 28.75 g of MP 270° to 275.5°C. After an additional recrystallization from aqueous dimethylformamide, the MP was 274° to 279°C.

Preparation of 6α-Methyl-17α-Hydroxyprogesterone: A suspension was made by introducing 2 g of 5α,17α-dihydroxy-6β-methylallopregnane-3,20-dione into 200 ml of chloroform. The suspension was chilled in an ice bath with stirring, and thereupon hydrogen chloride was bubbled through the reaction mixture for 80 minutes with continuous cooling and stirring. After bubbling in nitrogen for a period of 15 minutes the solution was washed with water, 1 N sodium bicarbonate solution and again with water.

The aqueous layers were rewashed with one portion of chloroform, and the washings combined with the remainder of the chloroform solution. After drying over anhydrous magnesium sulfate, the chloroform solution was concentrated to dryness, then taken up in a small volume of methylene chloride, treated with Magnesol anhydrous magnesium silicate and filtered. Acetone was added to the solution and the solution was boiled to remove the methylene chloride. After the solution was concentrated to a volume of about 15 ml it was chilled and the crystals were collected through filtration. The 1.37 g of crystals so obtained were recrystallized from acetone to give pure 6α-methyl-17α-hydroxyprogesterone of MP 220° to 223.5°C.

Preparation of 6α-Methyl-17-Hydroxyprogesterone 17-Acetate: 1 g of 6α-methyl-17α-hydroxyprogesterone was dissolved in a mixture of 10 ml of acetic acid and 2 ml of acetic anhydride by heating. After solution was effected the mixture was cooled to 15°C, and 0.3 g of p-toluenesulfonic acid was added. After allowing the mixture to stand for a period of 2.5 hours at room temperature, the pink solution was poured into ice water to give an amorphous solid which was recovered by filtration.

The precipitate was washed carefully with water and was then dissolved in 10 ml of methanol and 1.5 ml of methylene chloride. The solution was

concentrated to 10 ml, diluted with 0.5 ml of 10% sodium hydroxide, boiled for one minute and cooled. The product, which crystallized on cooling, was recrystallized to give flakes of 6α-methyl-17α-hydroxyprogesterone 17-acetate, having a MP 205° to 209°C, according to US Patent 3,147,290.

References

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Kleeman and Engel p. 546
PDR pp. 777, 1447, 1839, 1858
OCDS Vol. 1 pp. 180, 186 (1977) and 2, 165 (1980)
DOT 4 (1) 14 (1968)
I.N. p. 586
REM p. 992
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de Ruggieri, P. and Ferrari, C.; US Patent 3,043,832; July 10, 1962; assigned to Ormonoterapia Richter S.p.A., Italy
Camerino, B., Modelli, R., Patelli, B., Sala, G. and Baldratti, G.; US Patent 3,061,616; October 30, 1962; assigned to Societa Farmaceutici Italia, Italy
Patchett, A.A. and Hoffman, F.G.; US Patent 3,084,174; April 2, 1963; assigned to Merck and Co., Inc.
Beyler, R.E.; US Patent 3,105,840; October 1, 1963; assigned to Merck and Co.
Spero, G.B.; US Patent 3,147,290; September 1, 1964; assigned to The Upjohn Company

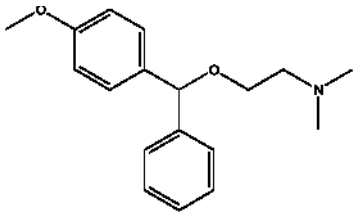
MEDRYLAMINE

Therapeutic Function: Antihistaminic

Chemical Name: 2-(p-Methoxy-alpha-phenylbenzyloxy)-N,N-dimethylethylamine

Common Name: Medrylamine

Structural Formula:



Chemical Abstracts Registry No.: 524-99-2

Trade Name	Manufacturer	Country	Year Introduced
Medrylamine	Shanghai Lansheng Corporation	-	-

Raw Materials

4-Methoxybenzhydryl chloride
2-Dimethylaminoethanol

Manufacturing Process

A 116 parts by weight of phenyl-p-methoxy-chloromethane (4-methoxybenzhydryl chloride) were added to 500 parts by weight of toluene and to the resulting mixture 65 parts by weight of 2-dimethylaminoethanol was added. Then the entire mixture was refluxed for two hours. The refluxed mixture was cooled and 250 parts by weight of a 10% solution of sodium hydroxide were added. This alkaline mixture was then steam distilled until the distillate was only weakly alkaline, for example a pH 7.5-8.

The residue of this steam distillation was then mixed with 200 parts by weight of benzene and washed with water until the wash waters were practically neutral. The benzene solution was then evaporated to dryness until the resulting mixture was of constant weight (145 parts). This product was oily and was then dissolved in 3000 parts by weight of dry ether; and treated while being agitated with the theoretically equivalent amount of dry hydrochloric acid dissolved in ether. This product is an oily product, which solidified after standing overnight in an ice box. The ether solution was decanted off and the solidified residue was dissolved in 1500 parts by weight of dioxane, and then precipitated with 3000 parts by weight of ether while being continuously agitated. The resulting solid product was the hydrochloride of 2-(p-methoxy-α-phenylbenzyloxy)-N,N-dimethylethylamine 100 parts by weight of the desired product were obtained corresponding to a yield of 62% and having a melting point of 141°C.

References

Morren H.; US Patent No. 2,668,856; Feb. 9, 1954; Assigned to Union Chemique Belge, S. A., Brussels, Belgium, a corporation of Belgium

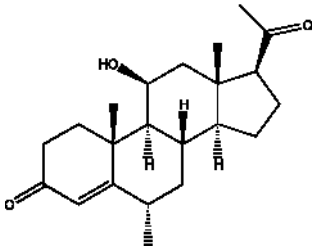
MEDRYSONE

Therapeutic Function: Glucocorticoid

Chemical Name: 11β-Hydroxy-6α-methylpregn-4-ene-3,20-dione

Common Name: Hydroxymesterone; 6α-Methyl-11β-hydroxyprogesterone

Structural Formula:



Chemical Abstracts Registry No.: 2668-66-8

Trade Name	Manufacturer	Country	Year Introduced
HMS	Allergan	US	1970
Visudrisone	Italseber	Italy	1970
Spectamedryn	Pharm-Allergan	W. Germany	1975
Medrysone Faure	Faure	France	1976
Ipoflogin	Tubi Lux	Italy	-
Medrifar	Farmila	Italy	-
Medritonic	Llorens	Spain	-
Medroptil	Farmigea	Italy	-
Ophthocortin	Winzer	W. Germany	-
Sedestrol	Poen	Argentina	-

Raw Materials

11-Keto-6β-methylprogesterone
Ethylene glycol
Lithium aluminum hydride

Manufacturing Process

Preparation of 11-Keto-6β-Methylprogesterone 3,20-bis-(Ethylene Ketal): A mixture of 5 g of 11-keto-6β-methylprogesterone [Spero et al, A Am. Chem. Soc., 78, 6213 (1956)], 503 ml of benzene, 26 ml of ethylene glycol, and 0.152 g of p-toluenesulfonic acid monohydrate was stirred and heated under reflux for 22 hours while water was removed by means of a water trap. The reaction mixture was then cooled to 30°C, 0.4 ml of pyridine was added, and stirring was continued for 10 minutes.

The reaction mixture was then shaken with 110 ml of water and the organic and aqueous layers separated. The organic layer was dried over sodium sulfate and evaporated under diminished pressure giving a residue. The thus obtained residue was recrystallized from methanol giving 2.68 g of 11-keto-6β-methyl progesterone 3,20-bis-(ethylene ketal) having a MP of 168° to 175°C.

Preparation of 11β-Hydroxy-6α-Methylprogesterone: A mixture of 2.68 g of

11-keto-6β-methylprogesterone 3,20-bis-(ethylene ketal), 161 ml of tetrahydrofuran (previously distilled from lithium aluminum hydride), 1.34 g of lithium aluminum hydride and 14.5 ml of absolute ether was stirred and refluxed under nitrogen for 1.5 hours, then 27 ml of water was added cautiously, to decompose excess hydride. The resulting mixture was filtered and the filter cake was washed with 135 ml of ether. The combined filtrate and wash was shaken with 135 ml of water and separated. The aqueous layer was washed with four 55-ml portions of ether, then the organic layer and the washes were combined, washed once with water, and evaporated to dryness under diminished pressure leaving a tan residue.

The thus-obtained residue was dissolved in a mixture of 268 ml of methanol and 26.8 mi of 3 N aqueous sulfuric acid and heated under reflux for 40 minutes, with a color change from yellow to green. The reaction mixture was then cooled, neutralized by addition of 127 ml of 5% sodium bicarbonate solution, and concentrated under reduced pressure until almost all the methanol was removed. The resulting solid was removed by filtration, washed with water, dried, and twice crystallized from ethyl acetate to give 1.1 g of 11β-hydroxy-6α-methylprogesterone having a MP of 155° to 158°C, according to US Patent 2,864,837.

References

Merck Index 5616
Kleeman and Engel p. 548
OCDS Vol. 2 p. 200 (1980)
DOT 6 (5) 184 (1970)
I.N. p. 587
REM p. 972
Sebek, O.K., Spero, G.B. and Thompson, J.L.; US Patent 2,864,837; assigned to The Upjohn Company
Spero, G.B. and Thompson, J.L.; US Patent 2,968,655; January 17,1961; assigned to The Upjohn Company

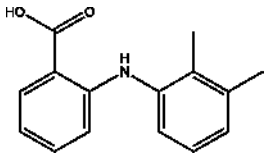
MEFENAMIC ACID

Therapeutic Function: Analgesic

Chemical Name: 2-[2,3-Dimethylphenyl)amino]benzoic acid

Common Name: N-(2,3-Xylyl)anthranilic acid

Structural Formula:



Chemical Abstracts Registry No.: 61-68-7

Trade Name	Manufacturer	Country	Year Introduced
Ponstan	Parke Davis	UK	1963
Ponalar	Parke Davis	W. Germany	1964
Ponstyl	Parke Davis	France	1967
Ponstel	Parke Davis	US	1967
Bafameritin	Hishiyama	Japan	-
Bonabol	Sawai	Japan	-
Fenamin	Yurtoglu	Turkey	-
Lysalgo	Schiapparelli	Italy	-
Mefacit	Polfa	Poland	-
Mefedolo	Ion	Italy	-
Parkemed	Parke Davis	W. Germany	-
Rolan	Nobel	Turkey	-
Spantac	Uji	Japan	-
Vialidin	Italfarmaco	Italy	-

Raw Materials

Potassium o-bromobenzoate
2,3-Dimethylaniline

Manufacturing Process

A mixture of 800 g of potassium o-bromo-benzoate, 1,500 ml of bis-(2-methoxyethyl)ether, 355 g of N-ethyl-morpholine, 375 g of 2,3-dimethylaniline, and 30 g of cupric acetate is heated gradually with stirring to 140°C over a period of 90 minutes. The hot reaction mixture is then acidified with 260 mi of concentrated hydrochloric acid and the acidified mixture divided into 2 equal portions. One liter of water is added to each portion and the mixtures allowed to cool. The N-(2,3-dimethylphenyl)anthranilic acid which separates upon cooling is collected by filtration and recrystallized from bis(2-methoxyethyl)ether; MP 229° to 230°C (corr.).

References

Merck Index 5617
Kleeman and Engel p. 548
PDR p. 1383
OCDS Vol. 1 p. 110 (1977) and 2, 280 (1980)
DOT 1 (2) 59 (1965)
I.N. p. 31
REM p. 1118
Scherrer, R.A.; US Patent 3,138,636; June 23, 1964; assigned to Parke, Davis and Company

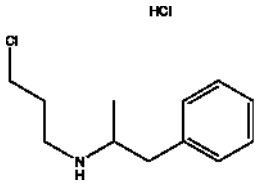
MEFENOREX HYDROCHLORIDE

Therapeutic Function: Anorexic

Chemical Name: N-(3-Chloropropyl)-α-methylphenylethylamine hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 5586-87-8; 17243-57-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Pondinil	Roche	France	1970
Rondimen	Homburg	W. Germany	1976
Anexate	Roche	US	-
Doracil	Gador	Argentina	-

Raw Materials

β-Chloropropionaldehyde
1-Phenyl-2-aminopropane
Hydrogen

Manufacturing Process

9.5 parts of β-chloropropionaldehyde were added slowly, at a temperature of 0°C to a solution of 31.5 parts of 1-phenyl-2-aminopropane in 150 parts of methanol. Thereafter, 0.2 part of platinum oxide was added to the reaction mixture following which the mixture was reacted with hydrogen, in a shaking vessel, until the theoretical quantity of hydrogen had been taken up. When the hydrogenation reaction was completed, the catalyst was removed by filtration and the filtrate neutralized with hydrochloric acid. Subsequently, the filtrate was evaporated to dryness and recrystallized from isopropyl alcohol. The thus-obtained N-(3-chloropropyl)-α-methylphenethylamine hydrochloride melted at 128°C to 130°C.

References

Merck Index 5618
Kleeman and Engel p. 549

OCDS Vol. 2 p. 47 (1980)
DOT 6 (4) 133 (1970)
I.N. p. 587
Schuler, W.A., Schlichtegroll, A.V., Beschke, H. and Klingler, K.H.; US Patent 3,485,926; December 23, 1969; assigned to Hoffmann-LaRoche, Inc.

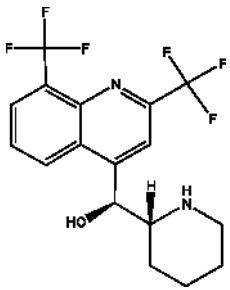
MEFLOQUINE

Therapeutic Function: Antimalarial

Chemical Name: 4-Quinolinemethanol, 2,8-bis(trifluoromethyl)-α-2-piperidinyl-, (R*,S*)-, (+-)-

Common Name: Meflochina; Mefloquine

Structural Formula:



Chemical Abstracts Registry No.: 53230-10-7

Trade Name	Manufacturer	Country	Year Introduced
Lariam	Roche Pharmaceuticals	Switz.	-
Mephaquin	Mepha	-	-

Raw Materials

1,1'-Carbonyldiimidazole
2-Bromopyridine
Butyl lithium
2-Pyridylacetonitrile
2,8-Bis(trifluoromethyl)quinoline-4-carboxylic acid
4-Chloro-2,8-bis(trifluoromethyl)quinoline
N,O-Dimethylhydroxylamine hydrochloride
Benzyltriethylammonium chloride
Sodium hydroxide

Manufacturing Process

The first method of synthesis of 2,8-bis(trifluoromethyl)-4-quinolinyl-2-pyridinylmethanone

N-Methoxy-N-methyl-2,8-bis(trifluoromethyl)-quinoline-4-carboxamide was prepared using synthetic methodology reported by Thiesen et al (J. Org. Chem. 1988, 53, 2374). To a suspension of 12.5 g (40.4 mmol) 2,8-bis(trifluoromethyl)quinoline-4-carboxylic acid (was prepared by the method of Hickmann et al. (U.S. Patent No. 4,327,215)) in 200 ml CH_2Cl_2 was added 1,1'-carbonyldiimidazole (7.3 g, 45 mmol) and N,O-dimethylhydroxylamine hydrochloride (4.25 g, 45 mmol). The resulting deep red solution was stirred overnight, then poured into dilute hydrochloric acid (0.25 M, 200 ml). The organic phase was separated, and washed with dilute sodium hydroxide and brine, and dried ($MgSO_4$). The solvents was evaporated to leave a viscous brown oil, which was filtered through a pad of silica gel using ethyl acetate-hexane (1:1) as eluent to give N-methoxy-N-methyl-2,8-bis(trifluoromethyl)-quinoline-4-carboxamide as a yellowish oil, 14.3 g (98%), which solidified on standing. This material was broken up under hexane to afford the product as a solid, melting point 93-95°C. Analysis of this material by HPLC showed it to be >99.8% pure.

To a solution of the N-methoxy-N-methyl-2,8-bis(trifluoromethyl)-quinoline-4-carboxamide amide (10 g, 28.4 mmol) in anhydrous ether (100 ml) was added a solution of 2-pyridyl lithium (Pinder et al (J. Med. Chem. 1968, 11, 267)) [formed by addition of 2-bromopyridine (3.3 ml, 34.6 mmol) to a solution of butyl lithium (29.7 ml of a commercial 1.6 M solution, diluted with an equal quantity of ether) at -78°C] at -78°C. Analysis of the reaction by TLC after 10 min showed that no starting material remained. The reaction was allowed to warm to room temperature, then poured into aqueous ammonium acetate, and extracted with ether, the combined organic layers washed with brine and dried ($MgSO_4$). Filtration through a pad of silica gel using ethyl acetate-hexane (1:1) afforded 9.0 g (84%) of the crude 2,8-bis(trifluoromethyl)-4-quinolinyl-2-pyridinylmethanone. This was recrystallised from isopropyl alcohol to give the product as colourless needles, identical to that described in the literature (Hickmann et al.; Pinder et al.; Ohnmacht et al.; and Adam et al. (Tetrahedron 1991, 36, 7609)).

The second method of synthesis of 2,8-bis(trifluoromethyl)-4-quinolinyl-2-pyridinylmethanone

In a round bottom flask (100 ml) were placed 4-chloro-2,8-bis(trifluoromethyl)quinoline (0.0385 mole, 11.52 g), 2-pyridylacetonitrile (0.0423 mole, 5.0 g), benzyltriethylammonium chloride (0.26 g, 3 mole %), THF (35 ml) and aq NaOH (20 N, 9.63 ml, 0.192 moles). On stirring the colour of the solution became cherry red. The reaction temperature was increased to 5-0°C and stirred for further 1 hour. Monitoring of the reaction mixture by thin layer chromatography (TLC) or gas liquid chromatography (GLC) indicated complete consumption of 4-chloroquinoline to give nitrile. The reaction temperature was lowered to 20-25°C followed by addition of 30% H_2O_2 (13 ml, 0.1154 moles). TLC and GLC monitoring indicated complete conversion of nitrile compound to 2,8-bis(trifluoromethyl)-4-quinolinyl-2-pyridinylmethanone. Reaction mixture was cooled to 0-5°C and neutralized by ortho-phosphoric acid (85% aq, 4.5 ml). THF was distilled off, followed by addition of water (30 ml) and extraction with toluene. The crude product was crystallized from isopropanol to obtain 2,8-bis(trifluoromethyl)-4-quinolinyl]-2-pyridinylmethanone. Yield = 13.17 g (92%), melting point 123°C.

References

Chawla H.P.S. et al.; US Patent No. 6,500,955; Dec. 31, 2002; Assegned to National Institute of Pharmaceutical Education and Research
Fletcher A., Szhepard R., US Patent No. 6,664,397; Dec. 16, 2002; Assigned to Vernalis Research Limited

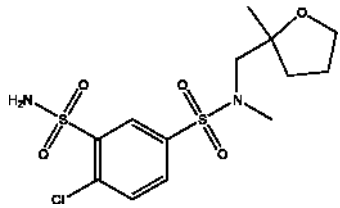
MEFRUSIDE

Therapeutic Function: Diuretic

Chemical Name: 4-Chloro-N'-methyl-N'-[tetrahydro-2-methyl-2-furanyl) methyl]-1,3-benzene-disulfonamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 7195-27-9

Trade Name	Manufacturer	Country	Year Introduced
Baycaron	Bayer	W. Germany	1967
Mefrusal	Bayropharm	Italy	1969
Baycaron	Bayer	UK	1971
Baycaron	Yoshitomi	Japan	1975
Bendigon	Bayer	W. Germany	-
Caprinol	Bayer	W. Germany	-
Sali-Presinol	Bayer	W. Germany	-

Raw Materials

Hydrogen
α-Methyl-α-cyanotetrahydrofuran
Dimethyl sulfate
4-Chloro-3-sulfamyl benzene sulfochloride

Manufacturing Process

By hydrogenation of α-methyl-α-cyanotetrahydrofuran with Raney nickel as catalyst, α-methyl-α-tetrahydrofurfuryl amine is obtained (BP 48°C/12 mm Hg) which is alkylated by dimethyl sulfate to give α-methyl-α-tetrahydrofurfurylmethylamine (BP 70°C/40 mm Hg). The amine is then reacted with 4-chloro-3-sulfamyl benzene sulfochloride in the presence of an acid acceptor. The mixture is stirred overnight, the solvent (acetone or pyridine) is driven off under vacuum and the residue is recrystallized from alcohol.

References

Merck Index 5621
Kleeman and Engel p. 550
OCDS Vol. 1 p. 134 (1977)
I.N. p. 588
Horstmann, H., Wollweber, H. and Meng, K.; British Patent 1,031,916; June 2, 1966; assigned to Farbenfabriken Bayer AG, Germany Horstmann, H., Wollweber, H. and Meng, K.; US Patent 3,356,692; December 5, 1967; assigned to Farbenfabriken Bayer AG

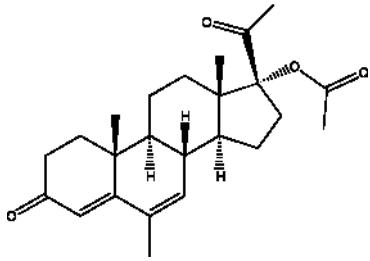
MEGESTROL ACETATE

Therapeutic Function: Cancer chemotherapy

Chemical Name: 17α-Hydroxy-6-methylpregna-4,6-diene-3,20-dione acetate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 595-33-5

Trade Name	Manufacturer	Country	Year Introduced
Megestat	Bristol	W. Germany	1964
Megace	Bristol	UK	1967
Megace	Mead Johnson	US	1982
Pallace	Bristol	US	1982

Trade Name	Manufacturer	Country	Year Introduced
Megestat	Bristol	Switz.	1983
Megeron	Neofarma	Finland	-
Minigest	Novo	-	-
Niagestin	Novo	-	-
Ovarid	Glaxo	-	-
Volplan	B.D.H.	UK	-

Raw Materials

17α-Acetoxy-3β-hydroxy-6-methylpregn-5-ene-20-one
Aluminum-t-butoxide
p-Benzoquinone

Manufacturing Process

The following preparation is given in US Patent 3,356,573. 17α-Acetoxy-3β-hydroxy-6-methylpregn-5-ene-20-one (1 g), aluminum tert-butoxide (1 g) and p-benzoquinone (6 g) were dissolved in dry benzene (100 ml) and the mixture was heated under reflux for 30 minutes. The reaction mixture was cooled and washed with potassium hydroxide solution until the benzene layer was colorless. The benzene was washed with water, dried and evaporated to dryness under reduced pressure. The residue crystallized from aqueous methanol to give 17α-acetoxy-6-methylpregna-4,6-diene-3,20-dione, needles, MP 214° to 216°C.

References

Merck Index 5623
Kleeman and Engel p. 550
PDR p. 721
OCDS Vol. 1 p. 180 (1977)
DOT4 (1) 17 (1968)
I.N. p. 588
REM p. 993
Dodson, R.M. and Sollman, P.B.; US Patent 2,891,079; June 16, 1959; assigned to G.D. Searle and Co.
Kirk, D.N., Petrow, V. and Williamson, D.M.; US Patent 3,356,573; December 5, 1967; assigned to The British Drug Houses Limited, England
Cross, A.D.; US Patent 3,400,137; September 3, 1968; assigned to Syntex Corporation, Panama

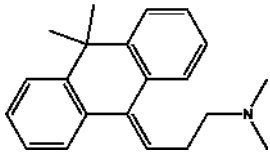
MELITRACEN

Therapeutic Function: Antidepressant

Chemical Name: 3-(10,10-Dimethyl-9(10H)-anthracenylidene)-N,N-dimethyl-1-propanamine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 5118-29-6; 10563-70-9 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Trausabun	Lusofarma	W. Germany	1965
Meixeran	Lusofarma	Italy	1975
Dixeran	Lundbeck	-	-
Thymeol	Takeda	Japan	-

Raw Materials

Magnesium
Sulfuric acid
Hydrogen chloride
2-o-Benzoylphenylpropanol-2
Dimethylaminopropyl chloride

Manufacturing Process

24 g of 2-o-benzoylphenylpropanol-2 (MP 116°C) were dissolved in 250 ml of anhydrous ether and the resulting solution was added dropwise while stirring to a suspension of 0.22 mol of dimethylaminopropylmagnesium chloride in 100 ml of ether. The reaction mixture was refluxed for one hour on a steam bath, and water and dilute hydrochloric acid were added until the reaction was pH 4-5. The aqueous phase was separated and 60 ml of concentrated aqueous ammonia were added. The mixture was extracted with ether, and the ether phase was separated, dried and evaporated in a steam bath. The residue was dissolved in hot petroleum ether and the solution left standing to cool for some time, whereupon 4-dimethylamino-1-phenyl-1-[2-(2-hydroxy-2-propyl)phenyl]-butanol-1 crystallized out as white crystals which were sucked off. After drying they melted at 88°C to 90°C.

10 g of this compound were cautiously dissolved in 50 ml of concentrated sulfuric acid under cooling and the mixture was kept at room temperature for 24 hours, whereupon the reaction mixture was poured into 200 g of finely crushed ice, and concentrated aqueous ammonia was added to about pH 9, whereupon the oil which separated out was extracted with ether. The ether phase was separated, dried and the ether evaporated on a steam bath. The residue was dissolved in 20 ml of acetone and the solution neutralized with a solution of dry hydrogen chloride in ether. The white crystals of 9-γ-dimethylaminopropylidene-10,10-dimethyl-9,10-dihydroanthracene hydrochloride which separated out was filtered off and dried. Yield 9 g. MP 245°C to 247°C.

References

Merck Index 5642
Kleeman and Engel p. 552
OCDS Vol. 2 p. 220 (1980)
I.N. p. 589
Holm, T.O.; US Patent 3,190,893; June 22, 1965; assigned to Kefalas A/S (Denmark)

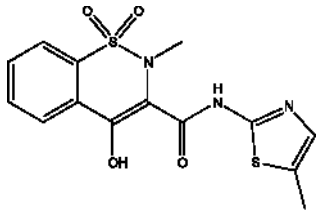
MELOXICAM

Therapeutic Function: Antiinflammatory

Chemical Name: 2H-1,2-Benzothiazine-3-carboxamide, 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-, 1,1-dioxide

Common Name: Meloxicam; Mesoxicam

Structural Formula:



Chemical Abstracts Registry No.: 71125-38-7

Trade Name	Manufacturer	Country	Year Introduced
Novo-Meloxicam	Novopharm	-	-
Mobic	Boehringer Ingelheim	-	-
Meloxicam	AroKor Holdings Inc.	-	-
Meloxicam	NANJING PHARMA CHEMICAL PLANT	-	-
Meloxicam	SMS Pharmaceuticals Limited	-	-
Meloxicam	Hangzhou Verychem Science and Technology Co., Ltd.	-	-
Meloxicam	Technodrugs and Intermediates (P) Ltd.	-	-
Mobicox	Boehringer Ingelheim	-	-
Flexidol	Raffo	-	-
Flogoten	Montpellier	-	-
Miogesil	Glaxco-Wellcome	-	-

Trade Name	Manufacturer	Country	Year Introduced
Skudal	Schering-Plough	-	-
Bronax	Roemmers	-	-
Dominadol	Craveri	-	-
Tenaron	Sandoz	-	-
Telaroid	Cetus	-	-
Flexium	Sidus	-	-
Loxitenk	Biotenk	-	-
Meloxid	Klonal	-	-
Merapiran	Finadiet	-	-
Leutrol	Istituto De Angeli Ph. Spa	-	-
Leutrol	Abbott	-	-

Raw Materials

1,1-Dioxide of methyl 4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxylate
2-Amino-5-methylthiazole

Manufacturing Process

A mixture of 26.9 g (0.1 mol) of the 1,1-dioxide of methyl 4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxylate and 12.5 g (0.11 mol) of 2-amino-5-methylthiazole was refluxed in 4 liters of xylene for 24 hours in a nitrogen atmosphere. The methanol formed by the reaction was removed by means of a 4-A-molecular sieve mounted in a Soxhlet-extractor. The hot reaction solution was filtered. Upon cooling and standing overnight, the crude product separated out of the filtrate in the form of crystals (32.0 g, 91% of theory). After recrystallization from ethylene chloride 26.0 g (74% of theory) of 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide were obtained; M.P.: 254°C (decomp.).

References

Trummlitz G., Engel W., Seeger E., Engelhardt G.; US Patent No. 4,233,299; November 11, 1980; Assigned to Boehringer Ingelheim GbH (DE)

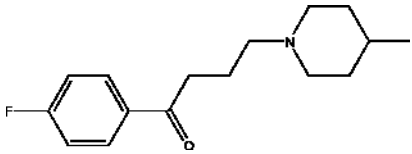
MELPERONE

Therapeutic Function: Neuroleptic

Chemical Name: 1-(4-Fluorophenyl)-4-(4-methyl-1-piperidinyl)-1-butanone

Common Name: Flubuperone; Methylperone

Structural Formula:



Chemical Abstracts Registry No.: 3575-80-2; 1622-79-3 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Eunerpan	Nordmark	W. Germany	1965
Buronil	Ferrosan	Sweden	-

Raw Materials

γ-Chloro-p-fluorobutyrophenone
4-Methylpiperidine

Manufacturing Process

A solution or dispersion consisting of 20.1 g (0.1 mol) of γ-chloro-p-fluorobutyrophenone, 19.8 g (0.2 mol) of 4-methylpiperidine and 0.1 g of potassium iodide in 150 ml toluene is heated in a sealed glass tube for 15 hours at 100°C to 110°C. The potassium iodide and the 4-methylpiperidine hydrochloride formed in the reaction are separated by filtration and the solvent removed from the filtrate by evaporation in vacuum on a steam bath. The residue is distilled and the fraction obtained at 120°C to 125°C and at a pressure lower than 0.1 mm Hg is collected. The base is dissolved in ether and the 4-fluoro-γ-(4-methylpiperidino)-butyrophenone precipitated as the hydrochloride. The reaction product is purified by recrystallization in ethanol/ether.

Yield 22.0 g (73% of theory). MP 209°C to 211°C.

References

Merck Index 5645
Kleeman and Engel p. 552
I.N. p. 590
Hernestam, S.E.H., Sterner, N.O.B. and Lassen, J.; US Patent 3,816,433; June 11, 1974; assigned to A.B. Ferrosan (Sweden)

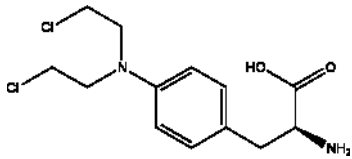
MELPHALAN

Therapeutic Function: Cancer chemotherapy

Chemical Name: 4-[Bis(2-chloroethyl)amino]-L-phenylalanine

Common Name: Alanine nitrogen mustard; L-Sarcolysine

Structural Formula:



Chemical Abstracts Registry No.: 148-82-3

Trade Name	Manufacturer	Country	Year Introduced
Alkeran	Burroughs-Wellcome	US	1964
Alkeran	Wellcome	UK	1964
Alkeran	Wellcome	W. Germany	1965
Alkeran	Wellcome	France	1966
Alkeran	Wellcome	Italy	1968
Alkeran	Wellcome	Japan	1979

Raw Materials

Sodium carbonate
Acetic anhydride
Cinchonidine
Hydrogen
Phosphorus oxychloride
Diethyl sodium phthalidomalonate
p-Nitrobenzoyl chloride
Hydrogen chloride
Ethylene oxide

Manufacturing Process

Diethyl sodium phthalimidomalonate (Barger and Weichselbaum, Organic Syntheses, 1943, Coll. Vol. II, 384) (6.52 g) was dissolved in boiling methyl ethyl ketone (80 ml) and a solution of p-nitrobenzyl chloride (3.44 g; 1.0 mol) in the same solvent (20 ml) was added, Sodium iodide (ca 0.5 g) dissolved in hot methyl ethyl ketone (10 ml) was introduced, and produced an immediate precipitation. The mixture was refluxed for 1.5 hours, cooled, filtered, evaporated under vacuum and the residual gum crystallized from ethanol. The di-ethyl-p-nitrobenzyl-phthalimidomalonate formed colorless prisms (88%), MP 103° to 105°C, sharpening to 104° to 105°C on recrystallizing from ethanol.

Diethyl-p-nitrobenzyl-phthalimidomalonate (70 g) and sodium carbonate (70 g) in water (700 ml) were refluxed overnight with mechanical stirring (to avoid bumping). The clear brown solution was acidified with hydrochloric acid and refluxing and stirring were continued for a further 40 minutes. The mixture was cooled and the colorless precipitate (31 g) collected. A second crop (18.5 g) was obtained on evaporation of the mother liquors. Crystallization from aqueous ethanol gave the compound N-carboxybenzoyl-p-

nitro-DL-phenylalanine as small needles, MP 198° to 200°C.

The N-carboxybenzoyl compound (2.7 g) was refluxed for 30 minutes with acetic anhydride (10 ml), the mixture taken to dryness (vacuum) and the residue heated with water. The cooled gummy product became granular on rubbing and crystallized from methyl ethyl ketone-petrol or aqueous ethanol in almost colorless needles, MP 184° to 186°C, of p-nitro-N-phthaloyl-DL-phenylalanine.

A solution of p-nitro-N-phthaloyl-DL-phenylalanine (1.0 g) in methanol (25 ml) and a solution of cinchonidine (0.865 g) in methanol (30 ml) were mixed. Crystallization soon set in. The mixture was left overnight, and the colorless needles (0.97 g), MP 209° to 210°C, collected. After two recrystallizations from methanol the cinchonidine salt of the D-acid had MP 211°C.

Evaporation of the mother liquors from the original cinchonidine experiment gave a gum which crystallized readily from aqueous ethanol in almost colorless needles (0.73 g), MP 191° to 192.5°C. Two recrystallizations from aqueous ethanol gave the cinchonidine salt of the L-acid, MP 192.5° to 194°C. To the salt (2.9 g) in warm ethanol (50 ml) was added water (50 ml) and a slight excess (ca 10 ml) of N aqueous sodium hydroxide. The mixture was diluted with water, cooled, filtered from the precipitated base and the filtrate acidified with hydrochloric acid. Refluxing with 2 N ethanolic hydrogen chloride yielded p-nitro-N-phthaloyl-L-phenylalanine ethyl ester, according to US Patent 3,032,585.

Then, as described in US Patent 3,032,584, ethyl N-phthaloyl p-nitrophenylalaninate (9.0 g) was hydrogenated in a mixture of ethyl acetate (120 g) and methanol (80 g) with a palladium-calcium carbonate (1% Pd) catalyst (1.4 g). When gas uptake was complete, the filtrate from the hydrogenation mixture was evaporated under reduced pressure. The residual gum was taken up in ether, the solution filtered, and a slight excess of a dry ethereal hydrogen chloride solution added slowly with stirring. The gummy precipitate became granular on rubbing and the ether-washed product was crystallized from ethyl acetate-acetone [1st crop, 2.8 g, MP 188° to 192°C (decomp.); 2nd crop, 3.9 g, MP 189° to 192°C (decomp.)] . Part of the first batch was recrystallized from ethyl acetate and gave very slightly tinted needles, MP 188° to 190°C (decomp.) of ethyl N-phthaloyl p-aminophenylalaninate hydrochloride.

The free base was obtained from the hydrochloride by adding a slight excess of dilute ammonium hydroxide to the aqueous solution, and crystallizing the product from aqueous methanol. A further recrystallization with charcoal treatment gave almost colorless needles, MP 110° to 112°C of ethyl N-phthaloyl p-aminophenylalaninate.

Ethyl N-phthaloyl p-aminophenylalaninate (3.15 g) (unrecrystallized) was suspended in water (50 g) and glacial acetic acid (30 g) added. To the clear solution, ethylene oxide (8.0 g) was added, the mixture allowed to stand for 17 hours, and then poured into water (350 g). The solution was neutralized with sodium hydrogen carbonate and the liberated gum extracted with ether. The ethereal solution was dried (magnesium sulfate) and evaporated. The residual gum (3.95 g) was dissolved in benzene (50 g) and the solution dried azeotropically by distilling off some of the solvent. Freshly distilled phosphorus

oxychloride (8 g) was added and the mixture heated under reflux for 30 minutes.

The solvent was evaporated off under reduced pressure, and the residual gum refluxed with concentrated hydrochloric acid (50 g) for 6 hours. The solution was allowed to cool overnight. It was filtered from the phthalic acid crystals, and freeze-dried, and to the pink residue was added acetone (160 g) and ethyl acetate (50 g). The mixture was left in the cold room overnight and the clear pink supernatant liquid poured off. The pink gummy hydrochloride remaining in the flask was dissolved in water (20 g), saturated sodium acetate solution added until precipitation was complete, and the product collected and dried in a desiccator. The crude p-bis-(2-chloroethyl)-aminophenylalanine (3.6 g) was crystallized from methanol giving colorless needles, MP 172° to 174°C (decomp.) of p-bis-(2-chloroethyl)-aminophenylalanine.

References

Merck Index 5646
Kleeman and Engel p. 552
PDR p. 733
OCDS Vol. 2 p. 120 (1980)
I.N. p. 590
REM p. 1151
Bergel, F. and Stock, J.A.; US Patent 3,032,584; May 1, 1962; assigned to National Research Development Corporation, England
Bergel, F. and Stock, J.A.; US Patent 3,032,585; May 1, 1962; assigned to National Research Development Corporation, England

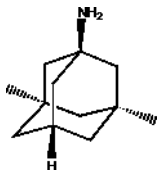
MEMANTINE

Therapeutic Function: Spasmolytic

Chemical Name: 3,5-Dimethyltricyclo[3.3.1.1^{3,7}]decanol-1-amine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 19982-08-2

Trade Name	Manufacturer	Country	Year Introduced
Akatinol	Merz	W. Germany	1983

Raw Materials

Acetonitrile	1,3-Dimethyladamantane
Bromine	Sodium hydroxide
Sulfuric acid	Hydrogen chloride

Manufacturing Process

A mixture of 24 g of 1,3-dimethyladamantane and 80 ml of bromine was refluxed for 6 hours. The reaction product mixture was cooled, taken up in about 200 ml of chloroform, and poured onto ice. The excess bromine was removed by adding sodium hydrosulfite. The chloroform layer was separated from the aqueous layer, dried, concentrated in vacuo, and distilled at reduced pressure to yield 30.5 g of product having a boiling point of about 118°C at 5-6 mm; n_D^{25} = 1.5169-1.5182. The product was identified by nuclear magnetic resonance (NMR) and elemental analyses as 1-bromo-3,5-dimethyladamantane.

A mixture of 20 g of 1-bromo-3,5-dimethyladamantane, 75 ml of acetonitrile, and 150 ml of concentrated sulfuric acid was allowed to react overnight at ambient room temperature. The red reaction product mixture was poured over crushed ice, and the white solid which precipitated was taken up in benzene and the benzene solution dried over sodium hydroxide pellets. The benzene solution was filtered from the drying agent and evaporated to dryness in vacuo to yield 18.2 g of product having a melting point of about 97°C and identified by infrared spectrum as 1-scetamido-3,5-dimethyladamantane.

A mixture of 18 g of 1-acetamido-3,5-dimethyladamantane, 38 g of sodium hydroxide, and 300 ml of diethylene glycol was refluxed for a period of 6 hours. The reaction product mixture was cooled and poured onto about 2,000 ml of crushed ice. The basic solution thus obtained was extracted five times with 250 ml portions of benzene and the aqueous layer was discarded. The combined benzene extracts were dried over sodium hydroxide and the dried benzene solution concentrated in vacuo to give a crude oil weighing 14 g and having n_D^{25} = 1.4941, A 4 g sample of the crude oil was dissolved in ether and the solution saturated with anhydrous hydrogen chloride. The solid which precipitated was filtered off and recrystallized from a mixture of alcohol and ether to yield product weighing 3.5 g and melting at 258°C.

It was identified by analysis as 1-amino-3,5-dimethyladamantane hydrochloride.

References

Merck Index A-7
DFU 1 (9) 427 (1976)
DOT 19 (6) 303 (1983)
I.N. p. 590
Mills, J. and Krumkalns, E.; US Patent 3,391,142; July 2, 1968; assigned to Eli Lilly and Co.

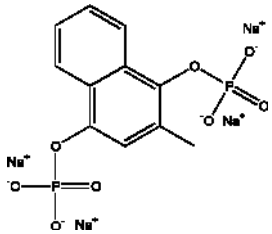
MENADIOL SODIUM DIPHOSPHATE

Therapeutic Function: Prothrombogenic vitamin

Chemical Name: 2-Methyl-1,4-naphthalenediol diphosphoric acid ester tetrasodium salt

Common Name:-

Structural Formula:



Chemical Abstracts Registry No.: 131-13-5; 84-98-0 (Phosphate)

Trade Name	Manufacturer	Country	Year Introduced
Synkayvite	Roche	US	1941
Analogue	Upjohn	US	1951
Kappadione	Lilly	US	1956
Carbocaina	Pierrel	Italy	-
Katij	Takeda	Japan	-
Thylokay	Squibb	-	-

Raw Materials

2-Methyl-1,4-naphthohydroquinone
Phosphorus oxychloride
Sodium hydroxide

Manufacturing Process

2,000 g 2-methyl-1,4-naphthohydroquinone diphosphoryl chloride (from the quinone and $POCl_3$) are dissolved in 2 liters ether and decomposed with 2 liters distilled water. The mixture is transferred to a separatory funnel and the aqueous layer separated from the ether layer, the latter being discarded. The aqueous layer is extracted with a further 2 liters of ether and again separated and discarded. The aqueous solution of the 2-methyl-1,4-naphthohydroquinone diphosphoric acid is extracted with successive portions of isobutyl carbinol in 500 cc quantities until the aqueous layer becomes almost colorless, after which this latter is discarded. The isobutyl carbinol solution is then concentrated to remove water and hydrochloric acid, and the crystalline residue neutralized with sodium hydroxide solution. The resulting solution of the sodium salt of 2-methyl-1,4-naphthohydroquinone diphosphoric

ester is extracted with two successive portions of 1 liter acetone each and the latter discarded. Methanol and acetone are then added, filtered, and the product brought to crystallization by heating. Crystals of the sodium salt of 2-methyl-1,4-naphthohydroquinone diphosphoric acid ester are sucked off. The substance contains much moisture of crystallization and is dried in vacuum until it contains 21-22% moisture of crystallization as determined by drying at 145°C at 2 mm vacuum.

References

Merck Index 5649
Kleeman and Engel p. 553
PDR p. 1502
I.N. p. 591
REM p. 1010
Solmssen, U.V.; US Patent 2,345,690; April 4, 1944; assigned to Hoffmann-LaRoche, Inc.

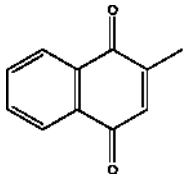
MENADIONE

Therapeutic Function: Prothrombogenic vitamin

Chemical Name: 1,4-Naphthalenedione, 2-methyl-

Common Name: Menadione; Menaphthone; Menaquinone; Methylnaphthochinon(um); Vitamin K_3

Structural Formula:



Chemical Abstracts Registry No.: 58-27-5

Trade Name	Manufacturer	Country	Year Introduced
Kappaxin	Sterling Winthrop	-	-
Kayquinone	Abbott	-	-
Thyloquinone	Bristol-Myers Squibb	-	-
K-Vitamin	Medica	-	-
Bilkaby	Bailly-Speab	-	-
Kapavit	Chropi	-	-
Kavitamin	Galenika	-	-
Vikaman	Disperga	-	-
Vit. K3	Agepha	-	-

Raw Materials

β-Methylnaphthalene
Sodium dichromate
Sulfuric acid

Manufacturing Process

Dissolve 100 g of β-methylnaphthalene in 500 g of carbon tetrachloride. Dissolve 500 g of commercial sodium dichromate in 175 g of hot water. Pour these two solutions into a 3-liter 3-necked flask, equipped with an efficient stirrer, a reflux condenser, and a dropping funnel. The flask should be put into a water bath held at 50°C. The contents of the flask agitated as violently as possible at adding (through the dropping funnel) 896 g of 77% (by weight) sulfuric acid. The rate of dropping depends on the efficiency of the reflux condenser. If the reaction tends to get out of hand due to overheating, cold water should be run into the water bath. After the addition of acid has been completed, keep the water bath at 70°C, for 1% to 2 hours. Then stop the agitation, cool the mixture and decant therefrom as much of the carbon tetrachloride layer as possible. Pour water into the flask; add 100 g more of carbon tetrachloride and stir for an additional ten minutes. The carbon tetrachloride layer will now settle to the bottom. The acid layer can be decanted and discarded, or worked up for those components desired. A complete separation of the acid from the carbon tetrachloride is effected by means of a separatory funnel. All of the carbon tetrachloride solutions are pooled and filtered to clarity through filter paper. The carbon tetrachloride may be distilled off from the quinone in a vacuum, using a water bath heated to 50°C.

The quinone is concentrated to a point where crystallization begins. Thereupon the concentrated solution is transferred to a beaker and allowed to crystallize at room temperature. Further crops of crystals are obtained by allowing the mother liquor to cool in an icebox, or by reducing it still further. If the β-methylnaphthalene starting material was pure, the 2-methyl-1,4-naphthoquinone obtained will have a melting point of 100°-104°C, without further purification. Vacuum sublimation has been found most effective to produce quinones of a very high purity. There is a rapid method of oxygenation of β-methylnaphthalene: 3 g of β-methylnaphthalene is dissolved in 180 grams of carbon tetrachloride. To this is added 15 grams of commercial sodium dichromate dissolved in 6 grams of hot water. The above solutions are placed in a 1-liter 3-necked flask equipped with an efficient stirrer, a dropping funnel, and a distilling condenser of large bore. The mixture is agitated energetically, and 25 grams of 77% sulfuric acid added through the dropping funnel. The time of addition need not be over 30 seconds. The flask is not subjected to exterior cooling, as the distilling carbon tetrachloride should hold the heat to the proper temperature, which should not exceed 85°C. After five minutes the reaction may be discontinued and the product handled similarly to the method outlined in above. The yield of 2-methyl-1,4-naphthoquinone will be around 80% of theoretical by the use of this rapid method.

References

Hyman J. et al; US Patent No. 2,402,226; June 18, 1946; Assigned to Velsicol Corporation, Chicago, Ill., a corporation of Illinois

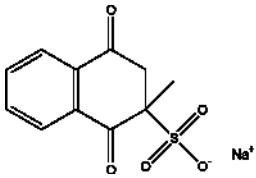
MENADIONE SODIUM BISULFITE

Therapeutic Function: Prothrombogenic vitamin

Chemical Name: 2-Naphthalenesulfonic acid, 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-, sodium salt

Common Name: Menachinonum natrium bisulfurosum; Menadione sodium bisulfite; Menadionnatriumbisulfit; Menaphthone sodium bisulphite; Vikasol(um)

Structural Formula:



Chemical Abstracts Registry No.: 130-37-0

Trade Name	Manufacturer	Country	Year Introduced
Kavitol	Lannacher Heilmittel	-	-
Kaergona	Ibys	-	-
Libavit	Liba	-	-
Vitaminum	Polfa Warszawa	-	-

Raw Materials

2-Methyl-1,4-naphthoquinone
Sodium bisulfite

Manufacturing Process

The 2-naphthalenesulfonic acid, 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-, sodium salt, trihydrate can be prepared by mixing the 2-methyl-1,4-naphthoquinone with the bisulphite salt in the presence of water. Ordinarily gentle warming of the aqueous mixture is preferred to facilitate solution. The mixture of 2-methyl-1,4-naphthoquinone (250 mg; 1 molar equivalent); sodium bisulphite (149 mg; 1 molar equivalent); distilled water (250 ml) or 2-methyl-1,4-naphthoquinone (250 mg; 1 molar equivalent); potassium bisulphate (349 mg; 2 molar equivalent); distilled water 250 ml may be used. These examples representing preferred ratios of ingredients are merely illustrative and are not to be interpreted as limiting.

The bisulphite addition compounds have been found to be stable in sunlight and also to be heat stable. Tests, for example, carried out in ampoules have shown aqueous solutions of the compounds not to be decomposed after exposure to a month's sunlight, while other tests have shown the solutions of

such compounds to retain their original potency (a) when stored in an oven at 60°C for 15 days or (b) when sterilized at 15 pounds for 0.5 hour in an autoclave at about 122°C. These properties emphasize the radical differences between the stable salts and the properties of 2-methyl-1,4-naphthoquinone, the characteristic instability of which is illustrated by its sensitivity, i. e., decomposition, when exposed to light.

The bisulphite addition compounds have a vitamin K activity equal to that of the 2-methyl-1,4-naphthoquinone contained in the molecule. The compounds, although suitable for oral administration, are particularly adaptable in aqueous solution for parenteral administration in the treatment of hemorrhagic conditions.

References

Moore M. B. et al; US Patent No. 2,367,302; Jan. 16, 1945; Assigned to Abbott Laboratories, North Chicago, Illinois

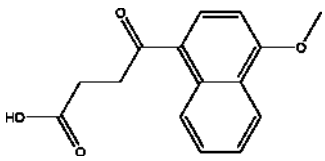
MENBUTONE

Therapeutic Function: Choleretic

Chemical Name: 4-Methoxy-6-oxo-1-naphthalene butanoic acid

Common Name: Methonaphthone

Structural Formula:



Chemical Abstracts Registry No.: 3562-99-0

Trade Name	Manufacturer	Country	Year Introduced
Hepalande	Delalande	W. Germany	1977
Sintobilina	A.F.I.	Italy	-

Raw Materials

α-Methoxynaphthalene
Succinic anhydride
Aluminum chloride
Hydrogen chloride
Sodium carbonate

Manufacturing Process

395 parts of (α-methoxynaphthalene and 265 parts of succinic anhydride are dissolved in 8,000 parts of dry benzene at room temperature. The resulting solution is stirred and 710 parts of anhydrous aluminum chloride are added over a period of twenty minutes. During the addition the temperature of the reaction mixture rises to about 60°C to 70°C. After the addition the reaction mixture is stirred for fifteen or twenty minutes at 60°C to 70°C and then refluxed for one hour. The hot reaction mixture is then poured onto a mixture of 5,000 parts of ice and 900 parts of concentrated hydrochloric acid. The benzene is removed by steam distillation and the hot aqueous residue is filtered to remove the insoluble β-(1-methoxy-4-naphthoyl)-propionic acid. The residue of the latter is dried and then dissolved in 16,000 parts of hot water containing 300 parts of sodium carbonate. The hot solution is treated with activated charcoal, filtered while hot, chilled and acidified. The residue of purified acid is collected on a filter, washed with water, and dried at 65°C. A yield of 552 parts of purified β-(1-methoxy)-4-naphthoyl)propionic acid, melting at 172°C to 173°C is obtained.

References

Merck Index 5656
I.N.p. 592
Burtner, R.R.; US Patent 2,623,065; December 23, 1952; assigned to G.D. Searle and Co.

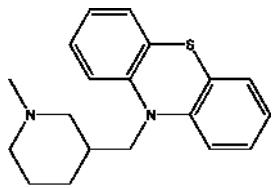
MEPAZINE

Therapeutic Function: Tranquilizer

Chemical Name: 10-[(1-Methyl-3-piperidinyl)methyl]-10H-phenothiazine

Common Name: Mepasin; Pecazine

Structural Formula:



Chemical Abstracts Registry No.: 60-89-9; 2975-36-2 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Pacatal	Warner Lambert	US	1957
Pacatal	Promonta	W. Germany	-

Trade Name	Manufacturer	Country	Year Introduced
Lacumin	Lundbeck	-	-
Ravenil	Caber	Italy	-

Raw Materials

1-Methyl-3-bromomethylpiperidine
Phenothiazine
Sodium amide
Acetic acid

Manufacturing Process

A 500 cc flask equipped with a mechanical stirrer, reflux condenser and a soda-lime tube was filled with 230 cc of absolute xylene, 27.5 g of 1-methyl-3-bromomethylpiperidine, 53.3 g of phenothiazine and 14.2 g of finely powdered sodium amide, and the solution was heated under reflux for 6 hours. After cooling water was added and the batch was extracted with ether. As the hydrochloric acid salt of the obtained phenothiazine derivative is difficultly soluble in water, the further processing was carried out by way of the acetate. The etheric solution was extracted several times in a separating funnel with dilute acetic acid. The combined aqueous extracts were basified, extracted with ether, dried with potassium carbonate and, after removal of the ether, distilled in vacuo.

Yield = 64%; boiling point 230°C to 235°C at 4 mm; melting point of hydrochloride is 180°C to 181°C.

References

Merck Index 5672
Kleeman and Engel p. 689
I.N. p. 735
Schuler, W.A.; US Patent 2,784,185; March 5, 1957; assigned to Chemische Fabrik Promonta GmbH

MEPENZOLATE BROMIDE

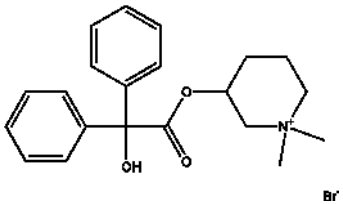
Therapeutic Function: Spasmolytic

Chemical Name: 3-[(Hydroxydiphenylacetyl)oxy]-1,1-dimethylpiperidinium bromide

Common Name: N-Methyl-3-piperidylbenzilate methobromide

2156 Mepenzolate bromide

Structural Formula:



Chemical Abstracts Registry No.: 76-90-4

Trade Name	Manufacturer	Country	Year Introduced
Cantil	Merrell National	US	1956
Cantilon	Draco	Sweden	-
Colibantil	Tosi-Novara	Italy	-
Colum	Jamco	Italy	-
Eftoron	Maruko	Japan	-
Gastropodil	Fabo	Italy	-
Sachicoron	Zensei	Japan	-
Tendalin	Nihon Yakuhin	Japan	-
Tralanta	Sawai	Japan	-
Trancolon	Fujisawa	Japan	-

Raw Materials

N-Methyl-3-chloropiperidine
Benzilic acid
Methyl bromide

Manufacturing Process

A mixture containing 8 g (0.06 mol) of N-methyl-3-chloro-piperidine and 13.6 g (0.06 mol) of benzilic acid in 50 cc of anhydrous isopropyl alcohol was refluxed for 3 days; the isopropyl alcohol was removed by distillation in vacuo, the residue treated with dilute aqueous hydrochloric acid and the aqueous acid mixture extracted repeatedly with ether. The aqueous phase was separated, made strongly alkaline with 20% aqueous sodium hydroxide and extracted with ether. The ether extracts were dried with potassium carbonate and distilled; the product was collected at 175° to 176°C (0.03 mm), yield 11.5 g (59 %).The ester base thus prepared was then dissolved in 75 cc of isopropyl alcohol and 3.4 g (0.037 mol) methyl bromide added. The reaction mixture was allowed to stand at 30°C for 2 days and the product isolated by filtration, yield, 13 g (87%), MP 228° to 229°C dec.

References

Merck Index 5673
Kleeman and Engel p. 555

PDR p. 1223
I.N. p. 593
REM p. 916
Biel, J.H.; US Patent 2,918,408; December 22, 1959; assigned to Lakeside Laboratories, Inc.

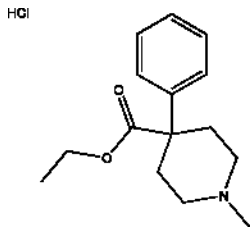
MEPERIDINE HYDROCHLORIDE

Therapeutic Function: Narcotic analgesic

Chemical Name: 1-Methyl-4-phenyl-4-piperidinecarboxylic acid ethyl ester hydrochloride

Common Name: Isonipecaine hydrochloride; Pethidine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 50-13-5; 57-42-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Dolosal	Specia	France	1943
Dolantin	Hoechst	W. Germany	1943
Demerol	Winthrop	US	1944
Algil	Maggioni	Italy	-
Alodan	Gerot	Austria	-
Centralgin	Amino	Switz.	-
Demer-Idine	Sabex	Canada	-
Dolanquifa	Uquifa	Spain	-
Dolcontral	Arzneimittelwerk Dresden	E. Germany	-
Dolestine	Teva	Israel	-
Doloneurin	O.P.G.	Netherlands	-
Dolopethin	Gattiker	Switz.	-
Medfina	Carlo Erba	-	-
Pethidine Roche	Roche	UK	-
Supplosal	Specia	France	-

Raw Materials

Thionyl chloride
Sodium amide
Sulfuric acid
Hydrogen chloride
Diethanol methylamine
Benzyl cyanide
Ethanol

Manufacturing Process

80 parts of finely pulverized sodium amide are added in portions each of about ½ of the entire quantity, while stirring and cooling in a suitable manner, to a mixture of 756 parts of methyl-di(β-chloroethyl)-amine (prepared from di-ethanol-methylamine by means of thionyl chloride), 117 parts of benzyl cyanide and 600 parts of toluene. The reaction sets in at once at room temperature. The temperature is maintained between 30° and 40°C; when self-heating no longer occurs a further portion of the sodium amide is introduced. During the reaction heat is liberated and gaseous ammonia escapes.

The mixture is then slowly heated to the boiling point of toluene and kept boiling for one hour under reflux. After the mixture has been allowed to cool the sodium chloride which precipitates is separated by extraction with water. The solution of toluene is then extracted with dilute hydrochloric acid. From the hydrochloric acid extract the basic substance is separated in the form of an oil by means of caustic soda solution and is introduced into ether. The ethereal solution is dried with the aid of potassium carbonate and then distilled.

Under a pressure of 4.5 ml the 1-methyl-4-phenyl-piperidine-4-carboxylic acid nitrile passes over at a temperature of about 148°C in the form of a colorless oil; under a pressure of 6 ml it passes over at about 158°C. After having been allowed to cool the distillate solidifies completely to form a crystalline mass. Its solidification point is at 53°C; the yield amounts to about 135 parts, that is, about 2/3 of the theoretical yield. When recrystallized from isopropyl alcohol the hydrochloride of the nitrile forms colorless crystals, readily soluble in water and melting at 221° to 222°C.

The nitrile may best be saponified with methyl alcoholic potash while heating to 190° to 200°C with application of pressure. After the methyl alcohol has evaporated the salt is introduced into water and by the addition of dilute mineral acid until the alkaline reaction to phenolphthalein has just disappeared, the amphoteric 1-methyl-4-phenyl-piperidine-4-carboxylic acid is precipitated while hot in the form of a colorless, coarsely crystalline powder. When dried on the water bath the acid still contains 1 mol of crystal water which is lost only at a raised temperature. The acid melts at 299°C. Reaction with ethanol yields the ester melting at 30°C and subsequent reaction with HCl gives the hydrochloride melting at 187° to 188°C.

References

Merck Index 5674
Kleeman and Engel p. 707
PDR pp. 872, 1908, 1959, 1989
OCDS Vol. 1 p. 300 (1977); 2, 328 (1980) and 3, 116 (1984)

I.N. p. 750
REM p. 1108
Eisleb, O.; US Patent 2,167,351; July 25, 1939; assigned to Winthrop Chemical Company, Inc.

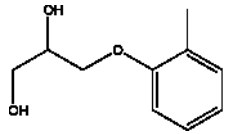
MEPHENESIN

Therapeutic Function: Muscle relaxant

Chemical Name: 3-(2-Methylphenoxy)-1,2-propanediol

Common Name: o-Cresyl glycerol ether; Glyceryl o-tolyl ether; Cresoxypropanediol; Cresoxydiol

Structural Formula:



Chemical Abstracts Registry No.: 59-47-2

Trade Name	Manufacturer	Country	Year Introduced
Tolserol	Squibb	US	1948
Oranixon	Organon	US	1949
Avosyl	Schenley	US	-
Curaresin	Kyoto	Japan	-
Decontractyl	Robert and Carriere	France	-
Glyotol	US Standard	US	-
Myanesin	B.D.H.	UK	-
Myanol	Chugai	Japan	-
Myocuran	Deutsches Hydrierwerk	E. Germany	-
Myoserol	Sankyo	Japan	-
Myoxane	Ascher	US	-
Noctynol	Moore	UK	-
Prolax	Cole	US	-
Relaxar	Bouty	Italy	-
Rhex	Hobein	W. Germany	-
Spasmolyn	Heun	US	-
Tolosate	Brewer	US	-
Tolulox	Miller	US	-
Tolyspaz	Chicago Pharmacal	US	-

Raw Materials

3-Cresol
Glycerol

Manufacturing Process

Into an iron or copper reaction vessel having an efficient stirring device and furnished with a refluxing column and condenser, were charged 330 lb of high quality meta-cresol and 150 lb of glycerol, together with 25 lb of sodium acetate to serve as the catalyst in the reaction. The reaction mixture, of this composition, was then heated to 250°C. The water of the reaction distilled off during the heating as the ether formation proceeded, this removal of water from the reaction chamber being promoted by the presence of the excess of phenol, some of which also continued to distill over. Towards the end of the reaction, after about 12 hours, when about 60% of the glycerol had been converted, at which point the reaction slowed down and the distillate was mainly cresol, the batch was cooled and 50 gallons of water were added to it along with 150 lb of xylene. As the result of these additions and the cooling down of the material the batch stratified into an aqueous layer containing unreacted glycerol, polyglycerols and sodium acetate, and a nonaqueous layer containing the ethers that had been formed in the reaction, together with unreacted cresol which remained in the reaction chamber, dissolved in the xylene that had been added to the batch. The aqueous layer was then separated and the water content removed therefrom by evaporation to a degree suitable for the recovery of the glycerol and sodium acetate contents of the layer, for their reuse in the process in a succeeding batch therein. The separated nonaqueous layer containing the ethers was distilled to recover the xylene and cresol contents respectively as the early fractions of the layer thus subjected to distillation. The cresol thus recovered, together with the cresol recovered from the distillate obtained during the heating of the reaction mixture, was returned to the process for reuse in a succeeding batch. Redistillation of the ether mixture recovered is usually necessary and desirable, particularly from the point of view of removing last traces of cresol therefrom. The yield of mixed ethers in this example was about 200 lb, in the relative proportions stated of about 70 parts of monoether to 30 of diether.

References

Merck Index 5675
Kleeman and Engel p. 556
OCDS Vol. 1 p. 118 (1977)
I.N. p. 593
Carroll, M.F. and A. Boake Roberts and Co., Ltd.; British Patent 589,821; July 1, 1947

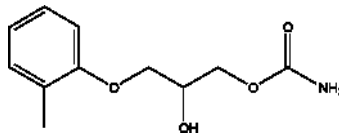
MEPHENESIN CARBAMATE

Therapeutic Function: Muscle relaxant

Chemical Name: 3-(2-Methylphenoxy)-1,2-propanediol 1-carbamate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 533-06-2

Trade Name	Manufacturer	Country	Year Introduced
Tolseram	Squibb	US	1954
Kinavosyl	Schenley	US	-

Raw Materials

3-o-Toloxy-1,2-propanediol
Phosgene
Ammonia

Manufacturing Process

A solution of 32 g (0.30 mol) phosgene in 200 ml benzene is added dropwise at 30°C to a stirred solution of 53.5 g (0.32 mol) 3-o-toloxy-1,2-propanediol in 400 ml benzene. The mixture is stirred for an hour after the addition is completed, and a solution of 39 g of dimethylaniline in 100 ml benzene is then added, and stirring continued for a half-hour. Ice water (about one-third volume) is then added, and the benzene layer formed is separated and stirred with 500 mi concentrated ammonia at 5°C for six hours. The precipitated solid (weighing about 55 g) is recovered and recrystallized from water. The product thus obtained in a yield of about 53 g is 3-(o-toloxy)-2-hydroxypropyl carbamate: it is a crystalline solid melting at about 93°C, and having a lower water-solubility and higher oil-solubility than 3-o-toloxy-1,2-propanediol.

References

Merck Index 5676
Kleeman and Engel p. 556
OCDS Vol. 1 p. 118 (1977)
I.N. p. 593
Lott, W.A. and Pribyl, E.; US Patent 2,609,386; September 2, 1952; assigned to E.R. Squibb and Sons

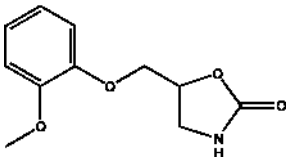
MEPHENOXALONE

Therapeutic Function: Tranquilizer

Chemical Name: 5-[(o-Methoxyphenoxy)methyl]-2-oxazolidinone

Common Name: Methoxadone

Structural Formula:



Chemical Abstracts Registry No.: 70-07-5

Trade Name	Manufacturer	Country	Year Introduced
Trepidone	Lederle	US	1961
Tranpoise	Robins	US	1962
Lenetran	Lakeside	US	1962
Xerene	Martinet	France	1964
Control-Om	O.M.	Switz.	-
Dorsiflex	Syntex-Medical	Switz.	-
Placidex	Toraude	-	-
Riself	Gibipharma	Italy	-

Raw Materials

3-o-Methoxyphenoxy-2-hydroxy-1-propylcarbamate
Urea

Manufacturing Process

A mixture of 24.1 g (0.10 mol) of 3-o-methoxyphenoxy-2-hydroxy-1-propyl carbamate and 6.0 g (0.10 mol) of urea was heated rapidly to the temperature range of 180°C to 200°C, and maintained there for five hours. The reaction melt was poured into 50% ethyl alcohol, from which the product crystallized as a white solid. The crude yield was 18.3 g (82%); melting point 131.5% to 137°C. Crystallization from water and 95% alcohol gave 9.0 g (40.3 %) of pure 5-o-methoxyphenoxymethyl-2-oxazolidone; melting point 141°C to 143°C. This melting point was not depressed when the material was mixed with an authentic sample. In additional runs acetone was used instead of ethyl alcohol with equivalent results.

It was found that when the heating time was reduced to three hours and a reaction temperature of 190°C to 200°C was maintained, equivalent yields (40 to 50%) were obtained, but that the yields were appreciably lowered when the heating time was further reduced to two hours. It was also found that when the temperature was lowered to the range of 170°C to 180°C the yield was significantly lowered.

When the material was isolated by extraction with chloroform and distillation, the yield of pure material was 58.5%.

References

Merck Index 5679
OCDS Vol. 1 p. 119 (1977)
I.N. p. 593
Lunsford, C.D.; US Patent 2,895,960; July 21, 1959; assigned to A.H. Robins Co., Inc.

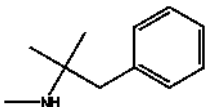
MEPHENTERMINE

Therapeutic Function: Adrenergic (vasopressor)

Chemical Name: N,α,α-Trimethylbenzene ethanamine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 100-92-5

Trade Name	Manufacturer	Country	Year Introduced
Wyamine	Wyeth	US	1947

Raw Materials

2-(N-Methylamino)-2-methyl-1-phenyl-1-propanol
Thionyl chloride
Hydrogen

Manufacturing Process

0.5 g of 2-(N-methylamino)-2-methyl-1-phenyl-1-propanol was treated with 1 cc of thionyl chloride at room temperature. A vigorous reaction set in. The gummy material was stirred with a small amount of petroleum ether and allowed to stand overnight. The brown crystalline solid after washing with petroleum ether was recrystallized from a small amount of absolute alcohol with addition of charcoal followed by filtration. On dilution with several volumes of ether and refrigeration white granular crystals of 1-chloro-2-(N-methamino)-2-methyl-1-phenyl propane hydrochloride were deposited.

250 mg of 1-chloro-2-(N-methylamino)-2-methyl-1-phenyl propane hydrochloride was dissolved in 2 cc of warm methanol and hydrogenated in the presence of 250 mg of palladium barium carbonate catalyst with provision for the absorption of the carbon-dioxide formed. When the theoretical amount of hydrogen had been taken up the mixture was filtered to remove the catalyst, concentrated to small volume and extracted with ether. After separating the ether the residue was further concentrated yielding a white crystalline solid. This solid on solution in water, strongly alkalizing, extraction with ether and removal of the ether yielded 2-(N-methylamino)-2-methyl-1-phenyl propane identified as the picrate by melting point 155°C to 156°C and mixed melting point 154.0°C to 154.5°C, with an authentic sample melting at 150°C to 153°C.

References

Merck Index 5680
OCDS Vol. 1 p. 72 (1977)
I.N. p. 593
REM p. 887 Bruce, W.F., Szabo, J.L. and Tubis, S.; US Patent 2,597,445; May 28, 1952; assigned to Wyeth, Inc.

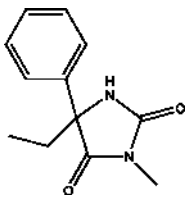
MEPHENYTOIN

Therapeutic Function: Anticonvulsant, Antiepileptic

Chemical Name: 2,4-Imidazolidinedione, 5-ethyl-3-methyl-5-phenyl-

Common Name: Mefenetoin; Mephenetoinum; Methantoinum; Mephenytoin; Methoin; Methylphenetoin; Methylphenylaethylhydatoinum

Structural Formula:



Chemical Abstracts Registry No.: 50-12-4

Trade Name	Manufacturer	Country	Year Introduced
Mesantoin	Sandoz	-	-
Sedantoinal	Sandoz	-	-
Gerot-Epilan	Gerot	-	-
Sacerno	EGYT	-	-

Raw Materials

Sodium
5-Phenylcyanacetamide
Bromine
Sodium bisulfite

Manufacturing Process

23 parts sodium was dissolved in 300 parts of ethanol and added to 160 parts of 5-phenylcyanacetamide in 750 parts of ethanol. A mixture was cooled straight away and a sodium salt of amide precipitated as a white powder. 200 parts of ethyl iodide was added to this mixture and heated for 1.5 hours. The ethanol was distilled off, water was added to the residue and rapidly hardened oil precipitated. After recrystallization from ethanol, 5-ethyl-5-phenylacetamide afforded; MP: 116°C.

100 parts of sodium hydroxide was solved in 500 parts of water and added to 83 parts of bromine by cooling. 5-Ethyl-5-phenylacetamide was added to above prepared mixture. It dissolved quickly, whereupon all mass was heated some time, cooled and stood at room temperature some hours. Then a solution of sodium bisulfite was added before the formed precipitate dissolved. The reaction mixture was filtered, the filtrate was acidified to give rapidly hardened oil. After recrystallization from ethanol 5-ethyl-3-methyl-5-phenyl-hydantoin was yielded as the bright needles; MP: 201°-202°C.

References

Chemishe Fabrik von Heyden Akt-Ges. in Radedeul b. Dresden; D.R. Patent No. 308,508; May 1914

MEPICYCLINE

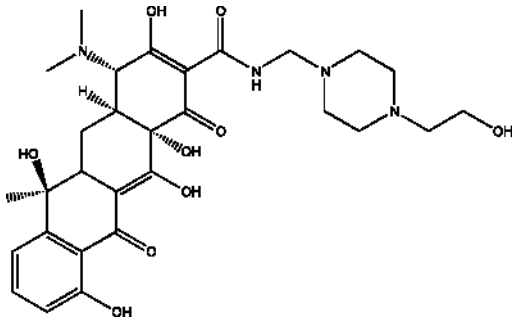
Therapeutic Function: Antimicrobial

Chemical Name: 4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-N-[[4-(2-hydroxyethyl)-1-piperazinyl] methyl]-6-methyl-1,11-dioxo-2-naphthacenecarboxamide

Common Name: N-[[4-(2-Hydroxyethyl)-1-piperazinyl]methyl]tetracycline; Pipacycline

Trade Name	Manufacturer	Country	Year Introduced
Sieromicin	Sierochimica	Italy	1962
Ambra-Vena	Lepetit	-	-
Boniciclina	Boniscontro-Gazzone	Italy	-
Tetrasolvina	N.C.S.N.	Italy	-
Valtomicina	Midy	-	-

Structural Formula:



Raw Materials

N-(β-Hydroxyethyl)diethylene diamine
Paraformaldehyde
Tetracycline

Manufacturing Process

1.55 g p-formaldehyde were added to a solution of 7 g N-(β-hydroxyethyl)-diethylene diamine in 150 cc isopropanol and the whole was heated to 60°C for 30 minutes, to obtain complete dissolution; after cooling the solution to 40°C, 22.2 g of anhydrous tetracycline base were added as a fine powder and the reaction was allowed to proceed for 3 hours with agitation and while passing through a current of dry nitrogen; the solution was then filtered on a Buchner funnel and the filter cake was washed twice with 20 cc isopropanol; the crystalline cake was resuspended in 100 cc anhydrous ether, again filtered and washed 3 times with 50 cc anhydrous ether; finally, it was dried in vacuo and 28.6 g of product were obtained, namely a yield of 98%.

The characteristics of this product are as follows. It is a pale yellow, nonodorous, slightly bitter, crystalline powder, very soluble in water (>1.5 g/cc), soluble in methanol and formamide, slightly soluble in ethanol and isopropanol, insoluble in ether, benzene and chloroform; MP 162° to 163°C with decomposition (uncorrected).

References

Merck Index 7325
I.N. p. 775
Gradnik, B., Pedrazzoli, A. and Cipelletti, G.; US Patent 3,149,114; September 15, 1964; assigned to Societe d'Etudes de Recherches et d'Applications Scientifiques et Medicales, France

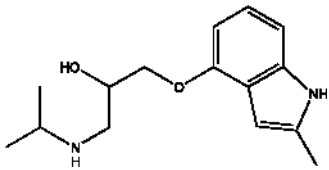
MEPINDOLOL

Therapeutic Function: Beta-adrenergic blocker

Chemical Name: 4-(2-Hydroxy-3-isopropylaminopropoxyl)-2-methylindole

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 56396-94-2 (Sulfate salt)

Trade Name	Manufacturer	Country	Year Introduced
Corindolan	Schering	W. Germany	1980

Raw Materials

4-Benzyloxy-2-dimethylamino-methylindole
Hydrogen
Epichlorohydrin
Isopropylamine

Manufacturing Process

The 4-hydroxy-2-methylindole (MP 112°C to 115°C from benzene/ethyl acetate), used as starting material, may be obtained by hydrogenation of 4-benzyloxy-2-dimethylamino-methylindole (MP 117°C to 120°C from benzene) in the presence of a palladium catalyst (5% on aluminum oxide).

11.6 g of 4-hydroxy-2-methylindole are added to a solution of 3.1 g of sodium hydroxide in 150 cc of water, and then 12.4 cc of epichlorhydrin are added while stirring and in an atmosphere of nitrogen. The reaction mixture is further stirred at room temperature for 24 hours, is extracted 4 times with methylene chloride, and the combined organic layers which have been dried over magnesium sulfate are concentrated by evaporation at reduced pressure. The resulting residue is taken up in 150 cc of dioxane and 50 cc of isopropylamine, and the mixture is heated to the boil for 6 hours. The reaction mixture is evaporated to dryness at reduced pressure, the residue is shaken 4 times between ethyl acetate and a 1 N aqueous tartaric acid solution, and a 5 N caustic soda solution is then added to the combined tartaric acid phases until an alkaline reaction is obtained. The alkaline solution is then shaken out 6 times with methylene chloride, the combined extracts are dried over magnesium sulfate, and the solvent is evaporated in a vacuum. The oily viscous residue may be crystallized from ethyl acetate. The title compound

has a MP of 95°C to 97°C.

References

Merck Index 5684
DFU 3 (5) 381 (1978)
DOT 17 (10) 426 (1981) and 18 (10) 551 (1982)
I.N. p. 594
Troxler, F. and Hofmann, A.; British Patent 1,260,907; January 19, 1972; assigned to Sandoz, Ltd.

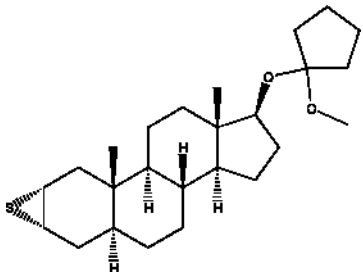
MEPITIOSTANE

Therapeutic Function: Antiestrogen

Chemical Name: 17β-(1-Ethoxycyclopentyl)oxy-2α,3α-epithio-5α-androstane

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 21362-69-6

Trade Name	Manufacturer	Country	Year Introduced
Thioderon	Shionogi	Japan	1979

Raw Materials

2α,3α-Epithio-5α-androstan-17β-ol
Methoxycyclopentene

Manufacturing Process

A mixture of 1.759 g of 2α,3α-epithio-5α-androstan-17β-ol, 2.3 ml of 1-methoxycyclopentene, 20 mg of pyridine salt of p-toluenesulfonic acid and 20 ml of t-butanol is stirred for 4 hours at room temperature. The reaction

mixture is poured into an aqueous solution of sodium carbonate and the whole extracted with dichloromethane. The extract is dried over anhydrous sodium sulfate and evaporated to remove solvent. Purification of the residue by chromatography over alumina gives 1.487 g of 17β-(1-methoxycyclopentyl) oxy-2α,3α-epithio-5α-androstane. Yield 68.2%. MP 98°C to 101°C.

References

Merck Index 5687
DFU 3 (4) 311 (1978)
Kleeman and Engel p. 557
I.N. p. 594
Komeno, T.; US Patent 3,567,713; March 2, 1971; assigned to Shionogi and Co.

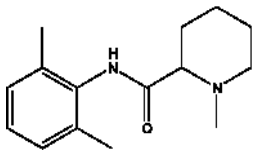
MEPIVACAINE

Therapeutic Function: Local anesthetic

Chemical Name: N-(2,6-Dimethylphenyl)-1-methyl-2-piperidinecarboxamide

Common Name: N-Methylpipecolic acid 2,6-dimethylanilide

Structural Formula:



Chemical Abstracts Registry No.: 96-88-8; 16452-56-5 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Carboraine	Winthrop	US	1960
Chlorocain	Pharmac. Mfg.	UK	-
Isocaine	Novocol	US	-
Meaverin	Woelm Pharma	W. Germany	-
Mepivastesin	Espe	W. Germany	-
Scandicain	Astra	Sweden	-
Tevacaine	Teva	Israel	-

Raw Materials

Ethyl bromide

Magnesium
N-Methylpipecolic acid ethyl ester
2,6-Dimethylaniline

Manufacturing Process

Ethyl magnesium bromide is prepared in the usual way by reacting 185 parts by weight of ethyl bromide in 800 parts of anhydrous ether with 37 parts by weight of magnesium turnings. Under vigorous stirring 121 parts of 2,6-dimethyl aniline are added at a rate depending on the vigor of the gas evaporation. When the evolution of gas has ceased, 85 parts by weight of N-methylpipecolic acid ethyl ester are added to the 2,6-dimethyl aniline magnesium bromide slurry. The mixture is refluxed for ½ hour with continued stirring, after which it is cooled down. Dilute hydrochloric acid is added carefully in order to dissolve and hydrolyze the magnesium compound formed.

The pH is adjusted to 5.5 and the water phase separated and extracted with additional ether in order to remove the surplus dimethyl aniline. After addition of an excess of ammonia to the solution, the reaction product, N-methylpipecolic acid 2,6-dimethyl anilide, is recovered by extraction with isoamyl alcohol. The isoamyl alcohol solution is evaporated to dryness, the product dissolved in dilute hydrochloric acid, treated with charcoal and reprecipitated with NaOH. N-methylpipecolic acid 2,6-dimethyl anilide is obtained in crystalline form.

References

Merck Index 5688
Kleeman and Engel p. 558
PDR pp. 824, 1906
OCDS Vol. 1 p. 17 (1977)
I.N. p. 594
REM p. 1052
af Ekenstam, B.T. and Egner, B.P.H.; US Patent 2,799,679; July 16, 1957; assigned to AB Bofors, Sweden
Pettersson, B.G.; US Patent 4,110,331; August 29, 1978; assigned to AB Bofors

MEPREDNISONE

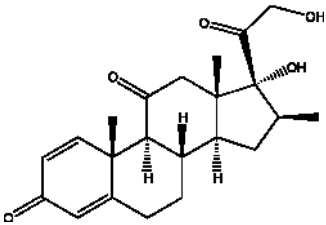
Therapeutic Function: Glucocorticoid

Chemical Name: 17,21-Dihydroxy-16β-methylpregna-1,4-diene-3,11,20-trione

Common Name: 16β-Methylprednisone

Chemical Abstracts Registry No.: 1247-42-3

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Betapar	Parke Davis	US	1970
Betalone	Lepetit	France	-
Betapred	Schering	US	-
Corti-Bi	Sidus	Italy	-

Raw Materials

16β-Methylprednisone-21-acetate
Potassium bicarbonate
Bacterium *Bacillus sphaericus var. fusifermis*
Nutrient broth

Manufacturing Process

16β-Methylprednisone 21-acetate (0.5 g), when hydrolyzed by means of aqueous alcoholic potassium bicarbonate yields 16β-ethylprednisone. An alternative method of the preparation of the compound of this example is as follows. Bacillus *sphaericus var. fusifermis* (A.T.C.C. 7055) is incubated on a nutrient agar (composed of Bacto-beef extract, 3 g; Bacto-peptone, 5 9; sodium chloride, 8 9; agar, 15 g; and tap water, 1 liter) for 24 hours at 28°C.

To 100 ml of a sterile nutrient broth (composed of Bacto-beef extract, 3 9; Bacto-peptone, 5 9; per liter of tap water) in a 300 ml flask is added one loopful of the incubated culture and the broth mixture is further incubated for 24 hours at 28°C on a shaking machine. The broth culture so obtained is employed as an inoculum (1%). Into each of ten flasks containing 100 ml of sterile nutrient broth is added 1 ml of the inoculum. The flasks are agitated on a rotary shaker for 8 hours at 28°C at 240 strokes per minute. After this growth period, a solution of 25 mg of 16β-methylcortisonein 0.5 ml of methanol is aseptically added to each flask which in turn is reshaken and incubated for an additional 24 hours. The final pH is 7.8.

The contents of the flasks are then combined and extracted 3 times with two liters of chloroform per extraction. The combined chloroform extracts are evaporated to dryness yielding 310 mg of crude product. The crude steroid is purified by chromatography on a chromatographic system described by G.M. Shull, Abstracts of Papers of the 126th Meeting of the American Chemical Society, December 12-17, 1954, page 9a, paper No. 24. Chromatographic evaluation shows a quantitative conversion of the starting material to the

diene when an authentic sample of the 16β-methylprednisone is used as a control. Alternatively, the crude product is recrystallized from acetone affording 225 mg of 16β-methylprednisone.

References

Merck Index 5689
Kleeman and Engel p. 558
I.N. p. 595
Rausser, R. and Oliveto, E.P.; US Patent 3,164,618; January 5, 1965; assigned to Schering Corporation

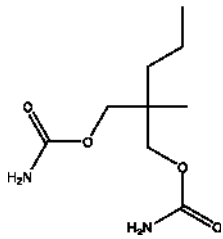
MEPROBAMATE

Therapeutic Function: Tranquilizer

Chemical Name: 2-Methyl-2-propyl-1,3-propanediol dicarbamate

Common Name: Procalmadiol; Procalmidol

Structural Formula:



Chemical Abstracts Registry No.: 57-53-4

Trade Name	Manufacturer	Country	Year Introduced
Equanil	Wyeth	US	1955
Miltown	Wallace	US	1955
Meprotabs	Wallace	US	1957
Meprospan	Wallace	US	1958
Viobamate	Rowell	US	1963
Meprocon	Consol. Midland	US	1964
Canquil	Canfield	US	1964
Klort	Lemmon	US	1964
Equanil	Clin Midy	France	1967
SK-Bamate	SKF	US	1971
Amepromamat	Arcana	Austria	-
Amosene	Ferndale	US	-

Trade Name	Manufacturer	Country	Year Introduced
Aneural	Wyeth	W. Germany	-
Ansietan	Italfarmaco	Italy	-
Ansiowas	Wassermann	Spain	-
Artolon	Roter	Netherlands	-
Atraxin	Daiichi	Japan	-
Carb-A-Med	Chemieprodukte	Austria	-
Coprobate	Coastal	US	-
Cyrpon	Tropon	W. Germany	-
Dabrobamat	Dabrowski	W. Germany	-
Dapaz	Alter	Spain	-
Deprol	Wallace	US	-
Dormabrol	Kwizda	Austria	-
Dystoid	Makara	W. Germany	-
Ecuanil	Orfi	Spain	-
Edenal	Wassermann	Italy	-
Epikur	Agepha	Austria	-
Equagesic	Wyeth	US	-
Erina	Sumitomo	Japan	-
Gene-Bamate	Franca	Canada	-
Harmonin	Yoshitomi	Japan	-
Kesso-Bamate	McKesson	US	-
Lan-Dol	Bio-Chimique	Canada	-
Marbate	Mardale	US	-
Meditran	Medic	Canada	-
Mepavlon	I.C.I.	UK	-
Meprate	DDSA	UK	-
Mepriam	Lennon	US	-
Mepro	Rekah	Israel	-
Meproban	Draco	Sweden	-
Meprocon CMC	Consol. Midland	US	-
Meprodil	Streuli	Switz.	-
Meprodiol	Pirri	Italy	-
Meprol	Lokman	Turkey	-
Mepron	Choseido	Japan	-
Mepron	Hamilton	Australia	-
Mepronel	Heather Drug	US	-
Meprosa	Chemipharma	W. Germany	-
Meprotil	Brunner-Tillman	US	-
Meriprobate	Meriot	Canada	-
Microbamat	Werfft	Austria	-
Midixin	Reid-Provident	US	-
Miltaun	Mack	W. Germany	-
Misedant	Lemmon	US	-
M.P. Trantabs	Martin-Phillips	US	-
My-Trans	Heather Drug	US	-
Neo-Tran	Neo	Canada	-
Nervonus	Orion	Finland	-

Trade Name	Manufacturer	Country	Year Introduced
Neuramate	Halsey	US	-
Novamato	Torlan	Spain	-
Novomepro	Novopharm	Canada	-
Oasil	Simes	Italy	-
Paxin	Pierrel	Italy	-
Pensive	Norbrook	UK	-
Perequil	Lepetit	Italy	-
PMB Ayerst	Ayerst	US	-
Probasan	I.C.N.	Canada	-
Quietidon	Pharma. Farm. Spec.	Italy	-
Relaksin	Deva	Turkey	-
Restanil	Kabi	W. Germany	-
Sedanyl	Washington	Italy	-
Selene	Biomedica Foscama	Italy	-
Sopanil	Sopar	Belgium	-
Sowell	Cophar	Switz.	-
Stensolo	Salfa	Italy	-
TCM	Zenith	US	-
Trankilin	Biofarma	Turkey	-
Tranlisant	Vita	Canada	-
Trelmar	Elliott-Marion	Canada	-
Urbilat	Hor-Fer-Vit	W. Germany	-
Wescomep	Saunders	Canada	-
Xalogen	Ono	Japan	-

Raw Materials

2-Methyl-2-propyl-1,3-propanediol
Phosgene
Ammonia

Manufacturing Process

A solution containing 52.8 parts of 2-methyl-2-n-propyl-1,3-propanediol and 128 parts of acetone is added with stirring to 112 parts of liquid phosgene at such a rate that the temperature of the reaction is maintained at -5° to 0°C. The reaction is stirred one hour at about 0°C then cooled to -15°C. A cooled 30% solution of 32 parts of sodium hydroxide is added with stirring to the reaction at such a rate that the temperature is maintained at -15° to -5°C. The mixture is stirred for an additional ½ hour at about 0°C then cooled to -20°C. 180 parts of cooled ammonium hydroxide solution (28.6% NH_3) are added while cooling and with stirring at such a rate that the temperature rises slowly to 20°C and stirring is continued for an additional ½ hour. The mixture is poured with agitation into 1,700 parts of ice water. The solid which separates is removed by filtration and dried. Recrystallization from water gives 55 parts (63% of theoretical yield) of 2-methyl-2-n-propyl-1,3-propanediol dicarbamate, MP 104° to 105°C.

References

Merck Index 5690
Kleeman and Engel p. 559
PDR pp. 634, 830, 1024, 1606, 1723, 1874, 1880, 1947, 1949
OCDS Vol. 1 p. 218 (1977) and 2, 21 (1980)
I.N. p. 595
REM p. 1072
Berger, F.M. and Ludwig, B.J.; US Patent 2,724,720; November 22, 1955; assigned to Carter Products, Inc.

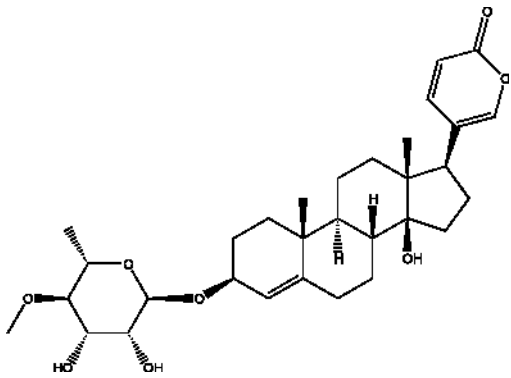
MEPROSCILLARIN

Therapeutic Function: Cardiotonic

Chemical Name: 14-β-Bufa-4,20,22-trienolide, 3-β-((6-deoxy-4-O-methyl-α-L-mannopyranosyl)oxy)-14-hydroxy-

Common Name: Meproscillarin; Methylproscilleridin; Rambufaside

Structural Formula:



Chemical Abstracts Registry No.: 33396-37-1

Trade Name	Manufacturer	Country	Year Introduced
Clift	Knoll	-	-
Clift	Abbott Laboratories	-	-
Talusin	Lek D.D.	-	-

Raw Materials

Proscillaridin

Triethyl orto-formiate
4-Toluenesulfonic acid
Methyl iodide
Sodium hydride

Manufacturing Process

100 g proscillaridin (from *Scilla maritima L.*, enzymatic hydrolysis) was dissolved in 500 ml dry tetrahydrofuran, mixed with 100 ml of triethyl orto-formiate and 50 mg p-tholuene sulfonic acid and stirred for 15 minutes at 20°C.

It was put into a separating funnel and shook with 1 L ethyl acetate and 200 ml of 5% sodium hydroxide. The an organic layer was separated, with 2-3 L water washed (portions 400-500 ml), dried over sodium sulfate and distilled in vacuum to dryness at about 60°C. 121.2 g crude proscillaridin-2,3-ethyl orto-formiate yielded. It was dissolved in 1 L dimethylformamide, mixed with 200 ml methyl iodide and stirred with 20 g 55-60% suspension of sodium hydride at 20°C for 1 hour. 14 L ethyl acetate was added, 5 times with 1-2 L water shook and the organic layer was distilled to 1/4 of volume. The solution of proscillaridin-2,3-ethyl ortho-formiate-4-methyl ester obtained (about 1 L) was mixed with 2 L 0.002 N HCl and stood for 2 hours at 20°C. Then it was neutralized with 0.1 N sodium hydroxide and distilled in vacuum to about 1 L. The solution was shook with 2 L chloroform and 1 L water, organic layer was separated, water layer was 2 times was extracted with still 1 L chloroform and the pooled organic phase dried over sodium sulfate. Then the solvent was removed and 147 g of obtained product was purified by chromatography on silica gel in system chloroform/acetone 4:1.

63 g of crude amorphic 4-O-methylproscillaridin was isolated and recrystallized from methylene chloride/ethyl acetate to give 49.3 g (53% yield) the desired product; MP: 213°-217°C.

References

Kubinyi H.; D.B. Patent No. 2,301,382; Jan. 12, 1973; Assigned to Knoll AG, Chemische Fabriken, 6700 Ludwigshafen

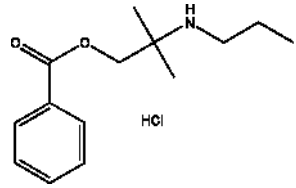
MEPRYLCAINE HYDROCHLORIDE

Therapeutic Function: Local anesthetic

Chemical Name: 1-Propanol, 2-methyl-2-(propylamino)-, benzoate, hydrochloride

Common Name: Meprylcaine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 956-03-6; 495-70-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Oracaine	ALK-Abello	-	-
Meprylcaine hydrochloride	Shanghai Lansheng Corporation	-	-

Raw Materials

N-(1,1-Dimethyl-2-hydroxyethyl)propylamine
Benzoyl chloride

Manufacturing Process

78 g of N-(1,1-dimethyl-2-hydroxy-ethyl)propylamine is added to a solution of 30 g of sodium hydroxide in 700 ml of water. To this is added 300 ml of ether and this is followed by the dropwise addition of 70 ml of benzoyl chloride benzoyl chloride while stirring and cooling. The benzoyl chloride is added at such a rate that the temperature does no rise above 30°C. When the addition is complete, the stirring is continued for another 30 minutes. The aqueous layer is removed and the ether layer is washed with water, dried and evaporated to leave an yellow oil 1-propanol, 2-methyl-2-(propylamino)-, benzoate. This is treated slowly with 45 ml of concentrated hydrochloric acid, during which addition a vigorous exothermic reaction ensues. When the reaction mixture is cooled, it solidifies to a pasty solid which is allowed to dry. This is dissolved in boiling isopropanol and allowed to cool when white crystals of the hydrochloride are formed. The resultant slurry is filtered and the hydrochloride of 1-propanol, 2-methyl-2-(propylamino)-, benzoate recrystallized from isopropanol to give white crystals; MP: 150°-151°C. It is useful in base and salt forms as such as a topical local anesthetic being administrable in oil or alcohol solution.

In practice it is usually used as hydrochloride.

References

Reasenberg J.R.; US Patent No. 2,767,207; Oct. 16, 1956; Assigned to Mizzy Inc., a corporation of New York

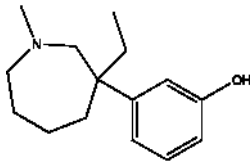
MEPTAZINOL

Therapeutic Function: Analgesic

Chemical Name: 3-Ethyl-3-(m-hydroxyphenyl)-1-methylhexahydro-1H-azepine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 54340-58-8

Trade Name	Manufacturer	Country	Year Introduced
Meptid	Wyeth	UK	1983

Raw Materials

Formaldehyde
Sodium amide
Hydrogen
Hydrogen bromide
2-(m-Methoxyphenyl)butyronitrile
Ethyl-4-iodobutyrate
Lithium aluminum hydride

Manufacturing Process

2-(m-Methoxyphenyl)butyronitrile in dry ether was added to a stirred suspension of sodium amide in liquid ammonia. The mixture was stirred for 30 minutes then ethyl-4-iodobutyrate (99.25 g, 0.4 mol) in dry ether (200 ml) was added dropwise. The mixture was stirred at the temperature of refluxing liquid ammonia for 5 hours. Ammonium chloride (10 g) was added and the mixture allowed to warm to room temperature. Water (300 ml) was added, the organic layer separated, washed with water, 2 N sulfuric acid and water. After drying over magnesium sulfate and removing the ether, the product was distilled yielding ethyl 5-cyano-5-(mmethoxyphenyl)heptanoate.

That material was hydrogenated in cyclohexane using a Raney nickel catalyst. The product after distillation was recrystallized from ethyl acetate affording 10.0 g of 6-ethyl-(m-methoxyphenyl)hexahydro-2H-azepin-2one, MP 87°C to 88°C.

The azepinone (9.1 g) in dry tetrahydrofuran (50 ml) and ether (50 ml) was added dropwise to a stirred suspension of aluminum lithium hydride (7.5 g) in dry ether (50 ml). After heating under reflux for 3 hours the reaction mixture was worked up and distilled yielding 7.66 g of a compound which was a

colorless oil, BP 108°C to 110°C/0.01 mm.

That product was then heated under reflux with 50% hydrobromic acid for 1.5 hours. The reaction mixture was evaporated to dryness and reevaporated with three portions of propan-2-ol. The oil obtained was dissolved in propan-2-ol and diluted with ether. 3-Ethyl-3-(m-hydroxyphenyl)hexahydro-1H-azepine was obtained. That material in turn was reductively methylated by hydrogenation in the presence of formaldehyde in absolute ethanol solution to give 3-ethyl-3-(m-methoxyphenyl)-1-methylhexahydro-1H-azepine.

The methoxy group was converted to a hydroxy group by refluxing with 80% HBr giving meptazinol hydrobromide.

References

Merck Index A-8
DFU 1 (2) 68 (1976)
DOT 19 (7) 415 (1983)
I.N. p. 597
Cavalla, J.F. and White, A.C.; British Patent 1,285,025; August 9, 1972; assigned to John Wyeth & Brother Ltd.
Cavalla, J.F. and White, A.C.; US Patent 3,729,465; April 24, 1973; assigned to John Wyeth & Brother Ltd.
Cavalla, J.F. and White, A.C.; US Patent 4,197,241; April 8, 1980; assigned to John Wyeth & Brother Ltd.

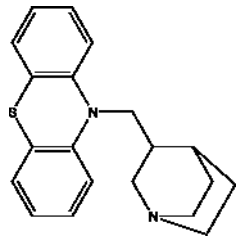
MEQUITAZINE

Therapeutic Function: Antihistaminic

Chemical Name: 10-(1-Azabicyclo[2.2.2]oct-3-yl-methyl)-10H-phenothiazine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 29216-28-2

Trade Name	Manufacturer	Country	Year Introduced
Primalan	Berk	UK	1976
Primalan	Spret-Mauchant	France	1976
Metaplexan	Bad. Arzneimittel	W. Germany	1977
Nipolazin	Nippon Shoji	Japan	1983
Zesulan	Toyo Jozo	Japan	1983
Instotal	IMA	Argentina	-
Mircol	Pharmuka	Belgium	-
Vigigan	Spret-Mauchant	France	-

Raw Materials

Phenothiazine
Sodium amide
3-Chloromethyl quinuclidine HCl

Manufacturing Process

30 g of phenothiazine were added, all at once, to a suspension of 6 g of sodium amide in 240 ml of anhydrous xylene. The mixture was agitated and heated to reflux. When evolution of ammonia ceased (5 hours), 15 g of 3-chloromethyl-quinuclidine hydrochloride were added portionwise over a period of 50 minutes and reflux was then maintained for 22 hours. After cooling to room temperature, 250 ml of distilled water and 250 ml of ethyl acetate were added to the reaction mixture. The aqueous phase was decanted and extracted twice with a total of 250 ml of methyl acetate. The combined organic extracts were extracted three times with a total of 750 ml of a 10% aqueous solution of tartaric acid. The combined acid solutions were treated with 5 g of animal charcoal, filtered and rendered alkaline on an ice bath with 96 ml of 10 N aqueous caustic soda. The oil which separated was extracted three times with a total of 1.500 ml of ethyl acetate. The combined organic extracts were washed to neutrality by washing twice with a total of 1 liter of distilled water, dried over anhydrous magnesium sulfate and evaporated under reduced pressure on a water bath at 45°C. 17 g of oil were obtained which was purified by chromatography on an inert alumina column. 13.3 g of crystallized product were obtained. 10-(3-Quinuclidinyl-methyl)-phenothiazine having a MP of 130°C to 131°C was obtained by recrystallization in boiling acetonitrile.

The 3-chloromethyl-quinuclidine hydrochloride used as starting material in this process can be obtained as described by Grob and coll., Helv. Chim. Acta, 37 (1954),1689.

References

Merck Index 5694
Kleeman and Engel p. 562
DOT 15 (4)199 (1979)
I.N. p. 597
Gueremy, C., Labey, R., Wirth, D. and Auclair, M.; US Patent 3,987,042; October 19, 1976

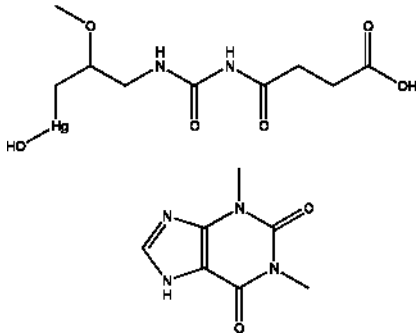
MERALLURIDE

Therapeutic Function: Diuretic

Chemical Name: [3-[[[(3-Carboxy-1-oxopropyl)amino]carbonyl]amino]-2-methoxypropyl]-hydroxymercury mixture with 3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione

Common Name: [3-[3-(3-Carboxypropionyl)ureido]-2-methoxypropyl] hydroxymercury mixture with theophylline

Structural Formula:



Chemical Abstracts Registry No.: 8069-64-5

Trade Name	Manufacturer	Country	Year Introduced
Mercuhydrin	Merrell National	US	1943
Mercardac	Parke Davis	US	-
Mercadon	Parke Davis	US	-

Raw Materials

Allyl carbamide
Succinic anhydride
Mercury acetate
Theophylline

Manufacturing Process

First, to produce the mercury component, a pulverized mixture of 50 g of allylcarbamide and 50 g of succinic anhydride is heated for 30 minutes at 110°C. After cooling the fused mass is ground with 50 cc of cold water and the crystalline mass after quick filtering from the liquid is recrystallized from hot water. The white crystalline needles having a MP of 142° to 144°C are allyl-succinyl-carbamide. In order to produce a mercury compound thereof a mixture of 20 g of the allyl-succinyl-carbamide and 30 g of mercury acetate is

shaken for 3 hours with methanol. The scarcely soluble precipitate of the mercury compound after filtration is washed with methanol and with water and dried in vacuum. The white powder melts at 185° to 186°C under decomposition. Then, condensation with an equimolar proportion of theophylline yields meralluride.

References

Merck Index 5696
OCDS Vol. 1 p, 224 (1977)
I.N. p. 598
Geiger, E., Vargha, L. and Richter, L.; US Patent 2,208,941; July 23, 1940; assigned to Chemical Works of Gedeon Richter Ltd., Hungary

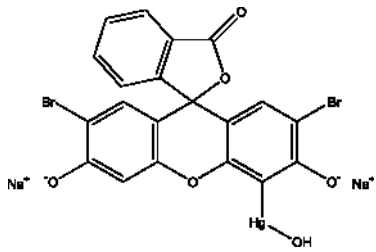
MERBROMIN

Therapeutic Function: Antiseptic

Chemical Name: Mercury, (2',7'-dibromo-3',6'-dihydroxy-3-oxospiro (isobenzofuran-1(3H),9'-(9H)xanthen)-4'-yl)hydroxy-, disodium salt

Common Name: Merbromin; Merbromine sodique; Mercuresceine; Mercurobromfluorescein; Mercurochrome; Mercurocromo

Structural Formula:



Chemical Abstracts Registry No.: 129-16-8

Trade Name	Manufacturer	Country	Year Introduced
Mercurin	Monik	-	-
Mersol	Merkez	-	-
Pharmadose mercuresceine	Gilbert	-	-

Raw Materials

2,7-Dibromofluorescein
Mercury (II) oxide

Manufacturing Process

49 g 2,7-dibromofluorescein are dissolved in a solution of 8 g of sodium hydroxide in 50 ml of water, and diluted to 200 ml 12.5 ml of glacial acetic acid are added to this solution with stirring. A homogeneous pasty precipitate results with vigorously stirring. A filtered solution of about 22.5 g of mercuric oxide in 25 ml of glacial acid and 50 ml water, diluted after solution to 100 ml, is then added to the suspended precipitate, and the whole diluted to about 500 ml. The mixture is boiled until a small portion of filtered solution gives no test for mercury when treated with ammonium sulfide, the approximate time required for this operation being about 4.5-6 hours. As the boiling continues the precipitate become darker in color and more granular. It is washed, preferably by centrifuging, to remove acetic acid and sodium acetate, and dried at about 110°C. By close adherence to above conditions an almost quantitative yield may be secured. The product may be regarded as consisting essentially of 2,7-dibromo-4-hydroxymercuryfluorescein, resulting from substantially complete hydrolysis of an acetoxy-mercury compound, which probably formed as an intermediate. It is red powder, which is insoluble in the usual solvents but dissolves in two equivalents of sodium hydroxide yielding a deep cherry-red solution. The solution has the tendency to decomposition on long standing.

References

White E. C.; US Patent No. 1,535,003; April 21, 1925

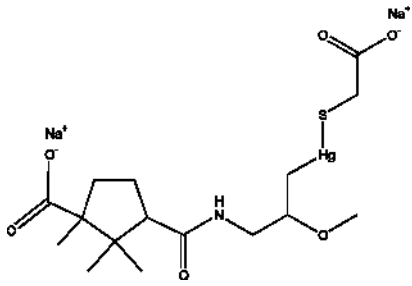
MERCAPTOMERIN SODIUM

Therapeutic Function: Diuretic

Chemical Name: [3-[[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl] amino]-2-methoxypropyl](mercaptoacetato-S)mercury disodium salt

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 21259-76-7

Trade Name	Manufacturer	Country	Year Introduced
Thiomerin	Wyeth	US	1949
Diucardyn	Ayerst	-	-
Thio-Novurit	Chinoin	Hungary	-

Raw Materials

dl-N-Allylcamphoramic acid
Mercury acetate
Sodium methylate
Thioglycolic acid

Manufacturing Process

(A) Preparation of dl-N-(γ-Chloromercuri-β-Methoxy)-Propylcamphoramic Acid: A suspension of 31.9 g (= 0.10 M) of mercuric acetate in 25 ml of methanol is stirred for 30 minutes at room temperature in a 4-necked flask equipped with stirrer, dropping funnel, drying tube and thermometer. To this suspension is added dropwise and with stirring, a solution of 23.9 g (= 0.10M) of dl-N-allylcamphoramic acid in 65 ml of methanol over a period of 30 minutes. The temperature of the reaction mixture should not rise over 30°C. The stirring is continued for one hour. The reaction mixture is allowed to stand at room temperature overnight in the dark to complete the reaction. A solution of 5.9 g (= 0.10M) of sodium chloride in 25 ml of water is added and the stirring is continued for four hours. The small amount of gray precipitate produced is removed by centrifuging. The colorless, clear supernatant is concentrated to about half of its original volume and then dropped into 300 ml of water with stirring.

The white precipitate which forms is filtered and dried at 80°C, yielding 45 g of chloromercuri acid (= 89% of the theory), MP 106° to 109°C (decomp.). This compound is finally obtained in analytically pure form and with a constant melting point by two recrystallizations from acetone-water giving a MP of 131° to 132°C with decomposition.

(B) Preparation of the Chloromercuri Acid Sodium Salt Solution: 50.6 g (= 0.100 M) of the chloromercuri acid (dried over $CaCl_2$, at 0.1 mm and room temperature overnight) is dissolved in 100 ml of warm methanol. To this solution 6.0 g (= 0.111 M) of sodium methylate is added in small portions with constant stirring, so that the temperature of the solution does not rise over 30°C. The solution is centrifuged, and the glass is rinsed with 10 ml of methanol. The final pH of the combined solutions is 8.5.

(C) Preparation of the Disodium Thioglycolate Solution: The following steps are carried out under nitrogen. To 9.2 g (= 0.100 M) of freshly distilled thioglycolic acid (BP at 2 mm, 84° to 85°C) in 100 ml of methanol in a flask is added 12.0 g (= 0.222 M) of sodium methylate in small portions with stirring. The turbid solution is poured into a dropping funnel and the flask is rinsed with 20 ml of methanol. The final pH of the combined methanolic solutions is 11, according to US Patent 2,834,795.

To 50 cc of a carefully purified aqueous solution of the sodium salt of N(γ-chloromercuri-β-methoxy-propyl)-d-α-camphoramic acid containing 40 mg of

mercury per cc is added 10 cc of a solution containing 1.14 g (1 mol equivalent) of sodium thioglycolate and the mixture is then evaporated to dryness at room temperature and reduced pressure in the presence of a desiccant. The product is an amorphous white powder which decomposes at 156° to 158°C (uncorr.), and which was found on analysis to have a mercury content of 33.0%, according to US Patent 2,576,349.

References

Merck Index 5701
OCDS Vol. 1 p. 224 (1977)
I.N. p. 599
Lehman, R.A.; US Patent 2,576,349; November 27, 1951; assigned to Wyeth Incorporated
Wendt, G.R.; US Patent 2,834,795; May 13,1958; assigned to American Home Products Corporation

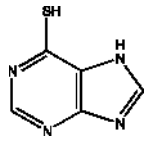
MERCAPTOPURINE

Therapeutic Function: Cancer chemotherapy

Chemical Name: 6-Purinethiol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 50-44-2

Trade Name	Manufacturer	Country	Year Introduced
Purinethol	Sandoz	France	1950
Purinethol	Burroughs-Wellcome	US	1953
Classen	Nippon Shoji	Japan	-
Ismipur	I.S.M.	Italy	-
Leukerin	Takeda	Japan	-
Mercaleukin	Arzneimittelwerk Dresden	E. Germany	-
Mern	Tanabe	Japan	-
6-MP	Dojin	Japan	-
Oncomercaptopurina	Simes	Belgium	-
Puri-Nethol	Burroughs-Wellcome	UK	-
Thioinosie	Morishita	Japan	-

Raw Materials

4-Amino-6-chloro-5-nitropyrimidine
Hydrogen sulfide
Formic acid
Sodium hydroxide

Manufacturing Process

7.5 g of 4-amino-6-chloro-5-nitropyrimidine was suspended in 200 ml of 1 N potassium hydrosulfide and heated on the steam bath for 2 hours while passing hydrogen sulfide through the reaction mixture. The reaction mixture was allowed to cool slowly, acidified with 10 N sulfuric acid and chilled. The precipitate consisted of 4,5-diamino-6-mercaptopyrimidine and sulfur. It was boiled with 300 ml of water, filtered hot and then chilled. The product precipitated as pale yellow needles (4.2 g); an additional 0.95 g was obtained by concentration of the mother liquors to 100 ml.

A mixture of 2 g of 4,5-diamino-6-mercaptopyrimidine and 10 ml of 98% formic acid was heated at 70°C for two hours and then evaporated to dryness on the steam bath to give as a residue, 7-amino-thiazolo (5,4-d) pyrimidine.

To 820 mg of 7-amino-thiazolo[5,4-d]pyrimidine was added 2.5 cc of 2 N sodium hydroxide. The water was removed under reduced pressure. The sodium salt was then heated at 240°C for one hour, during which time it melted, gave off water and resolidified. The sodium salt of 6-mercaptopurine was dissolved in 15 ml of water and acidified to pH 5 with acetic acid. Yellow crystals of 6-mercaptopurine hydrate precipitated, according to US Patent 2,933,498.

References

Merck Index 5702
Kleeman & Engel p. 563
PDR p. 759
I.N. p. 599
REM p. 1151
Hitchings, G.H. and Elion, G.B.; US Patent 2,721,866; October 25, 1955; assigned to Burroughs Wellcome & Co. (USA.) Inc.
Hitchings, G.H. and Elion, G.B.; US Patent 2,724,711; November 22, 1955; assigned to Burroughs Wellcome & Co. (USA.) Inc.
Hitchings, G.H. and Elion, G.B.; US Patent 2,933,498; April 19, 1960; assigned to Burroughs Wellcome & Co. (USA.) Inc.

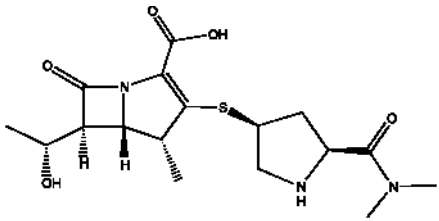
MEROPENEM

Therapeutic Function: Antibiotic

Chemical Name: 1-Azabicyclo(3.2.0)hept-2-ene-2-carboxylic acid, 3-((5-(2-dimethylamino)carbonyl)-3-pyrrolidinyl)thio)-6-(1-hydroxyethyl)-4-methyl-7-oxo-, trihydrate, (4R- (3(3S*,5S*),4alpha,5beta,6beta(R*)))-

Common Name: Meropenem

Structural Formula:



Chemical Abstracts Registry No.: 96036-03-2

Trade Name	Manufacturer	Country	Year Introduced
Merrem	AstraZeneca	-	-
Meronem	AstraZeneca	-	-
Meropenem	AstraZeneca	-	-
Merozen	AstraZeneca	-	-
Zeropenem	Hoechst Marion Roussel	-	-

Raw Materials

Ethyl chloroformate
Triethylamine
Thioacetic acid
Palladium on carbon
Zinc
Diphenyl chlorophosphate
Hydrogen
Diisopropylethylamine
(3R,4R)-4-Acetoxy-3-[(R)-1-(t-butyldimethylsilyloxy)ethyl]-2-azetidinone
Methanesulfonyl chloride
Diethylaluminium chloride
Orpholinopropanesulfonic acid buffer
Benzyl-α-bromopropionate
trans-1-(p-Nitrobenzyloxycarbonyl)-4-hydroxy-L-proline
Methanesulfonyl chloride
t-Butyldimethylsilyl chloride

Manufacturing Process

3.10 g of trans-1-(p-nitrobenzyloxycarbonyl)-4-hydroxy-L-proline and 1.10 g of triethylamine were dissolved in 40 ml of dried tetrahydrofuran, and a solution of 1.20 g of ethyl chloroformate in 10 ml of dried tetrahydrofuran was added dropwise thereto at -25-35°C. After stirring at the same temperature for 50 min, 10 ml of concentrated aqueous ammonia was added dropwise to the mixture at -25-40°C. The temperature was then gradually elevated to room temperature, and the reaction mixture was stirred for 1 hour, followed by concentration under reduced pressure. To the residue were added 20 ml of water and 50 ml of diethyl ether. After ice-cooling, the thus formed white crystals were separated by filtration, washed successively with cool water and cool diethyl ether, and dried under reduced pressure to yield trans-1-(p-nitrobenzyloxycarbonyl)-4-hydroxy-L-prolineamide. Melting point: 163.3-

164.0°C.

A solution of 1.89 g of methanesulfonyl chloride in 10 ml of dried tetrahydrofuran was added dropwise to a suspension of 2.32 g of trans-1-(p-nitrobenzyloxycarbonyl)-4-hydroxy-L-prolineamide and 1.67 g of triethylamine in 40 ml of dried tetrahydrofuran at room temperature. After stirring for 1 hour, the reaction mixture was concentrated under reduced pressure, and to the residue were added 30 ml of water and 30 ml of diethyl ether. After cooling, the resulting white crystals were separated by filtration, washed successively with cool water and cool diethyl ether and dried under reduced pressure to obtain trans-1-(p-nitrobenzyloxycarbonyl)-4-methanesulfonyloxy-L-prolineamide. Melting point: 149.5-151°C.

A solution of 642 mg of thioacetic acid in 14 ml of dried dimethylformamide was added to a suspension of 374 mg of 50% sodium hydride in 13 ml of dried dimethylformamide in a nitrogen stream, followed by stirring at room temperature for 25 minutes. To the mixture were added 975 mg of sodium iodide and then a solution of 2.52 g of trans-1-(p-nitrobenzyloxycarbonyl)-4-methanesulfonyloxy-L-prolineamide in 12 ml of dried dimethylformamide, and the resulting mixture was heated to 70°C for 6 hours while stirring. The reaction mixture was poured into a cool aqueous solution of sodium chloride and extracted with benzene. The extract was washed successively with a 10% aqueous solution of sodium sulfate and a sodium chloride aqueous solution, dried over sodium sulfate and distilled off to remove the solvent. The resulting crude crystals were washed with a warm mixed solvent of tetrahydrofuran and benzene to obtain (2S,4S)-1-(p-nitrobenzyloxycarbonyl)- 2-carbamoyl-4-acetylthio-L-prolineamide. Melting point: 168.5-169.5°C.

950 mg of (2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-carbamoyl-4-acetylthiopyrrolidine was dissolved in 95 ml of methanol, and 2.59 ml of a 1 N aqueous solution of sodium hydroxide was added thereto at room temperature in an argon stream, followed by stirring at that temperature for 15 min. The reaction mixture was neutralized with 2.59 ml of a 1 N aqueous solution of hydrochloric acid and distilled off under reduced pressure to remove the methanol. The thus precipitated crystals were filtered and washed with water to obtain (2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-carbamoyl-4-mercaptopyrrolidine. Melting point: 158-162°C.

To 1.33 g (20 mM) of activated zinc was added 20 ml of dried tetrahydrofuran, and 8.8 ml of a 15% n-hexane solution of diethylaluminium chloride was added thereto in a nitrogen stream under ice-cooling. A solution prepared by dissolving 1.49 g (5.2 mM) of (3R,4R)-4-acetoxy-3-[(R)-1-(t-butyldimethylsilyloxy)ethyl]-2-azetidinone and 3.73 g (15.3 mM) of benzyl-α-bromopropionate in 13.3 ml of dried tetrahydrofuran was added dropwise to the mixture over a period of 30 to 40 min, followed by stirring for 1 hours. Under ice-cooling, 2.8 ml of pyridine, 13.2 ml of water, 26.5 ml of ethyl acetate and 13.2 ml of a 1 N hydrochloric acid aqueous solution were successively added thereto, and the resulting mixture was filtered using Celite. The filtrate was washed with water, and the organic layer was dried over sodium sulfate and distilled off to remove the solvent. The resulting oily residue was subjected to silica gel column chromatography to obtain an isomeric mixture of 4-(1-benzyloxycarbonyl)ethyl-3-[(R)-1-(t-butyldimethylsilyloxy)ethyl]-2-azetidinone.

The isomeric mixture was separated into each compound by Lober column chromatography using silica gel and 1.5% isopropanol/n-hexane as an eluent to obtain the compound (1a) and the compound (1b) as oily substances.

200 mg of 4-(1-benzyloxycarbonyl)ethyl-3-[(R)-1-(t-butyl-dimethylsilyloxy) ethyl]-2-azetidinone (1a) was dissolved in 2 ml of dried dimethylformamide. 126 mg of triethylamine was added to the resulting solution, and then 151 mg of t-butyldimethylsilyl chloride was added thereto, followed by stirring at room temperature overnight. The reaction mixture was diluted with ethyl acetate, washed with water, dried over sodium sulfate and purified by silica gel chromatography to obtain 4-(1-benzyloxycarbonyl)ethyl-3-[(R)-1-(t-butyldimethylsilyloxy)ethyl]-1-(t-butyldimethylsilyl)-2-azetidinone (2a).

184 mg of (2a) was dissolved in 4 ml of methanol, and the resulting solution was stirred together with 20 mg of 10% palladium-on-carbon at an atmospheric pressure of hydrogen for 2 hours. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to obtain 4-(1-carboxy)ethyl-3-[(R)-1-(t-butyldimethylsilyloxy)ethyl]-1-(t-butyldimethylsilyl)-2-azetidinone (3a).

(4R,5R,6S,8R)-p-Nitrobenzyl-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo [3.2.0]-hept-3,7-dione-2-carboxylate was obtained from 170 mg of 4-(1-carboxy)ethyl-3-[(R)-1-(t-butyldimethylsilyloxy)ethyl]-1-(t-butyldimethylsilyl)-2-azetidinone (3a) according to the method described in Japanese Patent Application OPI No. 26887/83, pages 64-65.

(a) 53 mg of (4R,5R,6S,8R)-p-nitrobenzyl-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3,2,0]-hept-3,7-dione-2-carboxylate was dissolved in 5 ml of dry acetonitrile, and 57 mg of diisopropylethylamine and then 43 mg of diphenyl chlorophosphate were added thereto. After stirring for 2.5 hours, 57 mg of [2S,4S]-1-p-nitrobenzyloxycarbonyl-2-dimethylaminocarbonyl-4-mercaptopyrrolidine was added to the mixture, followed by stirring for 1 hour. The reaction solution was diluted with ethyl acetate, washed with water, dried over magnesium sulfate and the solvent was distilled off. The residue was purified by silica gel thin layer chromatography to obtain 35 mg of (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[4-(1-p-nitrobenzyloxycarbonyl-2-dimethylaminecarbonyl)pyrrolidinylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3,2,0]-hept-2-ene-7-one-2-carboxylate.

(b) 25 mg of (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[4-(1-p-nitrobenzyloxycarbonyl-2-dimethylaminecarbonyl)pyrrolidinylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3,2,0]hept-2-ene-7-one-2-carboxylate was dissolved in a mixture of 1.9 ml of tetrahydrofuran and 0.3 ml of ethanol, and the mixture was hydrogenated in a morpholinopropanesulfonic acid buffer solution (pH = 7.0, 1.9 ml) under atmospheric pressure of hydrogen for 3 hours at room temperature in the presence of 30 mg of 10% palladium-carbon, which had been activated in hydrogen atmosphere for 1 hour followed by washing with water. After filtering off the catalyst, tetrahydrofuran and ethanol were distilled off under reduced pressure, and the residual solution was washed with ethyl acetate. The aqueous layer was again distilled under reduced pressure to remove organic solvents, and the residual solution was subjected to polymer chromatography (CHP-20P) to obtain (4R,5S,6S,8R,2'S,4'S)-3-[4-(2-dimethylaminecarbonyl)pyrrolidinylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3,2,0]hept-2-ene-7-one-2-carboxylic

acid from the fraction eluted with water.

References

Merck Index, Monograph number: 5960, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Nishitani Y., Irie T.; US Patent No. 5,122,604; May 31, 1994; Assigned to: Shionogi Seiyaku Kabushiki Kaisha (Osaka, JP)
Sunagawa M.; US Patent No. 4,943,569; July 24, 1990; Assigned to Sumitomo Pharmaceuticals Co., Ltd. (Osaka, JP)
Sunagawa M. et al.; J. Antibiotics; 1990, 43, 519

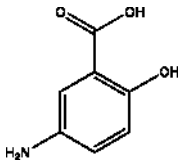
MESALAMINE

Therapeutic Function: Antibacterial

Chemical Name: Salicylic acid, 5-amino-

Common Name: Acidum metaminosalicylicum; Fisalamine; Mesalamine; Mesalazine

Structural Formula:



Chemical Abstracts Registry No.: 89-57-6

Trade Name	Manufacturer	Country	Year Introduced
Asacol	Proctor and Gamble	-	-
Asacol	Tillots Pharma AG Ziefen	-	-
Asalit	Merck	-	-
Mesacol	Sun Pharma	-	-
Mesalamine	Novopharm	-	-
Mesasal	Glaxol/Wellcome	-	-
Pentasa	Ferring	-	-
Salofalk	Minipharm	-	-
Walsa	Wallace Pharmaceuticals Ltd.	India	-

Raw Materials

5-Nitrosalicylic acid potassium salt
Hydrazine hydrate

Nickel Raney
Hydrogen

Manufacturing Process

Procedure A: To 5-nitrosalicylic acid potassium salt (55 g, 246 mmol) dissolved in water (200 mL) was added potassium hydroxide pellets to reach pH 11.5. To this solution 2 g of Raney nickel were added. The mixture was heated-up to reflux and hydrazine hydrate (40 mL, 80% in water, 64 mmol) was added dropwise during 3-4 hrs. The reflux was maintened until HPLC showed the disappearance of the starting material and the complete reduction of 5-nitrosalicylic acid (3-4 hrs). The hot mixture was filtered under nitrogen and the solution was collected. The solution was cooled to 40°C and the pH was adjusted to 2.3 by addition of 35% HCl aqueous solution. The precipitation of 5-aminosalicylic acid occurred. The solution was cooled at 0°C, and after standing at this temperature for 2 hr, the precipitate was filtered, washed with water, and dried at 60-70°C. 5-Aminosalicylic acid was obtained in 89% yield.

Procedure B: To 5-nitrosalicylic acid potassium salt (55 g, 246 mmol) dissolved in water (200 mL) was added potassium hydroxide pellets to reach pH 11.5. The solution was charged in a stainless steel autoclave and 2 g of Raney nickel are added. Hydrogen was introduced into the autoclave reaching a pressure of 8 atm. The mixture was heated-up to 100°C. The temperature was maintained until HPLC-test 5-aminosalicylic acid showed the disappearance of the starting material and the complete reduction of 5-aminosalicylic acid (6-8 hrs). Hydrogen was purged and replaced by nitrogen. The hot mixture was filtered under nitrogen, the filtrate was cooled to 40°C, and the pH was adjusted to 2.3 by addition of 35% HCl aqueous solution. The precipitation of the 5-aminosalicylic acid occurred. The solution was cooled at 0°C, and after standing at this temperature for 2 hr, the precipitate was filtered, washed with ion depleted water, and dried at 60-70°C.

References

Breviglieri G., Giacomo B., Contrini Sergio, Assanelli Cinzia, Eileen Campanab, Mauro Panunzio, Molecules 2001, 6, M260
Martelli, G., Spunta, G., Panunzio, M.; Tetrahedron Lett. 1998, 39, 6257-6260
Kennedy, J.F., Barker, S.A., Epton, J., Kennedy, G.R.; J. Chem. Soc. Perkin 1, 1973, 488-490

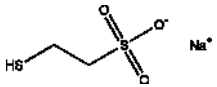
MESNA

Therapeutic Function: Mucolytic

Chemical Name: 2-Mercaptoethane sulfonic acid sodium salt

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 19767-45-4; 3375-50-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Mistabronco	UCB	W. Germany	1973
Mistabron	Diethelm	Switz.	1978
Mucofluid	UCB Fraysse	France	1978
Mucofluid	UCB	Italy	1981
Uromitexan	W.B. Pharm.	UK	1983
Uromitexan	Asta	W. Germany	-

Raw Materials

β-S-Thiuronium ethanesulfonate
Ammonia

Manufacturing Process

2,100 g of β-S-thiuronium ethanesulfonate were placed in a solution of 2,100 cc of concentrated aqueous ammonia and 400 cc of water. The mixture was carefully warmed on a steam bath and an exothermic reaction ensured, at which point the β-S-thiuronium ethanesulfonate passed into solution. After standing for two hours at room temperature, the solution was concentrated until all of the excess ammonia had been removed.

The resultant clear solution from the ammonolysis reaction was processed through "Amberlite IR-120" ion exchange resin and converted into β-S-mercaptoethanesulfonic acid in 93.7% yield (based on β-S-thiuronium ethanesulfonate).

It is expedient not to heat the reaction mixture rapidly since this increases the loss of ammonia and effects an incomplete reaction. Heating the mixture too rapidly may retard the ammonolysis reaction entirely. The amount of ammonia used is considered to be a satisfactory minimum and larger quantities of ammonia are not found to have any beneficial effect on the reaction. It is also expedient to remove the excess ammonia before processing the guanidinium β-mercaptoethanesulfonate solution through the ion exchange resin since the resin will also remove the ammonia with the result that the capacity of the resin for the exchange of guanidinium ions will be reduced.

Although the preparation of β-mercaptoethanesulfonic acid through the ammonolysis reaction is the preferred method, it is also possible to prepare the sulfonic acid by the sodium hydroxide hydrolysis of β-S-thiuronium

ethanesulfonate followed by the ion exchange treatment. The resulting acid, however, is generally not as satisfactory as that prepared by the ammonolysis reaction.

References

Merck Index 5754
Kleeman & Engel p. 563
DOT 8 (5) 180 (1972); 19 (10) 585 and (11) 608 (1983)
I.N. p. 601
Schramm, C.H. and Karlson, R.H.; US Patent 2,695,310; November 23, 1954; assigned to Lever Brothers Co.

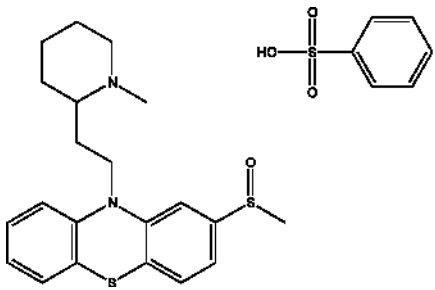
MESORIDAZINE BESYLATE

Therapeutic Function: Tranquilizer

Chemical Name: 10-[2-(1-Methyl-2-piperidinyl)ethyl]-2-methylsulfinyl-10H-phenothiazine benzene sulfonate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 32672-69-8; 5588-33-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Serentil	Sandoz	US	1970
Calodal	Heyden	Switz.	1980
Lidanil	Salvoxyl-Wander	France	-

Raw Materials

Acetic anhydride
Hydrogen peroxide
Sodium hydroxide
3-Methylmercaptophenothiazine
Potassium carbonate
2-(N-Methylpiperidyl-2')-1-chloroethane

Manufacturing Process

10.0 g of 3-methylmercapto phenothiazine and 17.5 cc of acetic acid anhydride are refluxed for 8 hours from an oil bath maintained at a temperature of 180°C. After concentration of the solution the residue is crystallized from ethanol. The pure 3-methylmercapto-10-acetyl phenothiazine melts at 89° to 91°C. For the purpose of oxidation 5.0 g of 3-methylmercapto-10-acetyl phenothiazine are dissolved in 50 cc of ethanol, refluxed from an oil bath maintained at 120°C and 1.6 cc of a 40% hydrogen peroxide solution are then added dropwise in the course of 30 minutes.

Heating is continued for another 5 hours and the reaction mixture is concentrated after 50 cc of water have been added. The residue is taken up in 40 cc of benzene and the benzene layer washed with 10 cc of water. After having been concentrated, the residue, crude 3-methylsulfinyl-10-acetyl phenothiazine, is dissolved in 55 cc of a 90% methanol solution for splitting off the acetyl group and, after 2.9 g of potassium carbonate have been added, it is boiled for 2 hours under reflux on an oil bath kept at a temperature of 120°C. After concentration, the residue is taken up in 50 cc of chloroform, the chloroform layer is washed with a total of 25 cc of water, dried over potassium carbonate, filtered and concentrated. After twice crystallizing the residue, each time from 50 cc of ethanol, analytically pure 3-methylsulfinyl phenothiazine (MP 193° to 195°C) is obtained.

A mixture of 10.0 g of 3-methylsulfinyl phenothiazine (MP 193° to 195°C), 6.1 g of finely powdered sodium hydroxide and 125 cc of toluene is boiled for 1 hour under reflux with a water separator on an oil bath kept at a temperature of 150°C, while the mixture is stirred. Without interrupting the boil a solution of 7.0 g of 2-(N-methyl-piperidyl-2')-1-chloroethane (BP 84°C/10 mm Hg) in 10 cc of toluene is added dropwise in the course of 1 hour, after which boiling is continued for another 3 hours. When the reaction mixture has cooled it is first washed with 25 cc of water three times and then extracted with 75 cc of a 15% aqueous tartaric acid solution. The tartaric acid extract is shaken out with 25 cc of benzene, 20 cc of concentrated caustic soda are added until the phenolphthalein reaction is alkaline, and the separated oily base is taken up in a total of 150 cc of benzene.

After having been washed with 50 cc of water the benzene layer is dried over potassium carbonate, filtered, allowed to stand over 10 g of alumina for about 1½ hours for partial decolorization, filtered again and concentrated under reduced pressure. The oily base which remains as a residue is directly converted into the tartrate. A solution cooled to 0°C, of 6.50 g of the free base in 100 cc of acetic acid ethyl ester is thoroughly shaken and poured into an ice cold solution of 2.66 g of tartaric acid in 410 cc of acetic acid ethyl ester. The precipitated, analytically pure, tartrate of 3-methylsulfinyl-10-[2'-N-methyl-piperidyl-2')-ethyl-l']-phenothiazine melts at 115° to 120°C (foam formation) and sinters above 80°C. The base is reacted with benzene sulfonic acid in a suitable solvent to give the besylate.

References

Merck Index 5755
Kleeman & Engel p. 564
PDR p. 681

OCDS Vol. 1 p. 389 (1977)
DOT 6 (6) 211 (1970) and 9 (6) 227 (1973)
I.N. p.601
REM p. 1089
Renz, J., Bourquin, J.-P. and Schwarb, G.; US Patent 3,084,161; April 2, 1963; assigned to Sandoz Ltd., Switzerland

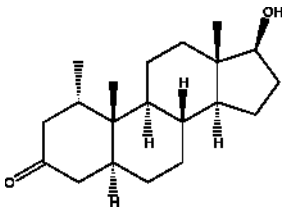
MESTEROLONE

Therapeutic Function: Androgen

Chemical Name: 17β-Hydroxy-1α-methyl-5α-androstan-3-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 1424-00-6

Trade Name	Manufacturer	Country	Year Introduced
Proviron	Schering	W. Germany	1967
Proviron	Schering	Italy	1971
Pro-Viron	Schering	UK	1971
Proviron	S.E.P.P.S.	France	1975
Mestoran	Schering	W. Germany	-
Vistimon	Jenapharm	E. Germany	-

Raw Materials

1α-Methyl-androstan-17β-ol-3-one-17-acetate
Sodium hydroxide

Manufacturing Process

500 mg of 1α-methyl-androstan-17β-ol-3-one-17-acetate are heated under reflux for 90 minutes in a nitrogen atmosphere in 5 ml of 4% methanolic sodium hydroxide solution. The reaction mixture is then stirred into ice water,

the precipitated product filtered with suction and recrystallized from isopropyl ether. 1α-Methyl-androstan-17β-ol-3-one melts at 203.5° to 205°C.

References

Merck Index 5760
Kleeman & Engel p. 565
OCDS Vol. 1 p. 174 (1977)
I.N. p. 602
Schering AG, Germany; British Patent 977,082; December 2, 1964
Schering AG, Germany; British Patent 977,083; December 2, 1964
Wiechert, R.; US Patent 3,361,773; January 2, 1968; assigned to Schering A.G.

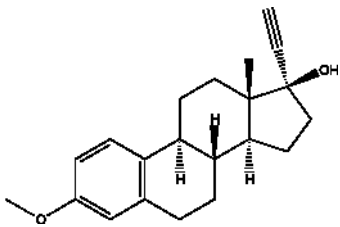
MESTRANOL

Therapeutic Function: Estrogen

Chemical Name: 3-Methoxy-19-nor-17α-pregna-1,3,5(10)-trien-20-yn-17-ol

Common Name: 17α-Ethynylestradiol 3-methyl ether

Structural Formula:



Chemical Abstracts Registry No.: 72-33-3

Trade Name	Manufacturer	Country	Year Introduced
Enovid	Searle	US	1957
Ortho-Novum	Ortho	US	1963
Enovid-E	Searle	US	1964
Norinyl	Syntex	US	1964
C-Quens	Lilly	US	1965
Ovulen	Searle	US	1966
Conceplan	Gruenenthal	W. Germany	-
Conovid	Searle	UK	-
Enavid	Dainippon	Japan	-
Estalor	Lilly	US	-
Gestamestrol	Hermal	W. Germany	-

Trade Name	Manufacturer	Country	Year Introduced
Lutedione	Teikoku Zoki	Japan	-
Lyndiol	Organon-Sankyo	Japan	-
Metrulen	Searle	UK	-
Noracycline	Ciba Geigy	France	-
Noriday	Syntex	US	-
Norinyl	Syntex	US	-
Norluten	Shionogi	Japan	-
Norquen	Syntex	US	-
Nuriphasic	Noury Pharma	W. Germany	-
Orgaluton	Organon	UK	-
O.V. 28	Biosedra	France	-
Ovanon	Organon	UK	-
Ovastol	Rendell	UK	-

Raw Materials

3-Methoxy-$\delta^{(1,3,5)}$-estratrien-17-one
Acetylene

Manufacturing Process

A stirred solution of 120 parts of 3-methoxy-$\delta^{1,3,5}$-estratrien-17-one in 2,600 parts of anhydrous toluene and 4,300 parts of anhydrous ether is saturated with a slow stream of acetylene. In the course of 30 minutes there is added a solution of 120 parts of potassium tert-amylate in 2,800 parts of anhydrous tert-pentanol. The passage of acetylene and stirring are continued for an additional 5 hours after which the reaction mixture is washed 5 times with 3,000-part portions of saturated ammonium chloride solution and then with water. It is then dried over anhydrous sodium sulfate and concentrated to dryness under vacuum. The residue is recrystallized from methanol. The 3-methoxy-17-ethynyl-$\delta^{1,3,5}$ estratrien-17-ol thus obtained melts at about 143° to 146°C. A further recrystallization from acetone yields crystals melting at about 150° to 151°C.

References

Merck Index 5762
Kleeman & Engel p. 566
PDR pp. 1297,1680,1793
OCDS Vol. 1 p. 162 (1977)
I.N. p. 602
REM p.989
Colton, F.B.; US Patent 2,666,769; January 19, 1954; assigned to G.D. Searle & Co.

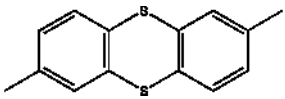
MESULFEN

Therapeutic Function: Scabicide

Chemical Name: 2,7-Dimethylthianthrene

Common Name: Mesulfen; Mesulphen; Thianthol

Structural Formula:



Chemical Abstracts Registry No.: 135-58-0

Trade Name	Manufacturer	Country	Year Introduced
Mesulfen	Synopharm GMBH and CO.KG	-	-
Odylen	Winthrop	-	-
Anacar	Teknofarma	-	-
Schwefelol	Solco	-	-
Sulfor	Takeda	-	-
Thiotal	Linz	-	-
Citemul S	Medopharm Arzneim	-	-

Raw Materials

Toluene
Sulfur
Aluminum chloride

Manufacturing Process

100 parts by weight of toluene, 330 parts of sulfur and 80 parts of aluminum chloride were heated to reflux on the oil bath before the formation of hydrogen sulfide and hydrogen chloride ended. The mixture was poured into water for removing the excess of aluminum chloride. A toluene layer was separated, dried and distilled in vacuum. When toluene was distilled off, about 500 parts by weight the residual yellow oil boiled at 150°-230°C/3 mm Hg was yielded. An objectionable odor was removed by shaking with sodium hydroxide. The residual sulfur (23-25%) was removed by washing with hydrogen peroxide. The residue (mesulfen) looked like fragile asphalt mass after distillation.

References

Weyland H. et al.; D.R. Patent No. 365,169; Sept. 4, 1919; Assigned to Farbenfabriken vorm. Friedr. Bayer and Co. in Leverkusen b. Koin a. Rh.

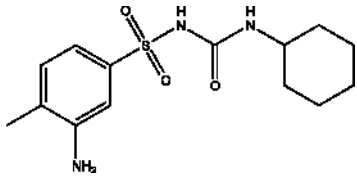
METAHEXAMIDE

Therapeutic Function: Oral hypoglycemic

Chemical Name: Benzenesulfonamide, 3-amino-N-((cyclohexylamino) carbonyl)-4-methyl-

Common Name: Metahexamide; Metahexanamide

Structural Formula:



Chemical Abstracts Registry No.: 565-33-3

Trade Name	Manufacturer	Country	Year Introduced
Metahexamide	Shanghai Lansheng Corporation	-	-
Melanex	Upjohn	-	-

Raw Materials

Ethyl chloroformate
3-Acetylamino-p-toluene sulphonic acid amide
Cyclohexylamine

Manufacturing Process

39 g ethyl chloroformate are added dropwise to a mixture of 68.4 g 3-acetylamino-p-toluene sulphonic acid amide, 123 g potassium carbonate and 450 ml acetone for one hour while boiling under reflux. Refluxing is then continued for a further nine hours. The reaction mixture is cooled and mixed, while stirring, with a mixture of 450 ml water and 50 ml 2 N potassium hydroxide solution. Thereby two layers are formed. The upper layer, which consists of aqueous acetone, is separated. Acetone is distilled off in a vacuum. The pH-value of the resulting aqueous solution is adjusted to a pH of 8.8 by passing in gaseous carbon dioxide. Precipitated unchanged starting material is filtered off. The filtrate is rendered congo acid by the addition of dilute hydrochloric acid. The precipitated 3-acetylamino-p-toluene sulfnyl ethyl urethane is filtered off by suction, washed with water, and dried in a vacuum. The yield is 77%. The resulting compound melts at 183°-194°C.

54.3 g above prepared 3-acetylamino-p-toluene sulphonyl ethyl urethane are mixed with 37 ml dimethylformamide and 18 g cyclohexylamine. The resulting

clear solution is heated at 70°C for 1.5 hours and at 110°C for 1.5 more hours. After cooling, the reaction mixture is poured into 500 ml water while stirring. The precipitated oily product crystallizes shortly. The crystals are filtered off by suction, washed with water and dried in a vacuum. Yield of 3-acetylamino-p-toluene sulphonyl cyclohexyl urea is 84%. MP: 174°C. The urea is saponified without further purification by heating it in 90 ml 5 N potassium hydroxide solution at 90°C for one hour. After dilution with 500 ml water the resulting reaction mixture is rendered acid (pH 6.5) by the addition of dilute hydrochloric acid. Thereby, 1-(3-amino-p-tolylsulfonyl)-3-cyclohexylurea separates in crystals, which are collected, washed with water, and dried. The yield is 86%. After recrystallization from ethanol the compound has MP: 151°-152°C.

References

Boehringer C.F., Soehne G.m.b.H., Germany; G.B. Patent No. 831,043; Feb. 26, 1957

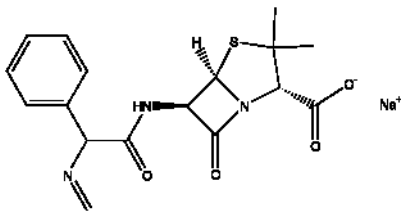
METAMPICILLIN SODIUM

Therapeutic Function: Antibacterial

Chemical Name: 3,3-Dimethyl-6-[[(methyleneamino)phenylacetyl]amino]-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid sodium salt

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 6489-61-8; 6489-97-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Magnipen	Clin-Comar-Byla	Italy	1969
Magnipen	Clin Midy	France	1970
Actuapen	Larma	Spain	-
Ampilprats	Prats	Spain	-
Apliopenil	Miluy	Spain	-
Co-Metampicil	Sanchez-Covisa	Spain	-
Daniven	Aldon	Spain	-

Trade Name	Manufacturer	Country	Year Introduced
Fedacilina	Fedal	Spain	-
Janopen	Janovich	Spain	-
Madecilina	Made	Spain	-
Maipen	Maipe	Spain	-
Mempil	Kairon	Spain	-
Metabacter	Rubio	Spain	-
Metacidan	Cidan	Spain	-
Meta-Ferran	Ferran	Spain	-
Metakes	Kessler	Spain	-
Metambac	Wolner	Spain	-
Metampicef	Cecef	Spain	-
Metamplimedix	Medix	Spain	-
Metiskia	Iskia	Spain	-
Ocelina	Roux-Ocefa	Argentina	-
Pluriespec	Vir	Spain	-
Ruticina	Bernabo	Argentina	-
Tisquibron	Bryan	Spain	-
Venzoquimpe	Quimpe	Spain	-
Vigocina	Europa	Spain	-

Raw Materials

6-[D-(-)α-Aminophenylacetamido]penicillanic acid
Sodium bicarbonate
Formaldehyde

Manufacturing Process

0.01 mol of 6-[D(-)α-(aminophenylacetamido)]-penicillanic acid was suspended in 150 cc of water cooled to +5°C and treated with 0.01 mol of sodium bicarbonate.

The solution was treated with 0.01 mol of formaldehyde in aqueous solution, with agitation. The solution was then filtered to eliminate traces of insoluble product and the filtrate was lyophilized. Sodium 6-[D(-)-alpha-(methylene-amino-phenylacetamido)]-penicillanate was obtained.

References

Merck Index 5775
Kleeman & Engel p. 569
OCDS Vol. 1 p. 414 (1977)
DOT 6 (3) 85 (1970)
I.N. p. 604
Gradnick, B.; British Patent 1,081,093; August 31, 1967; assigned to Societe d'Etudes de Recherches et d'Applications Scientifiques et Medicales (E.R.A.S.M.E.) (France)

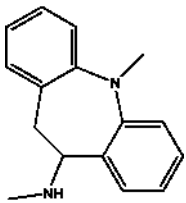
METAPRAMINE

Therapeutic Function: Antidepressant

Chemical Name: 10,11-Dihydro-5-methyl-10(methylamino)-5H-dibenz[b,f]azepine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 21730-16-5; 21737-55-3 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Timaxel	Specia	France	1983
Rodostene	Rhone Poulenc	France	-

Raw Materials

5-Methyl-dibenzo[b,f]azepine
Methylamine
Sodium hypochlorite

Manufacturing Process

5-Methyl-dibenzo[b,f]azepine (4.1 g), N-diethylaminoborane (1.7 g) and freshly distilled toluene (150 cc) are introduced into a 500 cc three-neck flask equipped with a dropping funnel and a condenser, and protected against moisture by a calcium chloride guard tube. The solution is heated under reflux (110°C) for 22 hours under a nitrogen atmosphere and then cooled. A 2 N aqueous sodium hydroxide solution (33 cc) is then run in followed by an 0.316 N aqueous methylchloramine solution (190 cc), the addition of which takes 9 minutes. The mixture is stirred for 1 hour and then decanted. The organic layer is washed with water until it has a pH of 6 and is then extracted with 2 N hydrochloric acid (5 times 50 cc), dried over sodium sulfate, filtered and evaporated. Recrystallization of the residue from petroleum ether yields some unconverted 5-methyl-dibenzo[b,f]azepine (2.17 g).

The aqueous acid solution is rendered alkaline by adding 2 N sodium hydroxide solution. After extracting with diethyl ether (3 times 100 cc), drying the extracts over potassium carbonate, treating them with decolorizing charcoal, filtering and evaporating the ether, a yellowish oil (0.9 g), identified

as 5-methyl-10-methylamino-10,11-dihydrodibenzo[b,f]azepine, is obtained in a yield of 37.5%.

Methylchloramine can be prepared by adding an aqueous solution of sodium hypochlorite to an aqueous solution of methylamine in accordance with the process described by W.S. Metcalf, J. Chem. Soc.1942,148.

References

Merck Index 5781
DFU 6 (8) 479 (1981)
Kleeman& Engel p. 569
I.N. p. 605
Linares, H.; British Patent 1,323,219; July 11, 1973; assigned to Rhone-Poulenc SA
Fouche, J.C.L. and Gueremy, C.G.A.; US Patent 3,622,565; November 23, 1971; assigned to Rhone-Poulenc S.A.

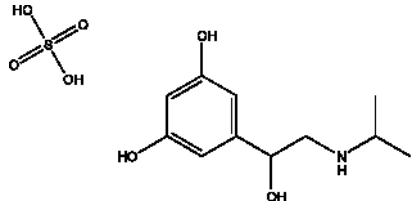
METAPROTERENOL SULFATE

Therapeutic Function: Bronchodilator

Chemical Name: 5-[1-Hydroxy-2-[(1-methylethyl)amino]ethyl]-1,3-benzenediol sulfate

Common Name: Orciprenaline sulfate

Structural Formula:



Chemical Abstracts Registry No.: 5874-97-5; 586-06-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Alupent	Boehringer Ingelheim	W. Germany	1961
Dosalupent	Boehringer Ingelheim	Italy	1963
Alupent	Badrial	France	1966
Alupent	Boehringer Ingelheim	US	1973
Metaprel	Dorsey	US	1973
Alotec	Tanabe	Japan	-
Astmopent	Polfa	Poland	-

Trade Name	Manufacturer	Country	Year Introduced
Astop	Rafa	Israel	-
Lenasma	Ravasini	Italy	-
Novasmasol	Zambeletti	Italy	-

Raw Materials

3,5-Diacetoxyacetophenone
Isopropylamine
Bromine
Hydrogen

Manufacturing Process

In an initial operation, 3,5-diacetoxyacetophenone was reacted first with bromine and then with isopropylamine to give 1-(3,5-dihydroxyphenyl)-2-isopropylaminoethanone.

59 g of 1-(3,5-dihydroxy-phenyl)-2-isopropylaminoethanone (free base) were dissolved in 590 cc of methanol, and the solution was hydrogenated in the presence of about 80 g Raney nickel at room temperature and under a pressure of 5 atm. Hydrogen absorption was terminated after a few minutes. The catalyst was separated by vacuum filtration, and the filtrate, an ethanolic solution of 1-(3,5-dihydroxyphenyl)-1-hydroxy-2-isopropylaminoethane, was admixed with the calculated amount of an alcoholic 20% sulfuric acid solution. A crystalline precipitate formed which was filtered off and washed with alcohol. For purification, the product was dissolved in water and the solution was filtered through iron-free charcoal.

Thereafter, the filtrate was evaporated to dryness in vacuo and the residue was taken up in alcohol. The crystalline precipitate which separated out after some standing was separated by vacuum filtration and washed with alcohol. After recrystallization from 90% alcohol, 61 g (83.2% of theory) of 1-(3,5-dihydroxyphenyl)-1-hydroxy-2-isopropylamino-ethane sulfate, MP 202° to 203°C, was obtained.

References

Merck Index 5782
Kleeman & Engel p. 658
PDR pp. 674, 848
OCDSVol. 1 p.64 (1977)
I.N. p. 705
REM p. 887
Thoma, O. and Zeile, K.; US Patent 3,341,594; September 12, 1967; assigned to Boehringer Ingelheim G.m.b.H., Germany

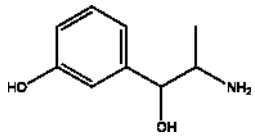
METARAMINOL

Therapeutic Function: Hypertensive

Chemical Name: α-(1-Aminoethyl)-3-hydroxybenzenemethanol

Common Name: m-Hydroxynorephedrine; m-Hydroxypropadrine; Metaradrine

Structural Formula:



Chemical Abstracts Registry No.: 54-49-9

Trade Name	Manufacturer	Country	Year Introduced
Aramine	MSD	US	1952
Pressoral	Travenol	US	1963
Pressonex	Winthrop	US	1963
Aramine	MSD-Chibret	France	1963
Araminiurn	Sharp and Dohme	W. Germany	-
Ararninon	Merck-Banyu	Japan	-
Icopal B	Bayer	-	-
Levicor	Bioindustria	Italy	-
Metaraminol	Bristol	US	-

Raw Materials

m-Hydroxyphenylethyl ketone
Butyl nitrite
Hydrogen

Manufacturing Process

The hydrochloride of the m-hydroxyphenylpropanolamine may be prepared by dissolving or suspending 90 parts of m-hydroxyphenylethyl ketone, O = $C(C_6H_4\text{-}OH)\text{-}C_2H_5$, in about 400 parts of ether. Hydrogen chloride is slowly bubbled through the solution or suspension while agitating it and 61.8 g of butyl nitrite is added during the course of 60 to 90 minutes. During the addition of the butyl nitrite the suspended m-hydroxyphenylethyl ketone gradually dissolves. The mixture or solution is allowed to stand for at least an hour, but preferably overnight. It is then repeatedly extracted with dilute alkali until all alkali-soluble material is removed. The alkaline extract is slowly acidified and the precipitate which forms is crude m-hydroxyphenyl-α-oximinoethyl ketone. After recrystallization from water this melts at 138°C.

10.8 parts of the meta ketone is dissolved in about 125 parts of absolute alcohol containing 5.6 parts of hydrogen chloride. The solution is agitated with a catalyst such as the palladium catalyst above described in an atmsophere of

hydrogen until no more hydrogen is absorbed. This requires from 60 to 90 minutes or more. When reduction is complete the catalyst is filtered off and the filtrate evaporated to dryness by being placed in a desiccator at ordinary temperature.

The residue is the hydrochloride of m-hydroxyphenyl-α-aminoethyl ketone. This is purified by recrystallization from absolute alcohol. It is then dissolved in 200 parts of water and agitated with a further quantity of the palladium catalyst in an atmosphere of hydrogen until saturated. The product thus recovered from the solution is the hydrochloride of m-hydroxyphenylpropanol amine. After recrystallization from absolute alcohol this melts at 177°C. The corresponding free base can be prepared from the hydrochloride by treatment with ammonia, according to US Patent 1,995,709.

Metaraminol is often used in the form of the bitartrate.

References

Merck Index 5783
Kleeman & Engel p. 570
PDR pp. 695, 1140
I.N. p. 605
REM p. 888
Bockmuhl, M., Ehrhart, G. and Stein, L.; US Patent 1,948,162; February 20, 1934; assigned to Winthrop Chemical Company, Inc.
Bockmuhl, M., Ehrhart, G. and Stein, L.; US Patent 1,951,302; March 13,1934; assigned to Winthrop Chemical Company, Inc.
Hartung, W.H.; US Patent 1,995,709; March 26,1935; assigned to Sharp & Dohme, Inc.

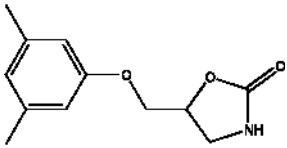
METAXALONE

Therapeutic Function: Muscle relaxant

Chemical Name: 5-(3,5-Dimethylphenoxymethyl)-2-oxazolidnone

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 1665-48-1

Trade Name	Manufacturer	Country	Year Introduced
Skelaxin	Robins	US	1962

Raw Materials

Urea
3-(3',5'-Dimethylphenoxy)-1,2-propanediol

Manufacturing Process

Urea (118 g, 1.96 mols) was added to 192 g (0.98 mol) of 3-(3',5'-dimethylphenoxy)-1,2-propane-diol which had previously been heated to 150°C. The reaction mixture was then heated rapidly to 195° to 200°C and maintained at this temperature for 5 hours with constant stirring. The resulting mixture was partitioned between water and ethyl acetate and the ethyl acetate layer was dried over sodium sulfate and concentrated. The residue was distilled in vacuo and the fraction boiling at 220° to 225°C/1.5 mm was collected. Yield, 172 g (79%). The distillate was crystallized from dry ethyl acetate; MP, 121.5° to 123°C.

References

Merck Index 5785
Kleeman & Engel. p.571
PDR p. 783
OCDS Vol. 1 p. 119 (1977)
I.N.p. 606
REMp. 927
Lunsford, C.D.; US Patent 3,062,827; November 6, 1962; assigned to A.H. Robins Company, Inc.

METERGOLINE

Therapeutic Function: Analgesic

Chemical Name: [[(8β)-1,6-Dimethylergolin-8-yl]methyl]carbamic acid phenylmethyl ester

Common Name: Methyl-N-carbobenzoxy-dihydro-lysergamine

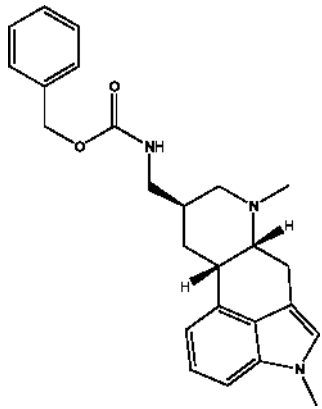
Chemical Abstracts Registry No.: 17692-51-2

Trade Name	Manufacturer	Country	Year Introduced
Liserdol	Farmitalia	Italy	1970

Raw Materials

1-Methyl-dihydro-lysergamine
Carbobenzoxy chloride

Structural Formula:



Manufacturing Process

16 g of 1-methyl-dihydro-lysergamine (the 10-position hydrogen has the α-configuration) are dissolved in 80 cc of anhydrous pyridine by mildly heating. To the solution, cooled to -10°C and stirred, 18 cc of 85% carbobenzoxy-chloride (in toluene) diluted in 36 cc of chloroform are added dropwise, rather rapidly. The mixture is kept at -10°C during the addition, and for 10 minutes afterwards. The cooling means is removed and the temperature is allowed to rise to room level in 10 minutes. The reaction mixture is diluted with 240 cc of chloroform and rapidly washed with 80 cc of 5% aqueous sodium hydroxide solution, with saturated aqueous sodium bicarbonate solution, and finally with water.

The chloroform solution is briefly dried over anhydrous sodium sulfate and evaporated to dryness in vacuo at 40°C. The oily residue is taken up in 160 cc of benzene and passed through a column containing 48 g of alumina. The column is then eluted with further 160 cc of benzene. The collected eluates are evaporated in vacuo at 40°C. The thick oily residue is mixed with a small amount of anhydrous diethyl ether. After some time a crystalline mass is obtained, which is collected and washed with a small amount of benzene and diethyl ether. 12 g of white crystals are obtained, melting at 146° to 148°C.

References

Merck Index 5790
I.N. p. 606
Camerino, B., Patelli, B. and Glaesser, A.; US Patent 3,238311; March 1, 1966; assigned to Societa Farmaceutici Italia, Italy

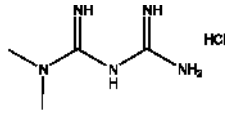
METFORMIN HYDROCHLORIDE

Therapeutic Function: Oral hypoglycemic

Chemical Name: Biguanide, 1,1-dimethyl-, hydrochloride

Common Name: Dimethylguanilguanidini chloridum; Metformin

Structural Formula:



Chemical Abstracts Registry No.: 1115-70-4; 15537-72-1; 657-24-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Diabetex	Germania	-	-
Diabetex	Terrapharm	-	-
Diaformin	Alphapharm	-	-
Diaphage	UPM	-	-
D.B.I.	Montpellier	-	-
Glucomet	USV	India	-
Glucophage	Laboratoires Aron	France	-
Glucophage	Bristol-Meyers Squibb	USA	-
Metforal	Menarini	Italy	-

Raw Materials

Dimethylamine
Dicyanamide
Hydrogen chloride

Manufacturing Process

The boiling mixture of 1,000 L xylene, 450 kg dimethylamine and 840 kg dicyanamide was added 365 kg hydrogene chloride. Yield of biguanide, 1,1-dimethyl-, hydrochloride 1,588 kg (96%). Biguanide, 1,1-dimethyl-, hydrochloride may be recrystallysed from methanol.

References

Patent DE 1023757
Patent FR 2,322,860; Sep. 1975; Assigned to ARON S.A.R.L.

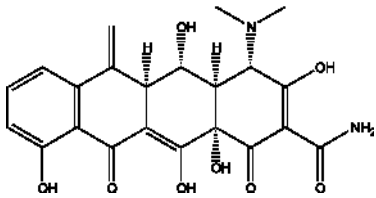
METHACYCLINE

Therapeutic Function: Antibiotic

Chemical Name: 4-Dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methylene-1,11-dioxo-2-naphthacenecarboxamide

Common Name: 6-Methylene-5-hydroxytetracycline

Structural Formula:



Chemical Abstracts Registry No.: 914-00-1; 3963-95-9 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Rondomycin	Pfizer	UK	1963
Megamycine	Creat	France	1966
Rondomycin	Wallace	US	1966
Adramycin	Janko	Japan	-
Apriclina	Lancet	Italy	-
Benciclina	Benvegna	Italy	-
Boscillina	Molteni	Italy	-
Brevicillina	Neopharmed	Italy	-
Ciclobiotic	Beta	Italy	-
Ciclum	Italsuisse	Italy	-
Duecap	Sam	Italy	-
Duplaciclina	Locatelli	Italy	-
Duramicina	Bergamon	Italy	-
Dynamicin	Medal	Italy	-
Esarondil	Terapeutico	Italy	-
Esquilin	Saita	Italy	-
Fitociclina	Ifisa	Italy	-
Franciclina	Francia	Italy	-
Francomicina	N.C.S.N.	Italy	-
Gammaciclina	Sthol	Italy	-
Globociclina	Importex	Italy	-
Idrossimicina	San Carlo	Italy	-
Isometa	Isom	Italy	-
Largomicina	Jamco	Italy	-
Medomycin	Medosan	Italy	-
Megamycine	C.R.E.A.T.	Italy	-
Metabiotic	Panther-Osfa	Italy	-
Metabioticon BG	Boniscontro-Gazzone	Italy	-

Trade Name	Manufacturer	Country	Year Introduced
Metac	Dima	Italy	-
Metacil	Ibirn	Italy	-
Metaclin	Medici	Italy	-
Metaclor	Esset	Italy	-
Metadomus	Medici Domus	Italy	-
Metagram	Zanardi	Italy	-
Metilenbiotic	Coli	Italy	-
Microcilina	Biotrading	Italy	-
Mit-Ciclina	Von Boch	Italy	-
Molciclina	Molteni	Italy	-
Optimicine	Biochemie	Austria	-
Ossirondil	Gazzini	Italy	-
Paveciclina	I.B.P.	Italy	-
Physiomycine	Roland-Marie	France	-
Piziacina	Farmochimica	Italy	-
Plurigram	Lafare	Italy	-
Prontomicina	Tosi-Novara	Italy	-
Quickmcina	Panthox and Burck	Italy	-
Radiomicin	Radiopharma	Italy	-
Rindex	Sidus	Italy	-
Rotilen	Arnelix	Italy	-
Sernamicina	Pharma Williams	Italy	-
Stafilon	A.G.I.P.S.	Italy	-
Tachiciclina	C.T.	Italy	-
Tetrabios	Ausonia	Italy	-
Tetranovo	Totalpharm	Italy	-
Tiberciclina	Tiber	Italy	-
Ticomicina	Benedetti	Italy	-
Treis-Ciclina	Ecobi	Italy	-
Valcin	Chemil	Italy	-
Vitabiotic	PHARMEX	Italy	-
Wassermicina	Wassermann	Italy	-
Yatrociclina	Italfarmaco	Italy	-
Zermicina	Pulitzer	Italy	-

Raw Materials

Oxytetracycline
Sulfur trioxide
Hydrogen fluoride

Manufacturing Process

To a stirred solution of 4.6 g (0.01 mol) of anhydrous oxytetracycline in 40 ml of dry tetrahydrofuran is added 3.5 g (0.021 mol) of pyridine-sulfur trioxide complex. After 16 hours of stirring at room temperature, the resulting suspension is filtered, and the solid is slurried with 25 ml of 2% hydrochloric acid for 10 minutes, filtered and thoroughly washed with methanol followed by ether. The pale yellow crystalline 5-oxytetracycline-6,12-hemiketal-12-sulfuric

acid ester melts at 210°C.

500 mg 5-oxytetracycline-6,12-hemiketal-12-sulfuric acid ester, prepared as described, is added to 4 ml dry liquid hydrogen fluoride, and the mixture is stirred for 1.5 hours at ice bath temperature. The hydrogen fluoride is then evaporated in a stream of nitrogen and the resulting gummy solids are triturated with about 15 ml ether and filtered. The resulting solid hydrofluoride salt is further purified by suspending in water, adjusting the pH to about 4, and extracting the 6-methylene-5-oxytetracycline free base from the aqueous phase with ethyl acetate. The extract is separated and evaporated to dryness under reduced pressure. The resulting residue is triturated with ether and filtered, and the solid is recrystallized from methanol-acetone-ether-concentrated hydrochloric acid to obtain the product as a purified hydrochloride, according to US Patent 3,026,354.

References

Merck Index 5798
Kleeman & Engel p. 567
PDR p. 1881
OCDS Vol. 2 p. 227 (1980)
DOT 1 (1) 10 (1965)
I.N. p. 603
REM p. 1205
Blackwood, R.K., Rennhard, H.H., Beereboom, J.J. and Stephens, C.R., Jr.; US Patent 2,984,686; May 16, 1961; assigned to Chas. Pfizer & Co., Inc.
Biackwood, R.K.; US Patent 3,026,354; March20, 1962; assigned to Chas. Pfizer & Co., Inc.

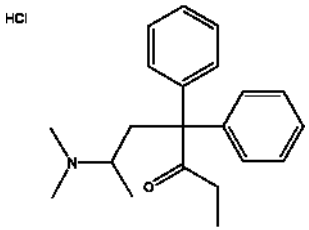
METHADONE HYDROCHLORIDE

Therapeutic Function: Narcotic analgesic

Chemical Name: 6-Dimethylamino-4,4-diphenyl-3-heptanone hydrochloride

Common Name: Amidone hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 1095-90-5; 76-99-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Dolophine	Lilly	US	1947
Adanon	Winthrop	US	1947
Westadone	Vitarine	US	1973
Adolan	Abic	Israel	-
Eptadone	Tosi	Italy	-
Heptadon	E.B.E.W.E.	Austria	-
Heptanal	Treupha	Switz.	-
Heptanon	Pliva	Yugoslavia	-
Ketalgin	Amino	Switz.	-
Mephenon	Spemsa	Italy	-
Optalgin	Dr. Wust	Switz.	-
Physeptone	Burroughs-Wellcome	UK	-

Raw Materials

Ethyl bromide
Diphenylacetonitrile
Hydrogen chloride
Magnesium
2-Chloro-1-dimethylaminopropane

Manufacturing Process

Diphenylacetonitrile is condensed with 2-chloro-1-dimethylaminopropane to give 4-(dimethylamino)-2,2-diphenyl valeronitrile. It is then reacted with ethyl magnesium bromide and then hydrolyzed using HCl to give methadone hydrochloride.

References

Merck Index 5799
Kleeman & Engel p. 573
PDR pp. 1048, 1061, 1571
OCDS Vol.1 pp.79, 289, 298 (1977) and 2, 328 (1980)
I.N. p. 607
REM p. 1109
Resolution of Optical Isomers:
Howe, E.E. and Tishler, M.; US Patent 2,644,010; June 30, 1953; assigned to Merck & Co., Inc.
Zaugg, H.E.; US Patent 2,983,757; May 9, 1961; assigned to Abbott Laboratories

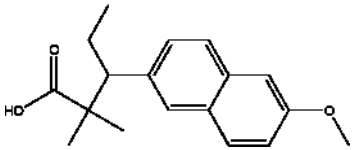
METHALLENESTRIL

Therapeutic Function: Estrogen

Chemical Name: β-Ethyl-6-methoxy-α,α-dimethyl-2-naphthalenepropionic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 517-18-0

Trade Name	Manufacturer	Country	Year Introduced
Vallestril	Searle	US	1952
Cur-Men	Novapharma	Italy	-
Ercostrol	Erco	Denmark	-
Ercostrol	Green Cross	Japan	-

Raw Materials

Copper cyanide
Ethyl bromide
Magnesium
Hydrogen
2-Bromo-6-methoxynaphthalene
Ethyl bromoisobutyrate
Potassium bisulfate
Sodium hydroxide

Manufacturing Process

A first step involves the preparation of 2-cyano-6-methoxynaphthalene (cyanonerolin). 90 g of 2-bromo-6-methoxynaphthalene are heated with 60 g of cuprous cyanide in a metal bath at 240° to 250°C stirring for one hour. At the instant when the cuprous cyanide begins to react and dissolves, the mass turns brown, liquefies and heats up strongly. The molten mass is poured onto a cold surface, is pulverized and sifted. This powder is treated with dilute ammonia (1 liter of water to 300 cc of commercial ammonia solution). The solution is filtered on a Buchner filter and the precipitate that remains on the filter is washed with dilute ammonia and then with water.

After drying, the residue is treated in a Kumagawa extracting apparatus with boiling benzene. The benzene is evaporated and the residue is distilled in vacuo. About 50 g of cyanonerolin (BP = 205° to 208°C/14 mm) are obtained with a yield of about 70%. By recrystallization in 200 cc of methyl alcohol, 40 g of the product are obtained in absolutely pure state, in the shape of beautiful colorless needles (MP = 103°C with the Maquene block). By concentrating the mother liquor to half its original volume, a further 3.6 g of pure product are obtained.

The 2-cyano-6-methoxy-naphthaleneis in turn converted by successive reactions into: (a) β-ketonic ester, (b) ester-alcohol, (c) β-ethylene ester by dehydration, (d) saturated ester, and (e) [3-(6-methoxy-2-naphthyl)]2,2-dimethyl pentanoic acid which is the required product.

(A) Obtaining a β-Ketonic Ester by Reacting Ethyl Bromoisobutyrate with Cyanonerolin: 9 g of cyanonerolin are heated in a reflux apparatus for 40 minutes with 7 g of zinc and 19 g of ethyl bromoisobutyrate in the presence

of 150 cc of anhydrous benzene. After cooling, the mixture is filtered to eliminate unreacted zinc and is hydrolyzed by stirring for one hour with dilute sulfuric acid (10 cc of sulfuric acid to 200 cc of water). The benzene layer is washed, dried and the solvent is eliminated. It is purified by recrystallization in methyl alcohol. 12.5 g of ketonic ester (MP = 72.5° to 73.5°C) are thus obtained in the form of large prismatic crystals.

(B) Obtaining an Ester-Alcohol by Reacting Magnesium Ethyl Bromide with the Previous Ketonic Ester: 10 g of the previous ester dissolved in 40 cc of anhydrous benzene are gradually poured while stirring into an iced solution of magnesium ethyl bromide prepared from 1.035 g of magnesium, 4.15 cc of ethyl bromide and 40 cc of anhydrous ether. After heating in a reflux apparatus for one-half hour, the mixture is poured into ice in the presence of ammonium chloride.

After washing the ether-benzene layer, the solvents are eliminated in vacuo and an ester-alcohol is thus obtained with a yield of 98%, in the form of a transparent resin. This resin, if treated with petroleum ether, yields 6.35 g of ester-alcohol in the form of fine needles (MP = 66.68°C) which are very soluble in the chief organic solvents and in petroleum ether.

(C) Conversion into Ethyl [3(6-Methoxy-2-Naphthyl)] 2,2-Dimethyl-3-Pentanoate by Dehydrating the Previous Ester-Alcohol: The semi-oily raw product of the previous reaction is dehydrated by heating with its own weight of potassium bisulfate to 180°C until boiling stops. After cooling, the magma is removed from the anhydrous ether in small portions. The ether is then evaporated and an ethylene ester is obtained in the form of an oil which slowly solidifies, with a yield of 98%. The product, after being purified by chromatography, melts at 48° to 51°C.

(D) Obtaining Ethyl [3-(6-Methoxy-2-Naphthyl)] 2,2-Dimethyl Pentanoate by Hydrogenation of the Previous Ethylene Ester: 3.5 g of the previous ethylene ester, purified by chromatography, are hydrogenated in the presence of 3.6 g of platinum in 30 cc of ether. The quantity of hydrogen fixed corresponds to the theoretical quantity calculated. After filtering, the ether is evaporated, 3.45 g of ester are thus obtained in the form of an oil which quickly solidifies. Purification is effected by chromatography.

(E) Obtaining [3-(6-Methoxy-2-Naphthyl)] 2,2-Dimethyl Pentanoic Acid: 2.5 g of the previous ester are saponified by means of 15 cc of soda lye and 25 cc of methyl glycol. The mixture is boiled for one hour, diluted with water and, after cooling, is treated twice with ether in order to eliminate the remaining neutral fractions. The aqueous layer is precipitated by means of 15 cc of acetic acid. 2.1 g of raw acid are obtained. After effecting two crystallizations in 10 parts of acetic acid mixed with 3 parts of water, fine needles are obtained which are grouped in rosettes and melt at 131.5° to 132.5°C.

References

Merck Index 5803
Kleeman & Engel p. 574
OCDS Vol. 1 p. 87 (1977)
I.N. p. 608
Horeau, A. and Jacques, J.; US Patent 2,547,123; April 3, 1951

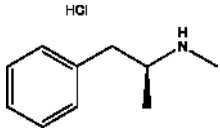
METHAMPHETAMINE HYDROCHLORIDE

Therapeutic Function: Sympathomimetic, Central stimulant

Chemical Name: Benzeneethanamine, N,alpha-dimethyl-, hydrochloride, (S)-

Common Name: Desoxyephedrine hydrochloride; Metamfetamine hydrochloride; Metamphetamine hydrochloride; Methaphetamine hydrochloride; Methylamphetamine hydrochloride; Phenylmethylaminopropane hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 51-57-0 ; 537-46-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Desoxyn	Abbott Laboratories	-	-
Amphedroxyn	Lilly	-	-
Destim	Central Pharm.	-	-
Drinalfa	Squibb	-	-
Gerobit	Gerot	-	-
Isophen	Knoll	-	-
Madrine	Langley	-	-
Methampex	Lemmon	-	-
Methampex	Teva	-	-
Methedrine	Burroughs-Wellcome	-	-
Pervitin	Temmler	-	-
Soxysympamine	Ferndale	-	-
Syndrox	McNeil	-	-
Tonedron	Grimault	-	-

Raw Materials

Ephedrine, (-)-	Platinum on carbon
Phenylisopropylamine	Hydrochloric acid

Manufacturing Process

2 Methods of prepearing of methamphetamine:

1. (-)-Ephedrin was reduced by hydrogenesation with hydrogen in the presence of Pt-C catalyst to give the (+)-N-α-dimethylphenethylamine (methamphetamine), melting point 172°-174°C.

2. Methamphetamine was obtained by the methylation of phenylisopropylamine.

To give methamphetamine hydrochloride the base methamphetamine was treated by eqimolar quantity of hydrochloric acid.

References

Haletsky A.M.; Pharmaceutical Chemistry, Medicina. L., 1966, 761p.
Emde H.; Helv. Chim. Acta 1929, v. 12, p. 365

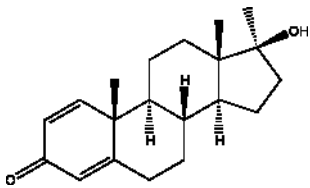
METHANDROSTENOLONE

Therapeutic Function: Androgen, Anabolic

Chemical Name: 17β-Hydroxy-17-methylandrosta-1,4-dien-3-one

Common Name: Methandienone

Structural Formula:



Chemical Abstracts Registry No.: 72-63-9

Trade Name	Manufacturer	Country	Year Introduced
Dianabol	Ciba	US	1960
Abirol	Takeda	Japan	-
Anabolin	Medica	Finland	-
Anoredan	Kodama	Japan	-
Encephan	Sato/Shinshin	-	-
Lanabolin	Labatec	Switz.	-
Metabolina	Guidi	Italy	-
Metanabol	Polfa	Poland	-
Metastenol	Farber-R.E.F.	Italy	-
Naposim	Terapia	Rumania	-
Nerobol	Galenika	Yugoslavia	-
Perbolin	Ion	Italy	-
Vanabol	Vitrum	Sweden	-

Raw Materials

Bacterium Didymella lycopersici
17β-Methyl testosterone
Selenium dioxide

Manufacturing Process

As described in US Patent 2,929,763, methandrostenolone may be made by a fermentation route. 2 g of sodium nitrate, 1 g of primary potassium orthophosphate, 0.5 g of magnesium sulfate heptahydrate, 0.5 g of potassium chloride, 50 g of glucose and 1 g of Difco yeast extract are dissolved in one liter of tap water, brought to pH 5 by addition of a sodium hydroxide solution and sterilized. The resulting nutrient solution is inoculated with 50 cc of a 4-day-old shaking culture of Didymella lycopersici and shaken for 48 hours at 27°C, whereby the culture becomes well developed.

To two liters of a culture so prepared there is added under sterile conditions a solution of 500 mg of 17α-methyl-testosterone in 15 cc of acetone. Shaking is carried out for 3 days at 27°C, the mycellium then filtered off with suction, washed with water and ethyl acetate and the combined filtrates extracted with ethyl acetate. The extraction residue obtained after evaporation of the solvent is dissolved in a little acetone. On addition of ether, the 1-dehydro-17α-methyl-testosterone is obtained in compact crystals. MP 163° to 164°C.

An alternative synthetic route is described in US Patent 2,900,398 as follows. A suspension of 30 g of 17α-methyl-testosterone and 10 g of selenium dioxide in 600 cc of tertiary amyl alcohol is treated with 60 g of magnesium powder and 6 cc of glacial acetic acid.

The mixture is refluxed for 24 hours with good stirring in an atmosphere of nitrogen, another 10 g of selenium dioxide being added after 10 hours. After some cooling, the suspension is filtered through some Hyflo and washed thoroughly with ethyl acetate. The resulting brown solution is evaporated in vacuo and the residue dissolved in ethyl acetate.

The ethyl acetate solution is then washed with water, dried and evaporated. To remove any selenium still present, the residue is dissolved in 200 cc of methanol and mixed with 100 g of iron powder and 2 g of active carbon. The mixture is heated for 30 minutes with stirring under reflux, then filtered with suction, washed with methanol and the solution evaporated in vacuo. The residue is then chromatographed on 900 g of aluminum oxide. The residues of the evaporated benzene and ether fractions are treated with active carbon in methanol or acetone, evaporated again, and the residue recrystallized from a mixture of acetone and ether. There are obtained 17.5 g of pure 1-dehydro-17α-methyl-testosterone which melts at 163° to 164°C.

References

Merck Index 5810
Kleeman & Engel p. 570
OCDS Vol. 1 p. 173 (1977)
I.N. p. 605

REM p.998
Wettstein, A., Hunger, A., Meystre, C. and Ehmann, L.; US Patent 2,900,398; August 18, 1959; assigned to Ciba Pharmaceutical Products, Inc.
Wettstein, A., Vischer, E. and Meystre, C.; US Patent 2,929,763; March 22, 1960; assigned to Ciba Pharmaceutical Products, Inc.

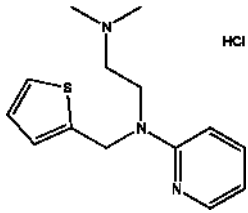
METHAPYRILENE HYDROCHLORIDE

Therapeutic Function: Antihistaminic

Chemical Name: N,N-Dimethyl-N'-2-pyridinyl-N'-(2-thienylmethyl)-1,2-ethanediamine hydrochloride

Common Name: Thenylpyramine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 135-23-9; 91-80-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Thenylene	Abbott	US	1947
Pyrathyn	Davis Sly	US	1947
Histadyl	Lilly	US	1948
Semikon	Beecham	US	1949
Lullamin	Reed Carnrick	US	1954
Dozar	Tutag	US	1956
Allergin	Myers-Carter	US	-
Allerest	Pharmacraft	US	-
Brexin	Savage	US	-
Citra	Boyle	US	-
Ephed-Organidin	Wallace	US	-
Excedrin P.M.	Bristol-Myers	US	-
Histadyl	Lilly	US	-
M.P.	Dymond	Canada	-
Sedanoct	Woalm-Pharma	W. Germany	-
Contac	Vonora	W. Germany	-
Co-Pyronil	Lilly	Italy	-

Raw Materials

2-Aminopyridine
2-Thenyl chloride
Hydrogen chloride
N,N-Dimethyl-β-chloroethylamine
Sodium amide

Manufacturing Process

To a slurry of sodamide in 200 cc of toluene representing 6.7 g of sodium was added at 30° to 40°C, 32.3 g (0.31 mol) of 2-aminopyridine. The mixture was heated to reflux temperature and was refluxed for 1½ hours. To the resulting mixture was added over a period of approximately one hour a solution of 32 g of freshly distilled N,N-dimethyl-β-chloroethylamine in 40 to 50 cc of dry toluene, The reaction mixture was then heated for 2 hours at reflux temperature. Thereafter, 200 cc of water was added and the toluene layer was separated and washed with water. The toluene was stripped from the mixture by distillation and the residue was distilled under reduced pressure. The distillate was refractionated and the portion distilled at 93° to 103°C/1 mm was recovered. Yield of N-(2-pyridyl)-N',N'-dimethyl-ethylenediamine, 60%.

A solution of 20 g (0.121 mol) of N-(2-pyridyl)-N',N'-dimethyl-ethylenediamine in 25 cc of toluene was added to a slurry of sodamide in 100 cc of toluene representing 2.8 g of sodium. The mixture was refluxed for one hour. To this mixture was added over a period of ½ hour a solution of 16 g (0.121 mol) of 2-thenyl chloride in 25 cc of toluene. The resulting reaction mixture was refluxed for 3 hours. Thereafter, water was added and the toluene layer was separated and washed with water.

The toluene was then stripped off by distillation and the residue was distilled under reduced pressure. The main fraction was redistilled. Yield of N-(2-pyridyl)-N-(2-thenyl)-N',N'-dimethyl-ethylenediamine was 69%; BP 130° to 140°C/0.4 mm. A portion of the product was dissolved in ether and an ether solution of hydrogen chloride was added. The monohydrochloride of N-(2-pyridyl)-N-(2-thenyl)-N',N'-dimethyl-ethylenediamine which separated was washed with ether and dried.

References

Merck Index 5819
Kleeman & Engel p. 575
OCDS Vol. 1 p. 54 (1977)
I.N. p. 609
Kyrides, L.P.; US Patent 2,581,868; January 8, 1952; assigned to Monsanto Chemical Company

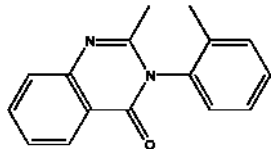
METHAQUALONE

Therapeutic Function: Hypnotic

Chemical Name: 2-Methyl-3-o-tolyl-4(3H)-quinazolinone

Common Name: Metolquizolone; Ortonal

Structural Formula:



Chemical Abstracts Registry No.: 72-44-6; 340-56-7 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Quaalude	Lemmon	US	1965
Sopor	Amer. Crit. Care	US	1967
Somnafac	Cooper	US	1968
Parest	Lemmon	US	1969
Quaalude	Rorer	Italy	1969
Optimil	Wallace	US	1972
Aqualon	Arcana	Austria	-
Cateudyl	Cavor	Belgium	-
Citexal	Draco	Sweden	-
Divinoctal	I.S.H.	France	-
Dormigoa	Scheurich	W. Germany	-
Dormir	Langley	Australia	-
Dormutil	Isis-Chemie	E. Germany	-
Hyptor	Bio-Chimique	Canada	-
Hyminal	Eisai	Japan	-
Mandrax	I.S.H.	France	-
Mequelon	Merck-Frosst	Canada	-
Meroctan	Sanwa	Japan	-
Methadorm	Eri	Canada	-
Metasedil	Cooper	Switz.	-
Mollinox	Asperal	Belgium	-
Motolon	Chinoin	Hungary	-
Nene	Sankyo	Japan	-
Nobadorm	Streuli	Switz.	-
Normi-Nox	Herbrand	W. Germany	-
Normorest	Doitsu-Aoi	Japan	-
Noxybel	Probel	Belgium	-
Oblioser	Gamaprod.	Australia	-
Optinoxan	Robisch	W. Germany	-
Parmilene	Chiesi	Italy	-
Paxidorm	Wallace	US	-
Pexaqualone	Therapex	Canada	-
Pro-Dorm	Schurholz	W. Germany	-
Revonal	Merck	UK	-
Rouqualone	Rougier	Canada	-

Trade Name	Manufacturer	Country	Year Introduced
Sedalone	Pharbec	Canada	-
Sleepinal	Medichem	Australia	-
Somnium	Fargal	Italy	-
Sovelin	Weifa	Norway	-
Sovinal	N.D. and K.	Denmark	-
Spasmipront	Mack	W. Germany	-
Tiqualone	Barlow Cote	Canada	-
Tualone	I.C.N.	Canada	-

Raw Materials

Anthranilic acid
o-Toluidine
Acetic anhydride
Hydrogen chloride

Manufacturing Process

Anthranilic acid (1 part) is dissolved in acetic anhydride (2 parts) and the temperature raised progressively to 190° to 200°C while distillation takes place. The last traces of acetic acid are removed under vacuum and, after cooling to about 50° to 60°C, o-toluidine (1 part) is added in portions.

The temperature is then raised to 170° to 200°C when the excess water and o-toluidine is gradually distilled off, finally maintaining the temperature at 180° to 200°C for 2 hours. After cooling to about 100°C dilute hydrochloric acid (3 parts) is added and the mixture boiled and stirred. The solution is then neutralized with NaOH with stirring and the product which separates is recrystallized twice from alcohol after decolorizing with carbon. Yield: 70% of theoretical, LIP 114° to 115°C.

References

Merck Index 5820
Kleeman & Engel p. 576
OCDS Vol. 1 p.353 (1977)
DOT 9 (6) 245 (1973)
I.N. p.610
REM p. 1072
Laboratoires Toraude, France; British Patent 843,073; August 4, 1960

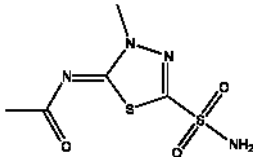
METHAZOLAMIDE

Therapeutic Function: Carbonic anhydrase inhibitor

Chemical Name: N-[5-(Aminosulfonyl)-3-methyl-1,3,4-thiadiazol-2(3H)-ylidene]acetamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 554-57-4

Trade Name	Manufacturer	Country	Year Introduced
Neptazane	Lederle	US	1959
Neptazane	Theraplix	France	1961

Raw Materials

5-Acetylimino-4-methyl-2-benzylmercapto-δ^2-1,3,4-thiadiazoline
Chlorine
Ammonia

Manufacturing Process

A suspension of 6 parts by weight of 5-acetylimino-4-methyl-2-benzylmercapto-δ^2-1,3,4-thiadiazoline in 180 parts by volume of 33% aqueous acetic acid was chlorinated at 5°C for 30 minutes. The solid was filtered off, dried, and added portion-wise to 100 parts by volume of liquid ammonia. The ammonia was removed under a stream of dry nitrogen.

The residual solid was partially dissolved in 10 parts by volume of water, filtered, and acidified to give 5-acetylimino-4-methyl-δ^2-1,3,4-thiadiazoline-2-sulfonamide. The product was purified by two recrystallizations from hot water.

References

Merck Index 5824
Kleeman & Engel p. 576
PDR p. 1021
OCDS Vol. 1 p. 250 (1977)
I.N. p. 610
REM p.936
Young, R.W., Wood, K.H. and Vaughan, J.R., Jr.; US Patent 2,783,241; February 26, 1957; assigned to American Cyanamid Company

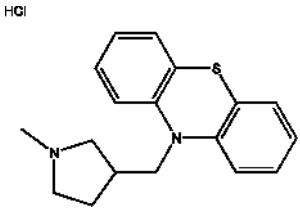
METHDILAZINE HYDROCHLORIDE

Therapeutic Function: Antipruritic

Chemical Name: 10-[(1-Methyl-3-pyrrolidinyl)methyl]phenothiazine hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 1229-35-2; 1982-37-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Tacaryl	Westwood	US	1960
Dilosyn	Duncan Flockhart	UK	-
Disyncran	Allard	France	-
Tacryl	Pharmacia	Sweden	-

Raw Materials

1-Methyl-3-pyrrolidylmethyl chloride
Phenothiazine
Hydrogen chloride

Manufacturing Process

10.8 parts of 10-(1-methyl-3-pyrrolidylmethyl) phenothiazine (prepared from 1-methyl-3-pyrrolidylmethyl chloride by reaction with phenothiazine) in 80 parts of 99% isopropyl alcohol were treated with a solution of 1.33 parts of hydrogen chloride in 30 parts of the same solvent. The clear light yellow solution soon deposited white crystals of the acid addition salt. After cooling overnight at 0°C, the crystalline product was collected on a filter, washed with 99% isopropyl alcohol and anhydrous ether and then dried in a vacuum oven at 95°C. Yield 10.4 parts, MP 187.5° to 189°C.

References

Merck Index 5826
Kleeman & Engel p. 577
PDR p. 1895

OCDS Vol. 1 p. 387 (1977)
I.N. p. 611
REM p. 1129
Feldkamp, R.F. and Wu, Y.H.; US Patent 2,945,855; July 19, 1960; assigned to Mead Johnson & Company

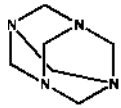
METHENAMINE HIPPURATE

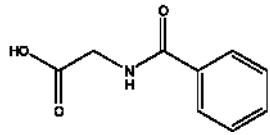
Therapeutic Function: Antibacterial (urinary)

Chemical Name: Hexamethylenetetramine hippurate

Common Name: -

Structural Formula:





Chemical Abstracts Registry No.: 5714-73-8

Trade Name	Manufacturer	Country	Year Introduced
Hiprex	Merrell National	US	1967
Hiprex	Riker	UK	1971
Hiprex	Kettelhack Riker	W. Germany	1975
Hipeksal	Leiras	Finland	-
Hippuran	Orion	Finland	-
Lisogerm	Labofarma	Brazil	-
Urotractan	Klinge	W. Germany	-

Raw Materials

Hexamethylenetetramine
Hippuric acid

Manufacturing Process

179 g (1 mol) hippuric acid (benzoyl glycine) and 140 g (1 mol) hexamethylenetetramine were heated under reflux in 500 ml methanol. The small amount of water necessary to give a clear, homogeneous solution was

added to the resulting reaction mixture which was then evaporated to dryness. The residue soon crystallized, a procedure that could be greatly accelerated by seeding with crystals of hexamethylenetetramine hippurate from a previous preparation. The resulting solid product was broken up and pulverized. Hexamethylenetetramine hippurate is stable on exposure to air and is soluble in water and alcohol. It melts at 105° to 110°C.

References

Merck Index 5832
PDR pp. 1227, 1453
DOT 4 (3) 108 (1968)
I.N. p. 611
REM p. 1167
Galat, A.; US Patent 3,004,026; October 10, 1961

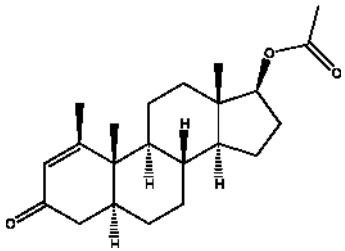
METHENOLONE ACETATE

Therapeutic Function: Anabolic

Chemical Name: 17β-Hydroxy-1β-methyl-5α-androst-l-ene-3-one acetate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 434-05-9; 153-00-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Primobolan	Schering	W. Germany	1961
Dacomid	Schering	W. Germany	-
Fortabol	Schering	W. Germany	-
Neuro-Fortabol	Schering	W. Germany	-

Raw Materials

Methyl iodide	$\Delta(^{1,4,6})$-Androstatrien-17β-ol-3-one-17-acetate
Magnesium	Hydrogen

Manufacturing Process

8.42 ml of methyl iodide are slowly added dropwise at room temperature with stirring in a nitrogen atmosphere to 3.067 g of magnesium turnings and 107 ml of absolute ether. After about 30 minutes, 185 ml of absolute tetrahydrofuran are slowly introduced and then liquid is distilled off until a boiling point of 62°C is reached. After cooling to room temperature, 613 mg of cuprous chloride are added and then 10 g of $\Delta^{1,4,6}$-androstatrien-17β-ol-3-one-17-acetate in 110 ml of tetrahydrofuran slowly introduced. After 30 minutes reaction time, the whole is cooled to 0C, the excess of Grignard reagent decomposed with saturated ammonium chloride solution, the product diluted with ether and the aqueous phase separated. The ethereal phase is washed consecutively with aqueous sodium thiosulfate solution, saturated ammonium chloride solution and water. It is dried over sodium sulfate and evaporated to dryness under vacuum. The residue is dissolved in 40 ml of pyridine and 20 ml of acetic anhydride and the solution kept for 16 hours at room temperature. It is then stirred into ice water and the precipitate filtered with suction, dried and recrystallized from isopropyl ether. 1α-Methyl-$\Delta^{4,6}$-androstadien-17β-ol-3-one-17-acetate is obtained. MP 156°C to 157°C; $[\alpha]_D^{25}$ = -33.8° (in $CHCl_3$; c = 0.9). Yield 65-70% of the theoretical.

4.67 g of 1α-methyl-$\Delta^{4,6}$-androstadien-17β-ol-3-one-17-acetate are dissolved in 273 ml of methanol and, after the addition of 350 mg of 10% palladium on calcium carbonate catalyst, hydrogenated until 1 mol equivalent of hydrogen has been taken up. After filtering off the catalyst, the solution is treated with 150 ml of 2N-hydrochloric acid and evaporated under vacuum to about 1/3 of the volume. The whole is then diluted with water and extracted with ether. The ethereal solution is washed with water until neutral, dried over sodium sulfate and evaporated. The crude product is heated on a steam bath for 90 minutes in 10 ml of pyridine and 10 ml of acetic anhydride. Extraction with ether is then carried out and the ethereal phase washed until neutral with water. The crude crystalline 1α-methyl-Δ^4-androsten-17β-ol-3-one-17-acetateobtained after drying and evaporation of the solution, melts at 122°C to 129°C. Yield 98% of the theoretical.

1α-Methyl-Δ^4-androsten-17β-ol-3-one-17-acetate when purified by recrystallization from isopropyl ether melts at 138°C to 139°C.

References

Merck Index 5839
Kleeman and Engel p. 571
OCDS Vol. 1 p. 175 (1977)
I.N. p. 606
Schering A.G.; British Patent 977,082; December 2, 1944

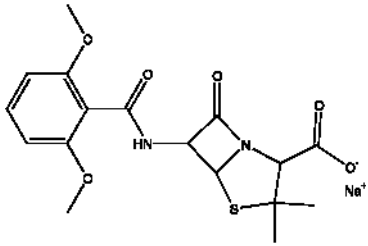
METHICILLIN SODIUM

Therapeutic Function: Antimicrobial

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

Common Name: 2,6-Dimethoxyphenylpenicillin sodium salt

Structural Formula:



Chemical Abstracts Registry No.: 7246-14-2

Trade Name	Manufacturer	Country	Year Introduced
Celbenin	Beecham	UK	1960
Staphcillin	Bristol	US	1960
Dimocillin	Squibb	US	1961
Flabelline	Delagrange	France	1961
Celbenin	Beecham	US	1973
Azapen	Pfizer	US	1975
Baclyn	Sifrochimica	Italy	-
Celpillina	Farmitalia	Italy	-
Ellecillina	Ellea	Italy	-
Esapenil B.G.	Boniscontro-Gazzone	Italy	-
Metin	C.S.L.	Australia	-
Methocillin	Meiji	Japan	-
Penysol	Saita	Italy	-
Sintespen	Coli	Italy	-
Staficyn	Firma	Italy	-

Raw Materials

6-Aminopenicillanic acid
2,6-Dimethoxybenzoyl chloride

Manufacturing Process

To a stirred suspension of 6-aminopenicillanic acid (540 g) in dry alcohol-free chloroform (3.75 liters) was added dry triethylamine (697 ml), and the mixture stirred for 10 minutes at room temperature. It was then cooled in a bath of crushed ice while a solution of 2,6-dimethoxybenzoyl chloride (500 g) in dry alcohol-free chloroform (3.75 liters) was added in a steady stream over 20 minutes. When all the acid chloride had been added the cooling bath was removed and the mixture stirred for 1 hour at room temperature. The mixture

was stirred vigorously and sufficient dilute hydrochloride acid (2.3 liters of 0.87 N) was added to give an aqueous layer of pH 2.5. The mixture was filtered, the layers separated, and only the chloroform layer was retained.

This was stirred vigorously while further dilute hydrochloric acid (0.69 liter of 0.87 N) was added to give an aqueous layer of pH 1. The layers were separated and again only the chloroform layer was retained. Then the chloroform layer was stirred vigorously while sufficient sodium bicarbonate solution (3.2 liters of 0.97 N) was added to give an aqueous layer of pH 6.7 to 7.0. The layers were separated and both were retained. The chloroform layer was stirred vigorously while sufficient sodium bicarbonate solution (50 ml of 0.97 N) was added to give an aqueous layer of pH 7.7, and again the layers were separated. The two bicarbonate extracts were combined, washed with ether (1 liter), and then concentrated at low temperature and pressure until the concentrate weighed 1,415 g.

The concentrate was treated with dry acetone (22 liters), the mixture well mixed, and then filtered to remove precipitated solid impurities. Further dry acetone (4 liters) was added to the filtrate, then the product started to crystallize slowly. Crystallization was allowed to proceed at a temperature between 0° and 3°C for 16 hours and then the product (563 g) was collected by filtration. Dry ether (7.5 liters) was added to the filtrate, and after several hours a second crop (203 g) of solid was collected. The two crops were combined to give sodium 2,6-dimethoxyphenylpenicillin monohydrate (766 g, 73%) as a white crystalline solid.

References

Merck Index 5842
Kleeman and Engel p. 591
PDR p. 713
OCDS Vol. 1 p.412 (1977)
I.N. p. 626
REM p. 1200
Doyle, F.P., Nayler, J.H.C. and Rolinson, G.N.; US Patent 2,951,839; September 6,1960

METHIMAZOLE

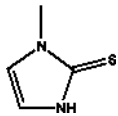
Therapeutic Function: Thyroid inhibitor

Chemical Name: 2H-Imidazole-2-thione, 1,3-dihydro-1-methyl-

Common Name: Mercazolyl(um); Methimazole; Methymazole; Thiamazole; Tiamazol

Chemical Abstracts Registry No.: 60-56-0

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Favistan	Asta	-	-
Favistan	Temmler Pharma	-	-
Tapazole	Lilly	-	-
Thiamazole	Marion Merrel Dow	-	-
Metisol	Polfa	-	-
Thyrozol	Merck	-	-

Raw Materials

Sulfuric acid
Bromine
Methylamine
Hydrochloric acid
3,3-Diethoxypropylamine
Potassium thiocyanate
Methylisothiocyanate
1,1-Diethoxyethane

Manufacturing Process

2 Methods of preparation of thiamazole:

1. To 2,2-diethoxyethylamine methylisothiocyanate was added and mixed after then 1-(2,2-diethoxy-ethyl)-3-methylthiourea was obtained.

The reaction of the 1-(2,2-diethoxyethyl)-3-methylthiourea with sulfuric acid yield thiamazole.

2. 1,1-Diethoxyethane was treated by bromine in the presence $CaCO_3$ and 2-bromo-1,1-diethoxyethane was obtained.

Then to the 2-bromo-1,1-diethoxyethane methylamine was added, mixed and reaction mixture was heated to 120°-130°C in autoclave. As the result (2,2-diethoxyethyl)methylamine was obtained.

(2,2-Diethoxyethyl)methylamine reacted with potassium thiocyanate in the presence of hydrochloric acid and give the thiamazole, yellow crystallic precipitate, melting point 144°-147°C.

References

Kleemann A., Engel J.; Pharmazeutische Wirkstoffe, GeorgThieme Verlag Stuttgart. New York, 1982
Chaletsky A.M. Pharmaceutical chemistry, Medicina, L., 1966, 761p.

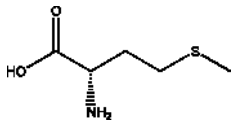
METHIONINE

Therapeutic Function: Lipotropic

Chemical Name: 2-Amino-4-(methylthio)butyric acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 63-68-3

Trade Name	Manufacturer	Country	Year Introduced
Meonine	Ives	US	1944
Lobamine	Opodex	France	1948
Oradash	Lambda	US	1955
Ammonil	Philips Roxane	US	1957
Dyprin	Lincoln	US	1958
Acimetion	Continental Pharma	Belgium	-
Amino-Serv	Milex	US	-
AminoPlex	Tyson	US	-
Antamon P.E.D.	Protea	S. Africa	-
Methnine	Medical Research	Australia	-
Monile	Cortunon	Canada	-
Ninol	Horner	Canada	-
Uracid	Wesley	US	-
Unanap	N. Amer. Pharm.	US	-
Urimeth	N. Amer. Pharm.	US	-

Raw Materials

Methyl mercaptan
Sodium cyanide
Sodium hydroxide
Acrolein
Ammonium chloride

Manufacturing Process

A 3-necked flask fitted with a stirrer, thermometer, gas inlet, dropping funnel, and brine-cooled reflux condenser was charged with 53 g (1.1 mol) methyl mercaptan and 0.35 g mercuric methyl mercaptide. After admitting 56 g (1.0

mol) of acrolein during the course of 15 minutes with an inside temperature of about 10°C, the temperature was allowed to rise spontaneously to 75°C, at which point an ice bath was applied. There was no indication of further reaction one hour after the addition of the acrolein. Distillation of the product gave 71 g (yield 68%) of β-methylmercaptopropionaldehyde, as described in US Patent 2,584,496.

Then as described in US Patent 2,732,400, β-methylmercaptopropionaldehyde (0.60 M) (56.5 g) is added to a stirred solution of sodium cyanide (0.66 M) (32.4 g) and ammonium chloride (0.63 M) (33.7 g) in water (140 ml). The temperature of the mixture rises to 49°C and is maintained at this point by heat evolution for about 5 minutes when it slowly begins to fall. Methanol (50 ml) is added and the mixture is stirred for 4 hours as the temperature falls to 28°C (room temperature).

After chilling to +12°C, additional methanol (35 ml) and a concentrated aqueous ammoniun hydroxide solution (1.4 M) (100 ml) are added and stirring is continued for 2 hours at a temperature maintained at from +5° to +15°C. The organic layer is separated and solvent is stripped from the aqueous layer at water aspirator pressure at a temperature below 40°C. The residue is extracted several times with chloroform and the chloroform extracts are combined with the separated oil. Chloroform is removed at water aspirator pressure at a temperature below 35°C to leave crude α-amino-γ-methylmercaptobutyronitrile (methionine nitrile) in 88% yield (68 g) as a clear, somewhat viscous oil.

The methionine nitrile (20 g) is dissolved in a solution prepared from 50 ml of aqueous 5 N sodium hydroxide solution and 65 ml of ethanol. The solution is then refluxed for 24 hours; ammonia is evolved. The solution is treated with activated carbon, filtered, acidified with glacial acetic acid (17 ml), chilled to -10°C and filtered to give crude product. This crude product is then slurried with a solution made up of 20 ml of water and 20 ml of methanol, filtered at -5° to +10°C and dried to give dl-methionine as white platelets.

References

Merck Index 5849
PDR pp. 1263,1807
I.N. p. 612
Pierson, E. and Tishler, M; US Patent 2,584,496; February 5, 1952; assigned to Merck and Co., Inc.
Weiss, M.J.; US Patent 2,732,400; January 24, 1956; assigned to American Cyanamid Company

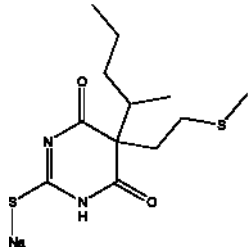
METHITURAL

Therapeutic Function: Hypnotic, Sedative

Chemical Name: Dihydro-5-(1-methylbutyl)-5-[2-(methylthio)ethyl]-2-thioxo-4,6-(1H,5H)pyrimidinedione monosodium salt

Common Name: Methioturiate

Structural Formula:



Chemical Abstracts Registry No.: 730-68-7

Trade Name	Manufacturer	Country	Year Introduced
Neraval	Schering	US	1956
Diogenal	Merck	-	-
Thiogenal	Merck	-	-

Raw Materials

Thiourea	Ethanol
Sodium	Sodium hydroxide
Sulfuric acid	β-Methyl-thioethyl-(1-methyl)-n-butyl-cyanoacetic acid ethyl ester

Manufacturing Process

A solution of 69 g of sodium in 1,380 cc of absolute alcohol is mixed with 257.4 g of β-methylthioethyl-(1-methyl)-n-butyl-cyano-acetic acid ethyl ester and 114 g of thiourea and the whole mass boiled under reflux with stirring for six hours. After concentration under vacuum the residue is taken up in 1.5 liters of water and shaken up thrice, each time with 300 cc of ether. The aqueous alcoholic layer is stripped, under vacuum, of the dissolved ether and mixed with 300 cc of 30% acetic acid under stirring and ice cooling. The precipitated material is sucked off, washed with water, dried and recrystallized from isopropyl alcohol. The thus obtained β-methyl-thioethyl-(1-methyl)-n-butyl-cyano-acetyl thiourea forms yellowish green crystals having a melting point of 229°C to 230C.

100 g of this product are boiled under reflux for three hours with 1 liter of 20% sulfuric acid. After cooling the mixture is taken up in ether, the ether solution washed with water, dried, filtered, concentrated and drawn off under vacuum. The residue is caused to crystallize by treatment with a mixture of 60 volume parts of methanol and 40 volume parts of petroleum benzene. The isolated crystals are recrystallized from the mentioned solvent mixture and yield thereby 5-β-methyl-thioethyl-5-(1-methyl)-n-butyl-2-thiobarbituric acid having a melting point of 79°C to 81°C.

20 g of the free acid are shaken up (in a machine) for one hour with 69.5 cc

n/l (normal) caustic soda. The filtered solution is concentrated under vacuum, the residue is taken up in absolute alcohol and again with drawn under vacuum. After two recrystallizations of the residue from isopropyl alcohol one obtains the readily water-soluble, analytically pure, sodium salt of the 5-β-methyl-thioethyl-5-(1 -methyl)-n-butyl-2-thiobarbituric acid.

References

Merck Index 5854
OCDS Vol. 1 p.275 (1977)
I.N. p. 612
Zima, O. and Von Werder, F.; US Patent 2,802,827; August 13,1957; assigned to Emanuel Merck (Germany)

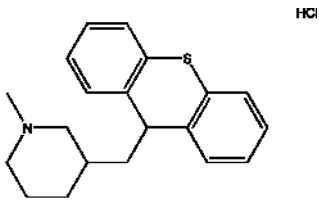
METHIXENE HYDROCHLORIDE

Therapeutic Function: Spasmolytic

Chemical Name: 1-Methyl-3-(9H-thioxanthen-9-yl-methyl)piperidine hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 1553-34-0; 4969-02-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Tremarit	Wander	W. Germany	1960
Tremaril	Wander	Italy	1962
Tremonil	Wander	UK	1963
Trest	Dorsey	US	1965
Atosil	Teikoku	Japan	-
Cholinfall	Tokyo Tanabe	Japan	-
Dalpan	Grelan	Japan	-
Inoball	Sawai	Japan	-
Methixart	Fuso	Japan	-
Methyloxan	Nippon Shoji	Japan	-

Trade Name	Manufacturer	Country	Year Introduced
Raunans	Kowa	Japan	-
Spasmenzyme	Salvoxyl-Wander	France	-
Thioperkin	Hokuriku	Japan	-

Raw Materials

Thioxanthene
Chlorobenzene
Sodium
N-Methyl-3-chloromethyl-piperidine
Hydrogen chloride

Manufacturing Process

To 4.9 g of finely pulverized sodium in 50 ml of absolute benzene add dropwise with stirring 12 g of chlorobenzene in 50 ml of absolute benzene. As soon as the exothermic reaction begins, maintain the temperature by cooling between 30° and 35°C, and continue stirring for 2 to 3 hours. To the resulting phenyl sodium add dropwise 19.8 g of thioxanthene in 120 ml of absolute benzene. The slightly exothermic reaction ceases after about 1 to 1½ hours.

To this newly formed 9-thioxanthyl sodium add dropwise, with stirring and cooling, 13.1 g of N-methyl-3-chloromethyl-piperidine in 30 to 40 ml of absolute benzene, then continue stirring at about 25°C for 1½ hours, and heat subsequently to 40°C for 1 hour. Decompose the resulting mixture by adding carefully a small amount of water, and then extract the newly formed base from the benzene solution by means of dilute hydrochloric acid. The aqueous hydrochloric solution is made alkaline by adding dilute sodium hydroxide, and the thioxanthene base is isolated by extraction with ether. This results in 22 g of a slightly yellow, viscous base of BP 171° to 175°C/0.07 mm.

The base is acidified with alcoholic hydrochloric acid. Alcohol-ether (1:2) is then added and the hydrochloride salt is crystallized as colorless flakes melting at 211° to 213°C.

References

Merck Index 5855
Kleeman and Engel p. 592
OCDS Vol. 1 p.400 (1977) and 2,413 (1980)
I.N. p. 628
REM p.919
Schmutz, J.; US Patent 2,905,590; September 22,1959; assigned to The Wander Company

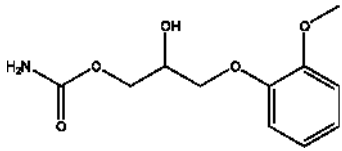
METHOCARBAMOL

Therapeutic Function: Muscle relaxant

Chemical Name: 3-(o-Methoxyphenoxy)-1,2-propanediol-1-carbamate

Common Name: Guaiacol glyceryl ether carbamate

Structural Formula:



Chemical Abstracts Registry No.: 532-03-6

Trade Name	Manufacturer	Country	Year Introduced
Robaxin	Robins	US	1957
Lumirelax	Sarbach	France	1968
Robaxin	Brenner	W. Germany	1976
Carbametin	Uji	Japan	-
Carxin	Kanto	Japan	-
Delaxin	Ferndale	US	-
Methocabal	Zeria	Japan	-
Methocal	Daiko	Japan	-
Miowas	Wassermann	Italy	-
Myomethol	Abic	Israel	-
Parabaxin	Parmed	US	-
Relax	Ion	Italy	-
Robamol	Cenci	Italy	-
Robaxisal	Robins	US	-
Romethocarb	Robinson	US	-
Traumacut	Brenner	W. Germany	-
Tresortil	Gea	Denmark	-

Raw Materials

Guaiacol glyceryl ether
Phosgene
Ammonia

Manufacturing Process

The starting material for methocarbamol is 3-o-methoxyphenoxy-1,2-propanediol (guaiacol glyceryl ether) (see entry under Guaifenesin for its preparation). To a stirred suspension of 198.2 g (1.0 mol) of 3-o-methoxyphenoxy-1,2-propanediol in 1,000 ml of dry benzene contained in a 5-liter, 3-neck, round bottom flask equipped with a thermometer, dropping funnel and blade stirrer, was added dropwise (in 30 minutes) a solution of 98.9 g (1.0 mol) of phosgene in 400 ml of cold dry benzene. The mixture was stirred at 30°C until all solid material dissolved (about 3 hours was required)

and stirring was continued for 30 minutes longer. To this mixture was added dropwise 79.1 g (1.0 mol) of dry pyridine, the temperature being held below 30°C by cooling. After addition of the pyridine, stirring at 30°C was continued for 30 minutes.

The mixture was cooled to 7°C, extracted with two 500-cc portions of ice water to remove pyridine hydrochloride, and the benzene solution of 3-o-methoxyphenoxy-2-hydroxypropyl chlorocarbonate was added to 500 ml of cold concentrated ammonium hydroxide. The mixture was vigorously stirred at 5°C for 6 hours, then the crude white precipitate of 3-o-methoxyphenoxy-2-hydroxypropyl carbamate was filtered off, dissolved in 1,500 ml of hot benzene and completely dried by codistillation of last traces of water with benzene, treated with decolorizing carbon and filtered while hot. On cooling 160 g of product crystallized as white needles melting at 88° to 90°C.

References

Merck Index 5856
Kleeman and Engel p. 578
PDR pp.830, 993, 1466, 1569, 1606, 1999
OCDS Vol. 1 p. 118 (1977)
I.N. p. 613
REM p. 927
Murphey, R.S.; US Patent 2,770,649; November 13,1956; assigned to A.H. Robins Company, Inc.

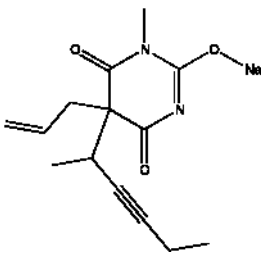
METHOHEXITAL SODIUM

Therapeutic Function: Anesthetic

Chemical Name: (+/-)-1-Methyl-5-(1-methyl-2-pentynyl)-5-(2-propenyl)-2,4,6-(1H,3H,5H)-pyrimidinetrione sodium salt

Common Name: Methohexitone

Structural Formula:



Chemical Abstracts Registry No.: 309-36-4

Trade Name	Manufacturer	Country	Year Introduced
Brevital	Lilly	US	1960
Brietal	Lilly	UK	1961
Brevimytal	Lilly	W. Germany	1963
Brietal	Lilly	Italy	1963

Raw Materials

Magnesium
Sodium
Allyl bromide
Acetaldehyde
Ethanol
Ethyl acetylene (1-butyne)
Phosphorus tribromide
Ethyl bromide
Diethyl malonate
Methyl urea

Manufacturing Process

Preparation of 3-Hexyne-2-ol: A solution of ethyl magnesium bromide was prepared by the reaction of 229 g of ethyl bromide and 48.6 g of magnesium in 750 ml of anhydrous ether. To the ether solution was then added with stirring a solution of 108 g of ethyl acetylene in 250 ml of cold anhydrous ether. The addition required approximately 3 hours, and the mixture was stirred and refluxed for a further period of 3½ hours. Thereafter there was added to the reaction mixture a solution of 88 g of freshly distilled acetaldehyde in 170 ml of anhydrous ether, over a period of about 45 minutes and at a temperature in the range of about -10° to 0°C.

The resulting reaction mixture was poured over about 1 kg of crushed ice, and neutralized with 10% aqueous hydrochloric acid. The organic phase of the resulting mixture was separated, and the aqueous phase was extracted 3 times with 250 ml portions of ether. The combined organic phase and ether washings were washed twice with water and dried over anhydrous potassium carbonate. The dried ether solution was fractionally distilled, and the 3-hexyne-2-ol formed in the reaction was collected as a fraction boiling at about 79° to 80°C at the pressure of 60 mm of mercury.

Preparation of 2-Bromo-3-Hexyne: A solution of 138 g of 3-hexyne-2-ol and 9 g of pyridine in 138 ml of anhydrous ether was treated with 175 g of phosphorus tribromide, added dropwise over a period of about 20 minutes at a temperature of about -10°C. The reaction mixture was permitted to come to room temperature while stirring for about 3 hours, and was then heated to refluxing for about 1 hour. After cooling, the reaction mixture was poured over about 50 g of crushed ice. A two-phase system formed, and the ether layer was separated, washed with dilute sodium bicarbonate solution, dried over anhydrous potassium carbonate and fractionally distilled. The 2-bromo-3-hexyne formed in the reaction was collected at 75°C at the pressure of 50 mm of mercury.

Preparation of Diethyl (1-Methyl-2-Pentynyl) Malonate: To a solution of 28.6 g of sodium in 430 ml of absolute ethanol were added 200 g of diethyl malonate. About half of the alcohol was removed by distillation in vacuo, and thereafter a solution of 200 g of 2bromo-3-hexyne in 100 ml of anhydrous ether was added slowly to the reaction mixture.

The heat of reaction brought about refluxing during the addition of the 2-bromo-3-hexyne, and when the addition was complete the reaction mixture was heated to refluxing for a further period of 30 minutes. A sufficient amount of water was then added to the reaction mixture to dissolve the sodium bromide which had formed, and the only organic layer was separated, washed with water and dried over anhydrous magnesium sulfate. The dried organic layer was then fractionally distilled under reduced pressure, and the diethyl (1-methyl-2-pentynyl) malonate formed in the reaction was collected at about 117° to 120°C at the pressure of 2 mm of mercury.

Preparation of Diethyl Allyl (1-Methyl-2-Pentynyl) Malonate: A solution of 12.1 g of sodium in 182 ml of absolute ethanol was prepared, and thereto were added 126.6 g of diethyl (1-methyl-2-pentynyl) malonate. Most of the ethanol was then distilled off under reduced pressure, and the residue was cooled and 63.5 g of allyl bromide were slowly added thereto. After completion of the addition, the mixture was refluxed for about 1 hour. The reaction mixture was cooled, treated with about 100 ml of water, and the oily organic layer which formed was removed, washed with water and dried over anhydrous magnesium sulfate. The dried oily organic material was fractionally distilled in vacuo, and diethyl allyl (1-methyl-2-pentynyl) malonate boiling at 105° to 107°C at the pressure of 1 mm of mercury was recovered.

Preparation of 1-Methyl-5-Allyl-5-(1-Methyl-2-Pentynyl) Barbituric Acid: A solution of 23.8 g of sodium in 360 ml of absolute alcohol was prepared and thereto were added 38.3 g of methyl urea and 96.8 g of diethyl allyl (1-methyl-2-pentynyl) malonate. The mixture was refluxed for about 20 hours, cooled, and the ethanol was removed by distillation in vacuo. The residue was dissolved in about 300 ml of water and the aqueous solution was washed with ether, and the washings were discarded. The aqueous solution was then acidified with acetic acid, and extracted with three 150 ml of portions of ether.

The combined ether extracts were washed with 5% aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate, and fractionally distilled in vacuo. The fraction boiling at about 145 to 150°C at the pressure of 0.5 mm of mercury, weighing 61 g and consisting of 1-methyl-5-allyl-5-(1-methyl-2-pentynyl) barbituric acid, was collected. The only distillate was substantially pure, and could be used as such in pharmaceutical preparation or a salt could be prepared therefrom according to the procedures disclosed hereinafter. On standing, the oil crystallized. The crystalline 1-methyl-5-allyl-5-(1-methyl-2-pentynyl) barbituric acid melted at about 60° to 64°C after recrystallization from dilute ethanol.

Preparation of Sodium 1-Methyl-5-Allyl-5-(1-Methyl-2-Pentynyl) Barbiturate: A solution of 61 g of 1-methyl-5-allyl-5-(1-methyl-2-pentynyl) barbituric acid in 100 ml of ether was extracted with 465 ml of 2% aqueous sodium hydroxide solution. The aqueous extract was washed with successive 75 ml and 50 ml portions of ether. The pH of the aqueous solution was adjusted to 11.7, using 5% aqueous sodium hydroxide solution. 5 g of decolorizing carbon were added to the solution with stirring; the mixture was permitted to stand for 20 minutes at room temperature, and the carbon was removed by filtration. A solution containing 4 g of sodium carbonate in 25 ml of water was added to the aqueous solution, and the mixture was filtered sterile through a porcelain filter candle of 02 porosity into sterile bottles. The aqueous solution was then dried from the frozen state, whereupon a sterile residue of sodium 1-methyl-

5-allyl-5-(1-methyl-2-pentynyl) barbiturate, weighing about 62 g was obtained.

References

Merck Index 5857
Kleeman and Engel p. 578
PDR p.1038
OCDS Vol. 1 p. 269 (1977)
I.N. p. 613
REM p.1046
Doran, W.J.; US Patent 2,872,448; February 3,1959; assigned to Eli Lilly and Company

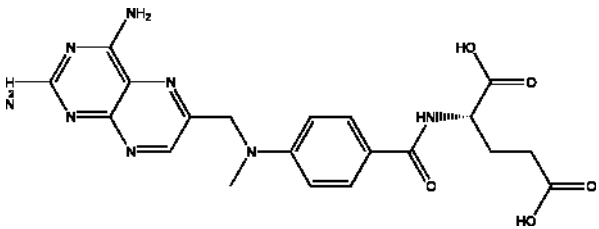
METHOTREXATE

Therapeutic Function: Antineoplastic

Chemical Name: N-[4-[[(2,4-Diamino-6-pteridinyl)methyl]methylamino]-benzoyl]-L-glutamic acid

Common Name: Amethopterin

Structural Formula:



Chemical Abstracts Registry No.: 59-05-2

Trade Name	Manufacturer	Country	Year Introduced
Methotrexate	Lederle	US	1955
Mexate	Bristol	US	1979
Emtexate	Nordic	UK	1981
Folex	Adria	US	1983
Abitrexate	Abic	Israel	-
Emthexate	Pharmachemie	Netherlands	-
Ledertrexate	Lederle	France	-

Raw Materials

Diethyl-p-methylaminobenzoyl-L-glutamate

Aminomalononitrile tosylate
β-Bromopyruvaldoxime
Guanidine acetate

Manufacturing Process

5 g (15 mmol) of diethyl-p-methylaminobenzoyl-L-glutamate and 8.0 g of aminomalononitrile tosylate (65% by NMR assay, 20 mmol) were dissolved in warm ethanol (65 ml, with 15% water by volume). To this solution, cooled to 0°C, was added all at once and with vigorous stirring, 3.6 g of β-bromopyruvaldoxime (89% by NMR assay, 19 mmol). After 30 minutes the stirred mixture, which was allowed to warm slowly to room temperature, was neutralized with powdered $NaHCO_3$ to pH 6, stirring continued for four additional hours, and the resulting mixture filtered through Celite. The filtrate was evaporated under reduced pressure to a glasslike substance, which was taken up in 500 ml of chloroform. The resulting suspension was then filtered using Celite, and the filtrate was washed with water, dried with anhydrous $MgSO_4$, and evaporated to give an orange glasslike substance which was used directly in the next step.

To a 20% solution of titanium trichloride in water (39 mmol), stirred under nitrogen, was added a solution of 18 g (230 mmol) of ammonium acetate in 55 ml of water. Then, to this mixture, cooled to 10°C and stirred with an air-driven stirrer, was added over a period of 5 minutes a solution of the orange glassy substance above distilled in 60 ml of tetrahydrofuran. The mixture was vigorously stirred for 15 minutes while a rapid stream of nitrogen was passed through. After this time, 15 g of powdered sodium sulfite (120 mmol) was added to the mixture, which after several minutes turned from green to yellowish white. This mixture was stirred into 1 liter of chloroform, and the heavy yellow layer separated by use of a separatory funnel. This chloroform layer was washed with water, dried using anhydrous $MgSO_4$, and evaporated under reduced pressure to give a light orange glass, which was then chromatographed rapidly on a column made from 80 g of Baker silica gel, using 5% ethyl acetate in chloroform as the eluent.

The product obtained by evaporation of the eluate was recrystallized from ethanol-ether (1:10) to give a light yellow powder, MP 85 to 88°C. The yield was 4.4 g (63%).

A solution containing 4.8 g (10.2 mmol) of diethyl-N-[p-[[(2-amino-3-cyano-5-pyrazinyl)methyl] methylamino]benzoyl]glutamate and 5 g (42 mmol) of guanidine acetate in 40 ml of dimethylformamide was stirred under nitrogen at 120°C for six hours. The resulting solution was cooled to room temperature, filtered and evaporated to a glassy product using a rotary evaporator and a mechanical vacuum pump to insure a better vacuum. The residual glass was taken up in 500 ml of chloroform, the resulting suspension filtered using Celite, and the filtrate washed with water, dried using anhydrous $MgSO_4$, and evaporated to dryness. (The residual material was chromatographed rapidly on a column prepared from 250 g of Baker silica gel using, initially, 2% ethanol in chloroform, and then 5% ethanol in chloroform as eluents.) The material obtained by evaporation of the eluates was crystallized from ethanol-chloroform (4:1) to give small, pale yellow lustrous platelets, MP 142°C to 154°C; yield, 3.8 g (73%). Further crystallization of

this material from ethanol-chloroform (4:1) raised the MP to 153°C to 155°C. The compound is completely racemic.

A sample of this product was hydrolyzed in a mixture of water and methanol in the presence of potassium hydroxide. Essentially pure methotrexate was thus obtained.

References

Merck Index 5861
Kleeman and Engel p. 579
PDR p. 1016
DOT 8 (11) 426 (1972) and 16 (5) 170 (1980)
I.N. p. 614
REM p. 1152
Wiecko, J.; US Patent 4,057,548; November 8,1977
Ellard, J.A.; US Patent 4,080,325; March 21,1978; assigned to US Dept. of Health, Education and Welfare

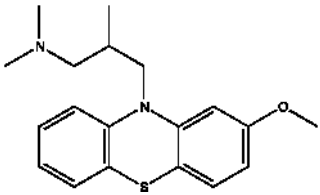
METHOTRIMEPRAZINE

Therapeutic Function: Analgesic

Chemical Name: 2-Methoxy-N,N,β-trimethyl-10H-phenothiazine-10-propanamine

Common Name: Levomepromazine

Structural Formula:



Chemical Abstracts Registry No.: 60-99-1; 1236-99-3 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Levoprome	Lederle	US	1966
Hirnamin	Shionogi	Japan	-
Levaru	Mohan	Japan	-
Levomezine	Toho	Japan	-
Levotomin	Shionogi	Japan	-
Nozinan	Farmalabor	Italy	-
Ronexine	Ikapharm	Israel	-

Trade Name	Manufacturer	Country	Year Introduced
Sinogan	Rhodia Iberica	Spain	-
Sofmin	Dainippon	Japan	-
Veractil	May and Baker	US	-

Raw Materials

3-Methoxyphenthiazine
Sodium amide
1-Dimethylamino-2-methyl-3-chloropropane

Manufacturing Process

95% sodamide (2.33 g) is added to a boiling solution of 3-methoxyphenthiazine (12 g) in anhydrous xylene (150 cc) and the mixture is heated with agitation under reflux for 1½ hours. A solution of 1-dimethylamino-2-methyl-3-chloropropane (8.2 g) in anhydrous xylene (90 cc) is then run in over a period of 45 minutes while the reaction temperature is maintained and heating under reflux is continued for 18 hours.

After cooling, the reaction mixture is agitated with a mixture of water (40 cc) and a normal solution of methanesulfonic acid (70 cc), the xylene layer is removed and the acid liquors are washed with ether (200 cc). The aqueous phase is then made alkaline with sodium hydroxide (d = 1.33; 10 cc) and the liberated base is extracted with ether. The ethereal solution is dried over anhydrous potassium carbonate and concentrated at normal pressure. On distillation of the residue under reduced pressure 3-(3-methoxy-10-phenthiazinyl)-2-methyl-1-dimethylaminopropane (11.3 g) is obtained, MP 103°C, BP 182° to 191°C/0.15 mm Hg. The hydrochloride prepared in isopropanol melts at about 90°C.

References

Merck Index 5862
Kleeman and Engel p. 522
DOT 3 (2) 62 (1967) and 9 (7) 227 (1971)
I.N. p. 556
REM p. 1113
Jacob, R.M. and Robert, J.G.; US Patent 2,837,518; June 3,1958; assigned to Societe des Usines Chimiques Rhone-Poulenc, France

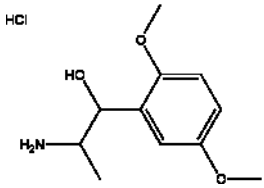
METHOXAMINE HYDROCHLORIDE

Therapeutic Function: Hypertensive

Chemical Name: α-(1-Aminoethyl)-2,5-dimethoxybenzenemethanol hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 61-16-5; 390-28-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Vasoxyl	Burroughs-Wellcome	US	1949
Idasal	Gayoso Wellcome	Spain	-
Mexan	Nippon Shinyaku	Japan	-
Vasylox	Burroughs-Wellcome	-	-

Raw Materials

2,5-Dimethoxypropiophenone
Methyl nitrite
Hydrogen

Manufacturing Process

2,5-Dimethoxypropiophenone is treated in absolute ether with methyl nitrite and hydrogen chloride. The hydrochloride of 2,5-dimethoxy-α-isonitrosopropiophenone crystallizes out of the solution. It is removed, the base is liberated and crystallized from benzene-heptane forming yellow leaflets that melt at about 97° to 98°C. This isonitrosoketone is dissolved in absolute alcohol containing an excess of hydrogen chloride and is hydrogenated with palladized charcoal, yielding β-(2,5-dimethoxyphenyl)-β-ketoisopropylamine hydrochloride, a salt that melts at about 176°C with decomposition.

12.3 g (1/20 mol) of β-(2,5-dimethoxyphenyl)-β-ketoisopropylamine hydrochloride (MP 176°C) is dissolved in 50 cc of water and hydrogenated with platinum oxide platinum black in the customary Adams-Burgess Parr apparatus. About 1/20 mol of hydrogen is absorbed, after which the solution is filtered off from the catalyst, evaporated to dryness in vacuo and recrystallized from absolute alcohol, absolute ether being added to decrease solubility. The hydrochloride is thus obtained in substantially theoretical yield. It crystallizes in plates and melts at 215°C.

References

Merck Index 5863
Kleeman and Engel p. 580
PDR p. 768
I.N. p. 614

REM p. 888
Baltzly, R., de Beer, E.J. and Buck, J.S.; US Patent 2,359,707; October 3,1944; assigned to Burroughs Wellcome and Co. (USA.) Inc.

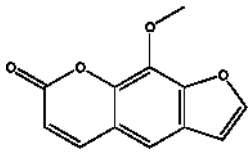
METHOXSALEN

Therapeutic Function: Dermal pigmentation enhancer

Chemical Name: 9-Methoxy-7H-furo[3,2-g][1]benzopyran-7-one

Common Name: 8-Methoxypsoralen; Ammoidin; Xanthotoxin

Structural Formula:



Chemical Abstracts Registry No.: 298-81-7

Trade Name	Manufacturer	Country	Year Introduced
Oxsoracen	Eider	US	1955
Meloxine	Upjohn	US	1958
Meladinine	Basotherm	W. Germany	-
Oxoralen	Farmochimica	Italy	-
Psoritin	Yurtoglu	Turkey	-
Puvalen	Star	Finland	-
Soloxsalen	I.C.N.	Canada	-

Raw Materials

8-Geranoxy psoralen
Sulfuric acid
Diazomethane

Manufacturing Process

It has been found that the compound 8-geranoxy psoralen is present in citrus oils, particularly lemon and lime oils. This compound can be isolated from the oil by a process which involves primarily absorption on an adsorbent material followed by elution with a suitable solvent.

(A) Cleavage of 8-Geranoxypsoralen: 275 mg of 8-geranoxypsoralen was dissolved with mechanical stirring in 4 ml glacial acetic acid. After 10 minutes,

one drop of concentrated sulfuric acid was added to the solution. In 4 minutes thereafter a light tan precipitate began to form. Stirring was continued for 35 minutes and the reaction mixture was refrigerated for one hour and 20 minutes. The precipitate was then removed by suction filtration and washed on the filter with glacial acetic acid followed by ice-cold ethyl ether. The product, 8-hydroxypsoralen, weighed 115 mg, that is, 74% of theory.

(B) Methylation of 8-Hydroxypsoralen: 115 mg of 8-hydroxypsoralen was dissolved in 10 ml absolute methanol, an excess of diazomethane dissolved in ether was added and the mixture allowed to stand at room temperature with occasional stirring for 3 hours. The next day the reaction mixture was reduced in volume to 3 ml by evaporation on the steam bath and the concentrate was held in a refrigerator overnight. The next day, fine needles (80 mg) of 8-methoxypsoralen were filtered from the solution. The compound had a MP of 145 to 146°C and was obtained in a yield of 65% of theory.

There is also a wholly synthetic route to Methoxsalen as outlined by Kleeman and Engel.

References

Merck Index 5864
Kleeman and Engel p. 580
PDR p. 867
OCDS Vol. 1 p. 333 (1977)
I.N. p. 614
REM p. 788
Stanley, W.L. and Vannier, S.H.; US Patent 2,889,337; June 2,1959; assigned to the US Secretary of Agriculture
Glunz, L.J. and Dickson, D.E.; US Patent 4,129,575; December 12, 1978; assigned to Thomas C. Elder, Inc.
Liebman, A.A. and Liu, Y.-Y.; US Patent 4,147,703; April 3,1979; assigned to Hoffmann-LaRoche, Inc.

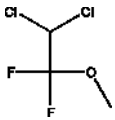
METHOXYFLURANE

Therapeutic Function: Inhalation anesthetic

Chemical Name: 2,2-Dichloro-1,1-difluoro-1-methoxyethane

Common Name: 1,1-Difluoro-2,2-dichloroethyl methyl ether

Structural Formula:



Chemical Abstracts Registry No.: 76-38-0

Trade Name	Manufacturer	Country	Year Introduced
Penthrane	Abbott	US	1962
Penthrane	Abbott	W. Germany	1962
Penthrane	Abbott	UK	1963
Anecotan	Spofa	Czechoslovakia	-
Methofane	Pitman-Moore	US	-

Raw Materials

1,1-Dichloro-2,2-difluoroethylene
Methanol

Manufacturing Process

Into a reactor equipped with agitator and temperature control jacket is charged approximately 100 lb (about 3 lb mols) of methanol, technical. This methanol is used in excess, and so it is both a reactant and a solvent in the synthesis.

Approximately 1 US gallon of ion exchange resin beads wet with methanol is then added to the methanol. This is in the hydroxide form with at least 0.7 milliequivalent OH^- per milliliter of wet beads. Approximately 190 lb of 1,1-dichloro-2,2-difluoroethylene (about 1.44 lb mols) is then added to the reactor and, within it, to the 100 lb of methanol through a sparge pipe while the beads are kept in suspension by agitation. Coolant is run through the jacket of the reactor during this addition because the reaction is exothermic. The temperature in the reaction medium is kept at 10° to 20°C, to prevent side reactions and to minimize losses of the dichlorodifluoroethylene, which boils at 17°C. Reaction time is affected by the rate of heat removal and the reaction normally takes from 4 to 8 hours, using the stated quantities and conditions. After the dichlorodifluoroethylene is added, the resin is checked for residual alkalinity. If the resin is alkaline to phenolphthalein, it is assumed to have been of sufficient capacity and is removed from the $CH_3OCF_2CHCl_2$-methanol mixture. If it is not alkaline to phenolphthalein, additional resin is added to insure complete reaction.

Essentially the same procedure can be carried out, employing as alkali any strongly alkaline substance, such as caustic soda in methanol solution. Control of the reaction rate may be accomplished by the rate of the addition of reactants and the amount of cooling applied to the reaction mixture. Agitation is employed to insure efficient contact of the reactants.

After removal of the resin catalyst, the excess methanol is extracted out of the mixture using three separate water washes, suitably of 25 gallons each. The water layer is decanted off, leaving product as an immiscible organic layer, after each wash. The 2,2-dichloro-1,1-difluoroethyl methyl ether containing intolerable unsaturated impurities may be purified and stabilized by a treatment with oxidizing agents such as air, oxygen, ozone, peroxy compounds, or other similar oxidizing agents, with subsequent removal of the decomposition or oxidation products and distilling if desired.

References

Merck Index 5869
Kleeman and Engel p. 581
PDR p. 547
I.N. p. 615
REM p. 1043
Larsen, E.R.; US Patent 3,264,356; August 2,1966; assigned to The Dow Chemical Company

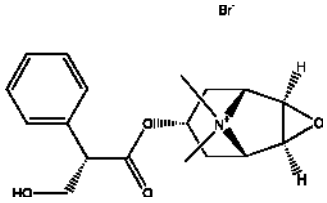
METHSCOPOLAMINE BROMIDE

Therapeutic Function: Spasmolytic

Chemical Name: 7-(3-Hydroxy-1-oxo-2-phenylpropoxy)-9,9-dimethyl-3-oxa-9-azoniatricyclo-[3.3.1.02,4]nonane bromide

Common Name: Hyoscine methyl bromide

Structural Formula:



Chemical Abstracts Registry No.: 155-41-9

Trade Name	Manufacturer	Country	Year Introduced
Pamine	Upjohn	US	1953
Daipin	Daiichi Seiyaku	Japan	1972
Ace	Ono	Japan	-
Blocan	Estedi	Spain	-
Lescopine	Lincoln	US	-
Meporamin	Taiyo	Japan	-
Neo Avagal	Andrews	Australia	-
Parantin	Teva	Israel	-
Proscomide	Miller	US	-
Scopolate	Strasenburgh	US	-
Scordin	Ono	Japan	-
Skopyl	Farillon	UK	-

Raw Materials

Scopolamine hydrobromide trihydrate
Methyl bromide

Manufacturing Process

In a one-liter separatory funnel, 94 g (0.215 mol) of scopolamine hydrobromide trihydrate was dissolved in 250 ml of water, made alkaline by shaking with 40 g (1 mol) of sodium hydroxide in 150 ml of water, and the free base immediately extracted with ether. As scopolamine is somewhat soluble in water, the aqueous layer was saturated with potassium carbonate and again extracted with ether. The combined ether extracts were dried over anhydrous magnesium sulfate and the ether removed by distillation, leaving 65 g (0.214 mol; 100% yield) of nearly colorless oil. Then 100 g (1.05 mols) of cold methyl bromide was added to a chilled, 500-ml pressure flask containing the 65 g of scopolamine, the flask stoppered tightly with a clamp, and allowed to stand at room temperature for 96 hours.

The flask was cooled before opening, excess methyl bromide removed by filtration, and the white solid washed thoroughly with dry ether. The yield of crude scopolamine methyl bromide was 80g (94% yield; 93.5% over-all yield).

The salt was recrystallized from 550 ml of alcohol; first crop, 70 g, MP 212° to 214°C; second crop, 6 g, MP 195° to 200°C. The combined crops were again recrystallized from 500 ml of 3-A alcohol; MP 210° to 212°C. The third recrystallization from 600 ml of alcohol yielded 64 g, MP 214° to 216°C, a 75% yield based on scopolamine hydrobromide trihydrate starting material.

References

Merck Index 5881
Kleeman and Engel p. 582
PDR p. 1857
I.N. p. 508
REM p. 917
Visscher, F.E.; US Patent 2,753,288; July 3,1956; assigned to The Upjohn Company

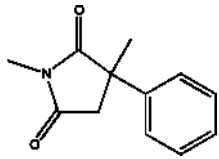
METHSUXIMIDE

Therapeutic Function: Anticonvulsant

Chemical Name: 1,3-Dimethyl-3-phenyl-2,5-pyrrolidinedione

Common Name: Mesuximid

Structural Formula:



Chemical Abstracts Registry No.: 77-41-8

Trade Name	Manufacturer	Country	Year Introduced
Celontin	Parke Davis	US	1957
Petinutin	Parke Davis	W. Germany	-

Raw Materials

α-Phenyl-α-methylsuccinic acid
Methylamine

Manufacturing Process

100 g of α-phenyl-α-methylsuccinic acid and 110 g of 40% aqueous methyl amine are heated together at 200 to 250°C until no more distillate is obtained. Upon vacuum distillation of the residue, the N-methyl-α-phenyl-α-methylsuccinimide, of BP 121° to 122°C at 0.1 mm is obtained. After recrystallization from aqueous ethanol, this compound melts at 52° to 53°C.

References

Merck Index 5882
Kleeman and Engel p. 567
PDR p. 1320
OCDS Vol. 1 p. 228 (1977)
I.N. p. 602
REM p. 1079
Miller, C.A. and Long, L.M.; US Patent 2,643,257; June 23, 1953; assigned to Parke, Davis and Company

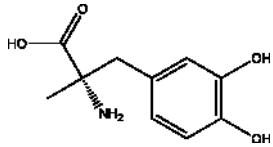
METHYLDOPA

Therapeutic Function: Antihypertensive

Chemical Name: 3-Hydroxy-α-methyl-L-tyrosine

Common Name: L-α-Methyl-3,4-dihydroxyphenylalanine

Structural Formula:



Chemical Abstracts Registry No.: 555-30-6

Trade Name	Manufacturer	Country	Year Introduced
Aldometil	MSD	W. Germany	1962
Aldomet	MSD	UK	1962
Aldomet	MSD	Italy	1962
Aldomet	MSD	US	1963
Aldomet	MSD-Chibret	France	1964
Adopal	Pharmacal	Finland	-
Aldomin	Teva	Israel	-
Aldoril	MSD	US	-
Alphamex	Protea	S. Africa	-
Becanta	Kissei Pharmaceutical Co., Ltd.	Japan	-
Caprinol	Bayer	W. Germany	-
Dansul	Nippon Yakko	Japan	-
Desens	Nissin	Japan	-
Dimal	Protea	Australia	-
Domecin	Sankyo	Japan	-
Dopamet	Berk	US	-
Dopamin	Hokuriku	Japan	-
Dopatec	Labatec	Switz.	-
Dopegyt	Gedeon Richter	Hungary	-
Equibar	Genekod	France	-
Grospisk	Toho Iyaku	Japan	-
Hydromet	MSD	France	-
Hyperten	Toho	Japan	-
Hypolag	Lagap	Switz.	-
Hy-Po-Tone	Lennon	S. Africa	-
Medimet	Medic	Canada	-
Medomet	D.D.S.A.	UK	-
Medopa	Kaigai	Japan	-
Medopal	A.L.	Norway	-
Medopren	Dietopharma	Italy	-
Metholes	Taisho	Japan	-
Methoplain	Kowa	Japan	-
Nichidopa	Nichiiko	Japan	-
Novomedopa	Novopharm	Canada	-
Polinal	Boehringer Yamanouchi	Japan	-
Sembrina	Boehringer Mannheim	Italy	-

Raw Materials

3-Hydroxy-4-methoxyphenylalanine
Hydrogen chloride

Manufacturing Process

The dl-α-methyl-3,4-dihydroxyphenylalanine may be made as described in US Patent 2,868,818. Five-tenths of a gram of 3-hydroxy-4-methoxyphenylalaninewas dissolved in 20 ml of concentrated hydrochloric acid, the solution saturated with hydrogen chloride and heated in a sealed tube at 150°C for 2 hours. The dark reaction mixture was concentrated to dryness in vacuo, excess acid removed by flushing several times with ethanol. On dissolving the dark residue in a minimum amount of water and adjusting the clarified solution to pH 6.5 with ammonium hydroxide the compound separated in fine crystals which were filtered, washed with alcohol and ether. The crystalline product had a MP of 299.5 to 300°C with decomposition.

Then, as described in US Patent 3,158,648, the optical isomers may be resolved as follows. 37 g of racemic α-methyl-3,4-dihydroxyphenylalanine are slurried at 35°C in 100 cc of 1.0 N hydrochloric acid. The excess solids are filtered leaving a saturated solution containing 34.6 g of racemic amino acid of which about 61% is present as the hydrochloride. The solution is then seeded at 35°C with 7 g of hydrated L-α-methyl-3,4-dihydroxyphenylalanine (6.2 g of anhydrous material). The mixture is then cooled to 20°C in 30 minutes and aged one hour at 20°C. The separated material is isolated by filtration, washed twice with 10 cc of cold water and dried in vacuo. The yield of product is 14.1 g of L-α-methyl-3,4-dihydroxyphenylalanine in the form of a sesquihydrate of 100% purity as determined by the rotation of the copper complex.

References

Merck Index 5928
Kleeman and Engel p. 583
PDR pp. 993, 1133
OCDS Vol. 1 p. 95 (1977)
DOT 10 (9) 323 (1974) and 19 (3) 170 (1983)
I.N. p. 618
REM p.846
Pfister, K., Ill and Stein, G.A.; US Patent 2,868,818; January 13, 1959; assigned to Merck and Co., Inc.
Jones, R.T., Krieger, K.H. and Lago, J.; US Patent 3,158,648; November 24,1964; assigned to Merck and Co., Inc.

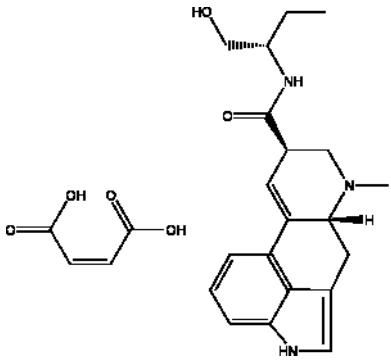
METHYLERGONOVINE MALEATE

Therapeutic Function: Oxytocic

Chemical Name: 9,10-Didehydro-N-[1-(hydroxymethyl)propyl]-6-methylergoline-8-carboxamide maleate

Common Name: d-Lysergic acid dl-hydroxybutylamide-2; Methylergometrin maleate

Structural Formula:



Chemical Abstracts Registry No.: 7054-07-1; 113-42-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Methergine	Sandoz	US	1948
Methergin	Sandoz	France	1953
Ergotrate	Lilly	US	-
Levospan	Isei	Japan	-
Metenarin	Teikoku Zoki	Japan	-
Methylergobrevin	Arzneimittelwerk Dresden	E. Germany	-
Metiler	Adika	Turkey	-
Myomergin	Leiras	Finland	-
Ryegonovin	Morishita	Japan	-
Spametrin M	Sanzen	Japan	-
Takimetrin M	Nakataki	Japan	-
Uterin	Biofarma	Turkey	-

Raw Materials

d-Isolysergic acid azide
d-2-Aminobutanol-1

Manufacturing Process

To a freshly prepared solution of 2 parts of d-isolysergic acid azide in 300 parts of either is added an ethereal solution of 2 parts of d-2-aminobutanol-1 and the mixture is left to stand at room temperature during 12 hours. The yellowish clear solution is then washed several times with some water, dried over sodium sulfate and the ether evaporated in vacuo. The crystallized residue is treated with a small quantity of acetone and filtered. Yield: 2.2

parts of d-isolysergic acid-d-1-hydroxybutylamide-2. On recrystallization from some hot methanol the new compound is obtained in form of beautiful polygonal crystals that melt with some decomposition at 192° to 194°C (corr.).

1 part of the iso-compound is then dissolved in 10 parts of absolute ethanol and an alcoholic potassium hydroxide solution is added thereto. The mixture is left to stand at room temperature during 45 minutes. After this time equilibrium is reached between lysergic acid and the isolysergic acid forms, which can be checked by determination of the constancy of the optical rotation of the solution. When this point is reached, potassium hydroxide is transformed into potassium carbonate by bubbling through the solution a stream of carbon dioxide; the thick crystal paste of potassium carbonate is then diluted with 50 parts of ether, filtered and washed again with 50 parts of ether.

The alcoholic ethereal filtrate is then dried over calcined potassium carbonate and the solution evaporated, whereby 0.9 to 1 part of a mixture of d-lysergic acid-d-1-hydroxybutylamide-2 and of d-isolysergic acid-d-1-hydroxybutylamide-2 is obtained. In order to separate the isomers, the residue is dissolved in 15 parts of hot chloroform and filtered from the small quantity of inorganic salt, whereby on cooling down, the difficultly soluble chloroform compound of d-lysergic acid-d-1-hydroxybutylamide-2 crystallizes out. Yield: 0.4 part. This compound can be recrystallized from hot benzene, whereby crystals melting with some decomposition at 172°C (corr.) are obtained. It may then be reacted with maleic acid to give the maleate.

References

Merck Index 5943
Kleeman and Engel p. 584
PDR p. 1587
I.N. p. 619
REM p. 948
Stoll, A. and Hofmann, A.; US Patent 2,265,207; December 9,1941; assigned to Sandoz AG, Switzerland

METHYLHEXANEAMINE CARBONATE

Therapeutic Function: Nasal decongestant

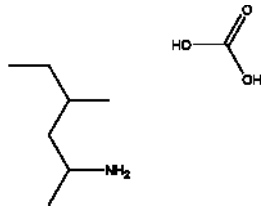
Chemical Name: 4-Methyl-2-hexylamine carbonate

Common Name: -

Chemical Abstracts Registry No.: 105-41-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Forthane	Lilly	US	1948

Structural Formula:



Raw Materials

4-Methylhexanone-2	Hydrogen
Hydroxylamine	Carbon dioxide

Manufacturing Process

One molecular equivalent of 4-methylhexanone-2 is reacted with slightly more than one molecular equivalent of hydroxylamine. Desirably, the hydroxylamine is prepared in the presence of the 4-methylhexanone-2 by reacting the hydrochloride or sulfate or other salt of the hydroxylamine with a suitable base, such as sodium carbonate or sodium hydroxide. Desirably, the reaction mixture is agitated for a few hours to insure the conversion of the 4-methylhexanone-2 to 4-methylhexanone-2 oxime.

The resulting 4-methylhexanone-2 oxime separates and is dried by any suitable means, such as with a dehydrating agent, for example, sodium sulfate or magnesium sulfate. After drying, 4-methylhexanone-2 oxime is reduced with hydrogen by means of a catalyst, such as Raney nickel, or by reaction of sodium and a primary alcohol, such as ethanol. The resulting 2-amino-4-methylhexane may be purified by distillation, as described in US Patent 2,350,318.

115 g (1 mol) of 2-amino-4-methylhexane and 9 g (0.5 mol) of water are placed in a tared 500 cc 3-necked flask which is equipped with a mechanical stirrer, a thermometer, and a gas delivery tube. The flask is surrounded by a cooling bath of ice and water. Dry carbon dioxide gas is introduced into the solution through the gas delivery tube, with constant stirring, until the increase in weight is approximately 22 g (0.5 mol). The temperature during this addition is maintained between 20° and 30°C. A viscous liquid results, and consists essentially of 2-amino-4-methylhexane carbonate. This also dissociates very slowly at room temperature to the free amine, carbon dioxide, and water; and is effective as an inhalant, according to US Patent 2,386,273.

References

Merck Index 5955
I.N. p. 620
Shonle, H.A. and Rohrmann, E.; US Patent 2,350,318; May 30,1944; assigned to Eli Lilly and Company
Shonle, H.A. and Rohrmann, E.; US Patent 2,386,273; October 9,1945; assigned to Eli Lilly and Company

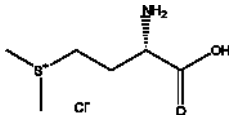
METHYLMETHIONINSULFONIUM CHLORIDE

Therapeutic Function: Hepatoprotectant

Chemical Name: (3-Amino-3-carboxypropyl)dimethylsulphonium chloride

Common Name: Methiosulfonii chloridum; Methylmethioninesulfonium chloride; U-Vitamin; Vitamin U

Structural Formula:



Chemical Abstracts Registry No.: 1115-84-0

Trade Name	Manufacturer	Country	Year Introduced
Cabagin-U	Kowa	-	-
Vitamin U	Medexport	-	-

Raw Materials

dl-Methionine
Methyl chloride

Manufacturing Process

298 g dl-methionine, 2000 ml water and 151.1 methyl chloride were put into autoclave (volume 3 L) made from V4-a steel. The mixture was heated at temperature 50°-55°C for 8 hours and pressure 12-13 atmospheres.

On cooling an excess of methyl chloride was evaporated, the slightly yellow residue was mixed with 0.2% activated coal and filtered. Water was evaporated in vacuum at 45°-55°C. 2 L methanol was poured into an almost colorless syrup obtained, cooled to -5°-(-10°)C. The methylmethioninesulfonium chloride crystallized.

It was filtered off to give 340 g (85.3%) of desired product 99.5 % purity (data of thin-layer chromatography).

References

Wagner H.; D.B. Patent No. 1,239,697; Feb. 20, 1963; Deutsche Gold- und Silber- Scheideanstalt vormals Roessler, Frankfurt/M.

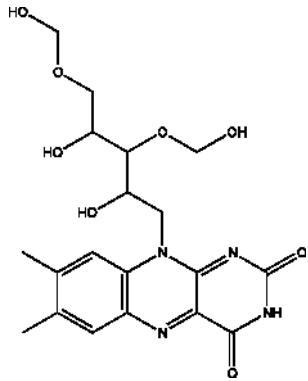
METHYLOL RIBOFLAVIN

Therapeutic Function: Enzyme cofactor vitamin source

Chemical Name: Riboflavin monomethylol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 83-88-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Hyflavin	Endo	US	1948

Raw Materials

Riboflavin
Formaldehyde

Manufacturing Process

100 g of riboflavin and 3 of potassium carbonate are suspended in 500 cc of the aqueous formaldehyde solution and the mixture is stirred at 30°C for 8 hours. At the end of this period, 5 cc of glacial acetic acid and 1 liter of methanol are added, with stirring. The solution is freed from undissolved material by filtration and the clear solution is poured slowly at about 20°C to 22°C with vigorous stirring into 8 liters of anhydrous acetone. The resultant precipitate is filtered off, washed repeatedly with anhydrous acetone and with ether, and then dried at room temperature and with vacuum. The resultant dried powder is dissolved in hot water at 95°C to give an aqueous solution of 20% by weight. This solution is kept in the dark at room temperature for 3 to 4 weeks, after which time a large amount of material crystallizes out of the solution. This crystallized material is removed by filtration and recrystallized from hot water. A small amount of dark red insoluble material is filtered from the hot solution. This recrystallization step is repeated four times. The

resultant end product is monomethylol riboflavin, which crystallized in small orange clusters. It has a melting point of 232°C to 234°C with decomposition, and it becomes dark when heated above 225°C.

References

Merck Index 5974
I.N. p. 621
Schoen, K. and Gordon, S.M.; US Patent 2,587,533; February 26,1952; assigned to Endo Products, Inc.

METHYLPENTYNOL

Therapeutic Function: Sedative

Chemical Name: 1-Pentyn-3-ol, 3-methyl-

Common Name: Meparfynol; Methylparafynol; Methylpentynol

Structural Formula:

Chemical Abstracts Registry No.: 77-75-8

Trade Name	Manufacturer	Country	Year Introduced
Citodorm	Haury	-	-
Dormiphen	Darck	-	-

Raw Materials

Sodium acetylene
Methyl ethyl ketone

Manufacturing Process

To 5 parts of sodium acetylene in absolute ether 6 parts of dry methyl ethyl ketone was slowly dropwise added with ice cooling and stirring. Than the reaction mixture was poured into excess of acetic acid by ice cooling and extracted with ether. The ether extract was washed with solution of potash for removing the diluted acetic acid and dried over potassium carbonate. The ether was distilled off and residual colorless oil methylpentynol had BP at 120°-121°C. Instead of sodium acetylene the solution of sodium acetylene in liquid ammonia may be successfully used.

References

Farbenfabriken vorm. Friedr. Bayer and CO. in Leverkusen b. Coln a. Rh.; D.R. Patent No. 285,770; Nov. 22, 1913

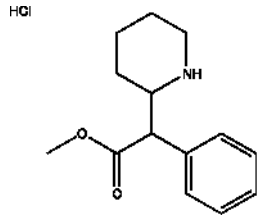
METHYLPHENIDATE HYDROCHLORIDE

Therapeutic Function: Psychostimulant

Chemical Name: α-Phenyl-2-piperidineacetic acid methyl ester hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 298-59-9; 113-45-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Ritalin	Ciba	US	1958
Rubifen	Rubio	Spain	-

Raw Materials

Phenylacetonitrile
Methanol
Sodium amide
Hydrogen chloride
2-Chloropyridine
Hydrogen
Sulfuric acid

Manufacturing Process

As described in US Patent 2,507,631, 80 g of pulverized sodium amide are gradually added, while stirring and cooling, to a solution of 117 g of phenyl-acetonitrile and 113 g of 2-chloropyridine in 400 cc of absolute toluene. The mixture is then slowly heated to 110° to 120°C and maintained at this temperature for 1 hour. Water is added thereto after cooling, the toluene solution is shaken with dilute hydrochloric acid and the hydrochloric acid extracts are made alkaline with concentrated caustic soda solution. A solid mass is separated thereby which is taken up in acetic ester and distilled, α-phenyl-α-pyridyl-(2)-acetonitrile passing over at 150° to 155°C under 0.5 mm

pressure. When recrystallized from ethyl acetate it melts at 88° to 89°C, the yield amounting to 135 g.

100 g of α-phenyl-α-pyridyl-(2)-acetonitrile are introduced into 400 cc of concentrated sulfuric acid, allowed to stand overnight at room temperature, poured into ice and rendered alkaline with sodium carbonate. α-Phenyl-α-pyridyl-(2)-acetamide is precipitated thereby which melts at 134°C after recrystallization from ethyl acetate.

100g of the resulting α-phenyl-α-pyridyl-(2)-acetamide, when dissolved in one liter of methyl alcohol and treated for 6 hours at water-bath temperature with hydrogen chloride, and after concentrating, diluting with water and rendering alkaline with sodium carbonate, yield 90 g of the α-phenyl-α-pyridyl-(2)-acetic acid methylester of MP 74° to 75°C (from alcohol of 50% strength).

The α-phenyl-α-piperidyl-(2)-acetic acid methylester of BP 135° to 137°C under 0.6 mm pressure is obtained in theoretical yield by hydrogenation of 50 g of α-phenyl-α-pyridyl(2)-acetic acid methylester in glacial acetic acid in the presence of 1 g of platinum catalyst at room temperature, while taking up 6 hydrogen atoms. Reaction with HCl gives the hydrochloride. Resolution of stereoisomers is described in US Patent 2,957,880.

References

Merck Index 5981
Kleeman and Engel p. 586
PDR p. 811
OCDS Vol. 1 p. 88 (1977)
I.N. p. 622
REM p. 1136
Hartmann, M. and Panizzon, L.; US Patent 2,507,631;May 16,1950; assigned to Ciba Pharmaceutical Products Inc.
Rornetsch, R.; US Patent 2,957,880; October 25,1960; assigned to Ciba Pharmaceutical Products Inc.

METHYLPHENOBARBITAL

Therapeutic Function: Anticonvulsant

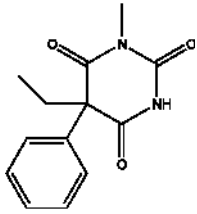
Chemical Name: Barbituric acid, 5-ethyl-1-methyl-5-phenyl-

Common Name: Acidum methyl-phenyl-aethyl-barbiuricum; Enfenemal; Enphenemal; Mefoberbital; Mephobarbital; Methylfenobarbital; Methylphenobarbital; Methylphenobarbitone; Metilfenobarbitale

Chemical Abstracts Registry No.: 115-38-8

Trade Name	Manufacturer	Country	Year Introduced
Isonal	Roussel	-	-

Structural Formula:



Raw Materials

Sodium
Phenyl ethyl malonic acid diethyl ester
Methylurea

Manufacturing Process

46 parts metallic sodium was dissolved in 1000 parts absolute alcohol. The obtained solution was mixed with 264 parts of phenyl ethyl malonic acid diethyl ester and 80 parts of monomethyl urea and heated for 8 hours at reflux. Alcohol was distilled off, the residue was dissolved in water and neutralized with diluted sulfuric acid. N-Methylethylphenylbarbituric acid precipitated as a powder. It was filtered off, washed to neutral and dissolved in 50 parts of boiling alcohol. On cooling the obtained methylphenobarbital precipitated as the colorless prisms. MP: 176.5°C. This compound may be also prepared by condensation of equivalents of phenyl malonic ester and monomethyl urea, which was dissolved in above described solution of sodium ethylate.

References

Taub L., Kropp W.; D.R. Patent No. 537,366; Oct. 15, 1931; I. G. Farbenindustrie Akt.-Ges. in Frankfurt a. M.

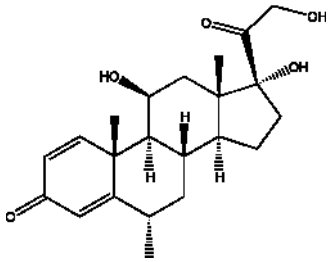
METHYLPREDNISOLONE

Therapeutic Function: Glucocorticoid

Chemical Name: 11β,17α,21-Trihydroxy-6α-methyl-l,4-pregnadiene-3,20-dione

Common Name: 1-Dehydro-6α-methylhydrocortisone

Structural Formula:



Chemical Abstracts Registry No.: 83-43-2

Trade Name	Manufacturer	Country	Year Introduced
Medrol	Upjohn	US	1957
Medrol	Upjohn	France	1959
A-Methapred	Abbott	US	1978
Solu-Medrol	Upjohn	Japan	1980
Caberdelta	Caber	Italy	-
Cortalfa	S.A.M.	Italy	-
Depo-Medrate	Upjohn	W. Germany	-
Emmetip	Magis	Italy	-
Esametone	Lisapharma	Italy	-
Eutisone	Eufarma	Italy	-
Firmacort	Firma	Italy	-
Horusona	Horus	Spain	-
Medesone	Fargal	Italy	-
Mega-Star	Ausonia	Italy	-
Metilbetasone	Coli	Italy	-
Metilcort	Gazzini	Italy	-
Metilprednilone	Guidi	Italy	-
Metilstendiolo	Panther-Osfa	Italy	-
Moderin	Alter	Spain	-
Nirypan	Jugoremedija	Yugoslavia	-
Nixolan	S.I.T.	Italy	-
Prednilen	Lenza	Italy	-
Prednol	Mustafa Nevzat	Turkey	-
Radiosone	Radiumpharma	Italy	-
Reactenol	Lafare	Italy	-
Sieropresol	Sierochimica	Italy	-
Summicort	Benvegna	Italy	-
Suprametil	Geistlich	Switz.	-
Urbason	Hoehst	Italy	-

Raw Materials

Bacterium *Septomyxa affinis*
Corn steep liquor
Glucose
64-α-Methylhydrocortisone

Manufacturing Process

The following process description is taken from US Patent 2,897,218. Six 100-ml portions of a medium in 250-ml Erlenmeyer flasks containing 1% glucose, 2% corn steep liquor (60% solids) and tap water was adjusted to a pH of 4.9. This medium was sterilized for 45 minutes at 15 psi pressure and inoculated with a one to two day growth of *Septomyxa affinis* ATCC 6737. The Erlenmeyer flasks were shaken at room temperature at about 24°C for a period of 3 days.

At the end of this period, this 600-ml volume was used as an inoculum for ten liters of the same glucose-corn steep liquor medium which in addition contained 10 ml of an antifoam (a mixture of lard oil and octadecanol). The fermentor was placed into the water bath, adjusted to 28°C, and the contents stirred (300 rpm) and aerated (0.5 liter air/10 liters beer). After 17 hours of incubation, when a good growth developed and the acidity rose to pH 6.7, 2 g of 6α-methylhydrocortisone plus 1 g of 3-ketobisnor-4-cholen-22-al, dissolved in 115 ml of dimethylformamide, was added and the incubation (conversion) carried out at the same temperature and aeration for 24 hours (final pH 7.9).

The mycelium (56 g dry weight) was filtered off and the steroidal material was extracted with methylene chloride, the methylene extracts evaporated to dryness, and the resulting residue chromatographed over a Florisil column. The column was packed with 200 g of Florisil and was developed with five 400-ml fractions each of methylene chloride, Skellysolve B-acetone mixtures of 9:1, 8:2, 7:3, 1:1, and methanol. The fraction eluted with Skellysolve B-acetone (7:3) weighed 1.545 g and on recrystallization from acetone gave, in three crops, 928 mg of product of MP 210° to 235°C. The sample prepared for analysis melted at 245° to 247°C.

References

Merck Index 5984
Kleeman and Engel p. 587
PDR pp. 1286,1606,1850
OCDS Vol. 1 p. 196 (1977)
I.N. p. 623
REM p.968
Sebek, O.K. and Spero, G.B.; US Patent 2,897,218; July 28, 1959; assigned to The Upjohn Company
Gould, D.H.; US Patent 3,053,832; September 11, 1962; assigned to Schering Corporation

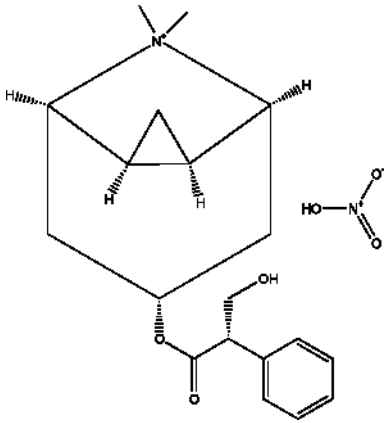
METHYLSCOPOLAMINE NITRATE

Therapeutic Function: Anticholinergic, Spasmolytic

Chemical Name: 1αH,5αH-Tropanium, 6β,7β-epoxy-3α-hydroxy-8-methyl-, nitrate, (-)-

Common Name: Hyocsine methonitrate; Methylscopolamine nitrate; Scopolamine methylnitrate

Structural Formula:



Chemical Abstracts Registry No.: 6106-46-3

Trade Name	Manufacturer	Country	Year Introduced
Transderm Scop	Novartis Consumer Health Inc.	-	-

Raw Materials

Scopolamine hydrobromide trihydrate
Methyl bromide
Silver nitrate

Manufacturing Process

In a one-liter separatory funnel, 94 g (0.215 mol) of scopolamine hydrobromide trihydrate was dissolved in 250 ml of water, made alkaline by shaking with 40 g (1 mol) of sodium hydroxide in 150 ml of water, and the free base immediately extracted with ether. As scopolamine is somewhat soluble in water, the aqueous layer was saturated with potassium carbonate and again extracted with ether. The combined ether extracts were dried over anhydrous magnesium sulfate and the ether removed by distillation, leaving 65 g (0.214 mol; 100% yield) of nearly colorless oil. Then 100 g (1.05 mol) of

cold methyl bromide was added to a chilled, 500-ml pressure flask containing the 65 g of scopolamine, the flask stoppered tightly with a clamp, and allowed to stand at room temperature for 96 hours. The flask was cooled before opening, excess methyl bromide removed by distilling, and the white solid washed thoroughly with dry ether. The yield of crude N-methylscopolammonium bromide was 80 g (94 %t yield). The salt was recrystallized from 550 ml of alcohol; first crop, 70 g, MP: 212-214°C; second crop, 6 g, melting point 195-200°C. The combined crops were again recrystallized from 500 ml of alcohol; melting point 210-212°C. The third recrystallization from 600 ml of alcohol yielded 64 g, melting point 214-216°C, a 75 % yield based on scopolamine hydro-bromide trihydrate starting material. N-Methylscopolammonium bromide may be dissolved in water. An equivalent of solution $AgNO_3$ was added, a precipitated AgBr was filtered off. The filtrate was evaporated to dryness to give the desired N-methylscopolammonium nitrate.

References

Visscher F. E.; US Patent No. 2,753,288; July 3, 1956; Assigned to The Upjohn Company, Kalamazoo, Mich., a corporation of Michigan

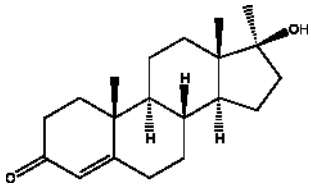
METHYLTESTOSTERONE

Therapeutic Function: Androgen

Chemical Name: 17β-Hydroxy-17-methyl-androst-4-ene-3-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 58-18-4

Trade Name	Manufacturer	Country	Year Introduced
Metandren	Ciba	US	1941
Oreton-M	Schering	US	1941
Neo-Hombreol	Organon	US	1941
Hormale	Key	US	1958
Android-S	Brown	US	-
Arcosterone	Arcum	US	-
Climaterine	Lucien	France	-

Trade Name	Manufacturer	Country	Year Introduced
Climatone	Paines and Byrne	UK	-
Dumone	Squibb	US	-
Estan	Schering	US	-
Gynosterone	Sam-On	Israel	-
Hormobin	Munir Sahin	Turkey	-
Malogen	Fellows-Testagar	US	-
Orchisterone	Negroni	Italy	-
Seksfort	Uranium	Turkey	-
Steronyl	Kay	US	-
Synandrets	Pfizer	US	-
Testipron	Kwizda	Austria	-
Testomet	Protea	Australia	-
Testora	Alcon	US	-
Testostelets	Barlow Cote	Canada	-
Testonic B	Sam-On	Israel	-
Testovis	Vister	Italy	-
Testred	I.C.N.	US	-
Virilon	Star	US	-

Raw Materials

17-Methyl-$\Delta^{(5,6)}$-androstenediol-(3,17)
Magnesium
Acetone
Methyl chloride

Manufacturing Process

0.6 g of 17-Methyl-$\Delta^{5,6}$-androstenediol-(3,17) is heated under reflux cooling during 20 hours in 50 cm^3 of benzene and 12 cm^3 of acetone with 3 g of tertiary chloromagnesium butylate, which may be prepared by conversion of acetone with methyl magnesium chloride. The magnesium is then removed by shaking out with dilute H_2SO_4; the benzene layer is washed with water, dried with sodium sulfate and then evaporated to dryness. Methyltestosterone (MP 160° to 162°C) is obtained in a yield of more than 75% of the theory, according to US Patent 2,384,335.

References

Merck Index 6000
Kleeman and Engel p. 588
PDR pp.645, 729, 802, 949, 1447, 1643, 1778
OCDS Vol. 1 p. 172 (1977)
I.N. p.625
REM p. 998
Miescher, K. and Wettstein, A.; US Patent 2,374,369; April 24, 1945; assigned to Ciba Pharmaceutical Products, Incorporated
Miescher, K. and Wettstein, A.; US Patent 2,374,370; April 24, 1945; assigned to Ciba Pharmaceutical Products, Incorporated

Oppenauer, R.; US Patent 2,384,335; September 4, 1946
Miescher, K.; US Patent 2,386,331; October 9, 1945; assigned to Ciba Pharmaceutical Products, Incorporated
Miescher, K.; US Patent 2,435,013; January 27,1948; assigned to Ciba Pharmaceutical Products, Incorporated

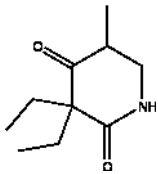
METHYPRYLON

Therapeutic Function: Sedative, Hypnotic

Chemical Name: 3,3-Diethyl-5-methyl-2,4-piperidinedione

Common Name: 2,4-Dioxo-3,3-diethyl-5-methylpiperidine

Structural Formula:



Chemical Abstracts Registry No.: 125-64-4

Trade Name	Manufacturer	Country	Year Introduced
Noludar	Roche	US	1955
Noctan	Yamanouchi	Japan	-
Nolurate	Roche	-	-

Raw Materials

2,4-Dioxo-3,3-diethyl-piperidine
Hydrogen
Sodium
Methyl formate

Manufacturing Process

24 parts by weight of powdered sodium are suspended in 100 parts by volume of absolute benzene and to this suspension is added a freshly prepared solution of 150 parts by weight of methyl formate and 165 parts by weight of 2,4-dioxo-3,3-diethyl-piperidine in 900 parts by volume of absolute benzene. By cooling with cold water, the temperature is maintained at 25° to 28°C. After being stirred for 12 hours 200 parts by volume of 0.6 N sodium hydroxide are added while cooling. The aqueous layer is separated and acidified to Congo red by means of 35% hydrochloric acid. The 2,4-dioxo-3,3-diethyl-5-oxymethylenepiperidine is precipitated in good yield as a solid. After having been recrystallized in chloroform/petroleum ether it melts at 140° to

141°C.

5 parts by weight of 2,4-dioxo-3,3-diethyl-5-oxymethylene-piperidine are hydrogenated in 25 parts by volume of methanol in the presence of about 2 parts by weight of Raney nickel at 120°C and under an elevated pressure of 100 atm. Once 2 mols of hydrogen are absorbed, the hydrogenation is interrupted, the solution is separated from the catalyst and concentrated and the residue is distilled in vacuo. The distillate, boiling between 178° and 185°C under a pressure of 16 mm, consists of 2,4-dioxo-3,3-diethyl-5-methyl-piperidine, which melts at 74° to 75°C.

The same compound is obtained when proceeding according to the following alternative procedure. A mixture of 39.4 parts by weight of 2,4-dioxo-3,3-diethyl-5-oxymethylenepiperidine and 27 parts by weight of dibutylamine are heated to 150°C in a closed vessel. The 2,4-dioxo-3,3-diethyl-5-dibutylamino-methylene-piperidine formed melts at 77°C after having been recrystallized in petroleum ether.

31 parts by weight of the latter compound are hydrogenated in 150 parts by volume of alcohol, containing 6 parts by weight of acetic acid, in the presence of 10 parts by weight of Raney nickel, at 120°C and under an elevated pressure of 100 atm. The catalyst is separated and the solution is distilled in vacuo. The 2,4-dioxo-3,3-diethyl-5-methyl-piperidine boils between 178° and 185°C under a pressure of 16 mm and melts at 74° to 75°C.

References

Merck Index 6010
Kleeman and Engel p. 590
PDR p. 1495
DOT 9 (6) 245 (1973)
I.N. p. 626
REM p. 1072
Frick, H.and Lutz, A.H.; US Patent 2,680,116; June 1, 1954; assigned to Hoffmann-LaRoche Inc.

METHYSERGIDE MALEATE

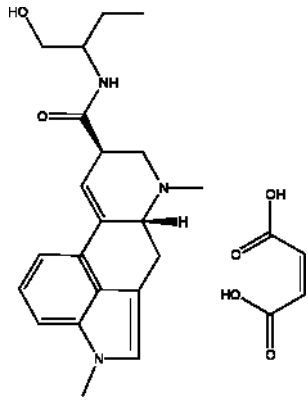
Therapeutic Function: Migraine therapy

Chemical Name: 9,10-Didehydro-N-[1-(hydroxymethyl)propyl]-1,6-dimethylergoline-8-carboxamide maleate

Common Name: 1-Methyl-d-lysergic acid butanolamide maleate

Chemical Abstracts Registry No.: 129-49-7; 361-37-5 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Sansert	Sandoz	US	1962
Desernil	Sandoz	France	1962
Deseril	Sandoz	UK	1963

Raw Materials

Potassium
Methyl iodide
Lysergic acid-1'hydroxy-butylamide-2'
Ammonia
Maleic acid

Manufacturing Process

As described in US Patent 3,218,324, 0.9 part of potassium are dissolved in 500 parts by volume of liquid ammonia, then oxidized with ferric nitrate to potassium amide, after which 4.85 parts of lysergic acid-1'-hydroxy-butylamide-2' are dissolved in the obtained mixture. After 15 minutes there are added to the obtained yellow solution 4.1 parts of methyl iodide in 5 parts by volume of ether, the mixture being allowed to stand for 30 more minutes at -60°C. The liquid ammonia is thereupon evaporated and the dry residue is shaken out between water and chloroform. The mixture of bases which remains after the evaporation of the chloroform is chromatographed on a column of 250 parts of aluminum oxide, the desired 1-methyl-lysergic acid-1'-hydroxy-butylamide-2' being washed into the filtrate with chloroform and chloroform-0.2% ethanol. The 1-methyl-lysergic acid-1'hydroxy-butylamide-2' crystallizes from chloroform in the form of plates which melt at 194° to 196°C. Reaction with maleic acid gives the dimaleate, melting at 187° to 188°C.

References

Merck Index 6011
Kleeman and Engel p. 590

PDR p. 1596
OCDS Vol. 2 p. 477 (1980)
I.N. p. 626
REM pp. 949, 1113
Hofmann, A. and Troxler, F.; US Patent 3,113,133; December 3,1963; assigned to Sandoz Ltd., Switzerland
Hofmann, A. and Troxler, F.; US Patent 3,218,324; November 16,1965; assigned to Sandoz Ltd., Switzerland

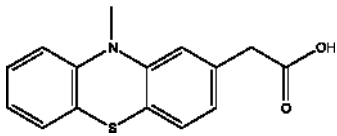
METIAZINIC ACID

Therapeutic Function: Antiinflammatory

Chemical Name: 10-Methylphenothiazine-2-acetic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 13993-65-2

Trade Name	Manufacturer	Country	Year Introduced
Soripan	Specia	France	1970
Soripal	Torii	Japan	1977
Soripal	Farmalabor	Italy	1978
Ambrunate	Rhodia	Argentina	-
Metian	Horus	Spain	-
Novartril	Andromaco	Spain	-
Roimal	Nippon Rhodia	Japan	-
Soridermal	Specia	France	-

Raw Materials

10-Methyl-3-acetylphenthiazine
Morpholine
Sulfur
Potassium hydroxide

Manufacturing Process

10-Methyl-3-acetylphenthiazine is prepared in accordance with G. Cauquil and A. Casadevall, Bull. Soc.Chim., p 768 (1955). (10-Methyl-3-

phenthiazinyl)acetic acid (MP 146°C; 21.4 g) is prepared by Willgerodt's reaction (action of sulfur and morpholine, followed by hydrolysis) employing 10-methyl-3-acetylphenthiazine as starting material.

References

Merck Index 6013
Kleeman and Engel p. 591
I.N. p. 32
Farge, D., Jeanmart, C. and Messer, M.N.; US Patent 3,424,748; January 28, 1969; assigned to Rhone-Poulenc S.A., France

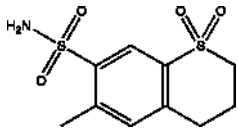
METICRANE

Therapeutic Function: Diuretic

Chemical Name: 2H-1-Benzothiopyran-7-sulfonamide, 3,4-dihydro-6-methyl-, 1,1-dioxide

Common Name: Meticrane

Structural Formula:



Chemical Abstracts Registry No.: 1084-65-7

Trade Name	Manufacturer	Country	Year Introduced
Fontilix	Diamant	-	-

Raw Materials

6-Methylthiachromane
Hydrogen peroxide
Chlorosulfonic acid
Ammonia

Manufacturing Process

64.5 g of 6-methylthiachromane were dissolved in 500 ml of acetic acid and 250 ml of 110-volume hydrogen peroxide were added. The solution was placed on a water bath for 1.5 hour; it was then diluted with iced water, the precipitate obtained was recovered, and this was washed and dried. There were obtained 59.6 g of 6-methylthiachromane-1,1-dioxide (yield: 77.5%; melting point 79°-81°C).

52 g of this product were added to 250 ml of chlorosulfonic acid and the mixture was placed on a water bath at a temperature of 70°-75°C for 2 hours. It was allowed to cool and poured onto crushed ice; the product was extracted by means of chloroform, the extracted solutions were washed and the chloroform was evaporated. There were obtained 67 g of crude 6-methyl-7-chloro-sulfonyl-thiachromane-1,1-dioxide (yield: 86%; melting point 158°-161°C).

47 g of this sulfochloride were introduced into 200 ml of liquid ammonia. The mixture was left to stand at ambient temperature until the ammonia evaporated. The residue was taken up in water and the solution was acidified. The precipitate formed was centrifuged, washed with water and dried. There were obtained 30.8 g of 6-methyl-7-sulfamido-thiachromane-1,1-dioxide, recrystallized from 2-methoxy ethanol (yield: 49%; MP: 236°-237°C).

References

Boissier J.R. et al.; US Patent No. 3,488,424; Jan. 6, 1970; Assigned to Societe Industrielle pour la Fabrication des Antibiotiques (S.I.F.A.), Paris, France, a French company

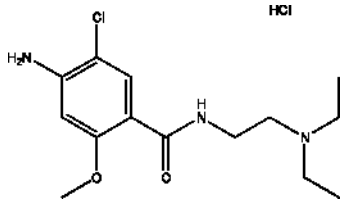
METOCLOPRAMIDE HYDROCHLORIDE

Therapeutic Function: Antiemetic

Chemical Name: 4-Amino-5-chloro-N-[(2-diethylamino)ethyl]-2-methoxybenzamide hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 7232-21-5; 364-62-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Primperan	Delagrange	France	1964
Paspertin	Kali-Chemie	W. Germany	1965
Maxolon	Beecham	UK	1967
Plasil	Richter	Italy	1967
Reglan	Robins	US	1979

Trade Name	Manufacturer	Country	Year Introduced
Metox	Steinhard	UK	1983
Ananda	Bonomelli-Hommel	Italy	-
Cerucal	Arzneimittelwerk Dresden	E. Germany	-
Clodil-Ion	Ion	Italy	-
Clopamon	Petersen	S. Africa	-
Clopan	Firma	Italy	-
Contromet	Script Intal	S. Africa	-
Digetres	Scalari	Italy	-
Donopon-GP	Sana	Japan	-
Elietin	Nippon Kayaku, Co.	Japan	-
Emesa	Mulda	Turkey	-
Emetisan	Phoenix	Argentina	-
Emperal	Neofarma	Finland	-
Gastronertron	Dolorgiet	W. Germany	-
Imperan	Bender	Austria	-
Kilozim	A.G.I.P.S.	Italy	-
Maxrean	Nordic	Canada	-
MCP-Ratiopharm	Ratiopharm	W. Germany	-
Meclopran	Lagap	Switz.	-
Metamide	Protea	Australia	-
Metoclol	Toyama	Japan	-
Metocobil	Beta	Italy	-
Metopram	Leiras	Finland	-
Metpamid	Sifar	Turkey	-
Moriperan	Morishita	Japan	-
Nadir	Oti	Italy	-
Netaf	Sintyal	Japan	-
Peraprin	Taiyo	Japan	-
Placitril	Sigurta	Italy	-
Pramiel	Nagase	Japan	-
Pramin	Rafa	Israel	-
Primperil	Lacefa	Argentina	-
Prindarl	Sawai	Japan	-
Prometin	Yamanouchi	Japan	-
Putoprin	Mohan	Japan	-
Quanto	Mediolanum	Italy	-
Randum	Scharper	Italy	-
Regastrol	Sarm	Italy	-
Reliveran	Finadiet	Argentina	-
Rimetin	Farmakhim	Bulgaria	-
Terperan	Teikoku Zoki	Japan	-
Viscal	Zoja	Italy	-

Raw Materials

o-Toluidine
Nitrous acid
Acetic anhydride
Nitric acid
Thionyl chloride
Chlorine
Potassium permanganate
N,N-Diethylene diamine
Hydrogen chloride
Dimethyl sulfate
Hydrogen

Manufacturing Process

The N-(diethylaminoethyl)-2-methoxy-4-aminobenzamide used as the starting material may be prepared from o-toluidine. The o-toluidine is initially nitrated with nitric acid to produce 4-nitro-o-toluidine. The 4-nitro-o-toluidine is then converted to 2-hydroxy-4-nitrotoluene by heating with nitrous acid. By reacting the resulting 2-hydroxy-4-nitrotoluene with dimethyl sulfate, 2-methoxy-4-nitrotoluene is formed. The 2-methoxy-4-nitrotoluene is oxidized with potassium permanganate to produce 2-methoxy-4-nitrobenzoic acid. The latter substituted benzoic acid is treated with thionyl chloride to form 2-methoxy-4-nitrobenzoyl chloride. A methyl ethyl ketone solution of the 2-methoxy-4-nitrobenzoyl chloride is added over a period of about 1½ hours to a methyl ethyl ketone solution containing an equal molecular quantity of N,N-diethylethylene diamine while stirring and maintaining the temperature between 0°C and 5°C. The N-(diethylaminoethyl)-2-methoxy-4-nitrobenzamide hydrochloride formed precipitates. It is filtered, washed twice with methyl ethyl ketone, dissolved in alcohol, and reduced catalytically in an absolute isopropyl alcohol solution to form N-(diethylaminoethyl)-2-methoxy-4-aminobenzamide. The base is obtained by precipitating with sodium hydroxide.

80 g (0.3mol) of N-(2-diethylaminoethyl)-2-methoxy-4-aminobenzamide are dissolved in small portions in 150 cc of acetic acid. The mixture is cooled and 45 g (0.45 mol) of acetic anhydride are added, and the solution obtained is heated for two hours on a water bath. After cooling, the solution is decanted into a round-bottomed flask with a stirrer, a thermometer and a tube for introducing the chlorine. It is stirred and the current of chlorine is passed through, the temperature being maintained between 20°C and 25°C. The stirring is continued for one hour after the completion of the absorption of the chlorine.

The mixture obtained is poured into 2 liters of water and the base is precipitated with 30% soda. The precipitated base is extracted with 400 cc of methylene chloride. After evaporation of the solvent, the N-(2-diethylaminoethyl)-2-methoxy-4-acetamino-5-chlorobenzamide formed crystallizes. The melting point is 86°C to 87°C and the yield is 95%.

To obtain the corresponding amino derivative, 109 g of base are heated under agitation in a round-bottomed flask with 300 cc of 35-36% concentrated hydrochloric acid and 600 cc of water. It is heated on a water bath until dissolution is complete, then maintained at boiling point for 90 minutes, cooled, diluted with 1 liter of water, and neutralized with about 350 cc of 30% soda. The N-(2-diethylaminoethyl)-2-methoxy-4-amino-5-chlorobenzamide formed crystallizes, is centrifuged and washed in water. Its melting point is 122°C and the yield is 74%.

To obtain the corresponding dihydrochloride, the base is dissolved in absolute alcohol (3 volumes) and to that solution is added 5 N alcoholic hydrochloric acid. The dihydrochloride precipitates, is centrifuged and washed with alcohol. It is a solid white material, having a melting point of 134°C to 135°C.

References

Merck Index 6019
Kleeman and Engel p. 593
PDR p. 1463
DOT 1 (2) 66 (1965); 16 (5) 159 (1980) and 19 (8) 476 (1983)
I.N. p. 629
REM p. 809
Thominet, M.L.; US Patent 3,177,252; April 6,1965; assigned to Soc. d'Etudes Scientifiques et Industrielles de l'Ile de France (France)

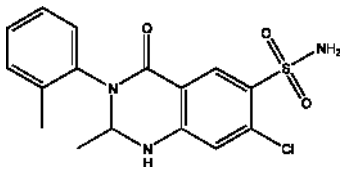
METOLAZONE

Therapeutic Function: Diuretic

Chemical Name: 7-Chloro-l,2,3,4-tetrahydro-2-methyl-3-(2-methylphenyl)-4-oxo-6-quinolinesulfonamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 17560-51-9

Trade Name	Manufacturer	Country	Year Introduced
Zaroxolyn	Pennwalt	UK	1973
Zaroxolyn	Pennwalt	US	1974
Diulo	Searle	US	1978
Zaroxolyn	Searle	W. Germany	1978
Zaroxolyn	Sandoz	Switz.	1978
Zaroxolyn	I.S.F.	Italy	1981
Normeran	Sankyo	Japan	1982
Metenix	Hoechst	UK	-
Oldren	Roemmers	Argentina	-

Raw Materials

5-Chloro-2-methylaniline
o-Toluidine
Acetic anhydride
Phosphorus trichloride
Chlorosulfonic acid
Sodium borohydride
Ammonia

Manufacturing Process

Preparation of Intermediate Compound N-Acetyl-5-Chloro-2-Methylaniline: To a well-stirred mixture of 1,270 g (9 mols) of 5-chloro-2-methylaniline in 7.5 liters of water at 34°C was added all at once 1,710 ml (18 mols) of acetic anhydride. A solution was obtained and then almost immediately the product started to crystallize. The temperature rose to 60°C. The mixture was stirred until the temperature dropped to 30°C. The product was filtered and washed well with water. Yield 97% (1,640 g), MP 134° to 138°C. Product was air dried and then in vacuum over P_2O_5.

Preparation of Intermediate Compound 5-Chloro-2-Methyl-4-Sulfamylacetanilide: Into a 3-necked 3-liter flask fitted with stirrer and thermometer 540 ml of chlorosulfonic acid were placed and cooled in an ice bath to 20°C. 300 g of the acetanilide were added portionwise while stirring and maintaining temperature at 20°C. This addition takes approximately 20 minutes. Remove the ice bath and add 88 g of sodium chloride portionwise (approximately 1 tsp every 10 minutes), This addition takes approximately 1 hour. Some foaming takes place. Using heating mantle bring temperature up slowly (approximately ½ hour) to 75°C. Considerable foaming takes place and heating is continued another ½ hour until 92°C is reached. Foaming can be controlled by shutting off heat and with good stirring. Once the temperature of 92°C has been reached and foaming has subsided reaction can be left unattended. Keep reaction at 92°C for a total of 2½ hours.

Pour the hot reaction mixture onto 4 liters of crushed ice. Pour slowly and stir the ice mixture. What remains in the flask can be worked up by adding ice to it and swirling the contents. After approximately 3/4 of an hour, the solid is filtered and washed with approximately 600 ml water.

Break up cake into small pieces and add to 2.5 liters concentrated NH_4OH in 4 liter beaker. Stir. Solid goes into solution and then the sulfonamide precipitates out. Heat to 50°C and then turn off heat. After ½ hour cool in ice bath and filter. Wash cake with 600 ml water. Add cake to 2 liters 5% NaOH (130 ml 50% NaOH to 2 liters water). Filter and discard insolubles. While cooling filtrate add concentrated HCl until mixture is acid. Filter and wash cake until filtrate is neutral. Suck cake as dry as possible then air dry. Yield approximately 200 g (45%), MP 255° to 260°C.

Preparation of Intermediate Compound 4-Chloro-5-Sulfamyl-N-Acetylanthranilic Acid: To a hot solution (80°C) of 366 g (1.482 mols) of magnesium sulfate (Epsom salts) in 2.8 liters of water was added 130 g (0.495 mol) of powdered 5-chloro-2-methyl-4-sulfamylacetanilide. With stirring and maintaining the temperature at 83°C, 234 g (1.482 mols) of potassium permanganate was added portionwise over a period of 2 hours. The mixture was then kept at 85°C with stirring for an additional 3 hours. By this

time the pink color of the permanganate had been discharged.

The mixture was cooled to 65°C and 250 g (2.0 mols) of sodium carbonate monohydrate was added. The warm reaction mixture was filtered and the cake washed with water. The filtrate was then slowly treated with concentrated hydrochloric acid until mixture tested acid. Product was then filtered, washed with water and dried. Yield 103 g (71.0%), MP 245° to 249°C (dec.).

Preparation of Intermediate Compound 2-Methyl-3-o-Tolyl-6-Sulfamyl-7-Chloro-4(3H)-Quinazolinone: Set up a 5-liter 3-necked flask fitted with a stirrer, condenser and a drying tube. To a stirred mixture of 100 g (0.342 mol) of powdered 4-chloro-5-sulfamyl-N-acetylanthranilic acid, 40.2 g (0.376 mol) of o-toluidine and 2.0 liters of dry toluene was added dropwise, over a period of 15 minutes, 21.7 ml (34.1 g) (0.248 mol) of phosphorus trichloride. The mixture was then refluxed for 10 hours. The solid turned somewhat gummy towards the latter part of the first hour. The mixture then became more free flowing as heating was continued. Let stand overnight. The yellow solid was filtered, washed with toluene and dried. The toluene filtrate was discarded. The dried solid was triturated with 1.5 liters of 10% sodium bicarbonate, filtered and the cake washed with water. The filtrate on acidification yielded 11.5 g of the starting acid. The damp product was dissolved in 4.5 liters of 95% ethanol and the solution treated with charcoal and filtered. On cooling filtrate yielded 69.5 g (55.5%) of the title compound, MP 271.5° to 274°C.

Preparation of the Final Compound 2-Methyl-3-o-Tolyl-6-Sulfamyl-7-Chloro-1,2,3,4-Tetrahydro-4(3H)-Quinazolinone: To 4 liters of dry diglyme in a 12-liter 3-necked flask fitted with a stirrer, thermometer and drying tube was added 5.34 g (0.04 mol) of aluminum chloride, while stirring. To the resulting solution was added 43.6 g (0.12 mol) of 2-methyl-3-o-tolyl-6-sulfamyl-7-chloro-4(3H)-quinazoline. A solution of 4.56 g (0.12 mol) of sodium borohydride in 1 liter of dry diglyme was added portionwise over a period of 1 hour while stirring the mixture. The mixture was then heated at 85°C, with stirring, for 1 hour.

After cooling the reaction mixture to 25°C in an ice bath 600 ml of water was added and then enough dilute hydrochloric acid (approximately 100 ml) to make the solution acid. The solvent was then removed under reduced pressure at 60° to 70°C. The very viscid residue solidified when triturated with water. The solid was filtered and washed with water. The solid was dissolved in approximately 400 ml 95% ethanol and the solution filtered through Celite. On cooling the solution yielded 30 g of colorless solid, MP 253° to 259°C. The filtrate was concentrated to 200 ml to yield another 4.6 g, MP 253° to 259°C.

The above product was then recrystallized from 900 ml of 95% ethanol after filtering the hot solution through Celite. Crystallization was initiated and the mixture agitated occasionally while being cooled in the refrigerator. Yield of product 29 g, MP 253° to 259°C. Concentration of the filtrate to 125 ml yielded another 7.5 g of product, MP 253° to 259°C. The product was recrystallized another time in the manner described above. Total yield, first and second crops, 28.8 g (66%), MP 250° to 255°C. Product was dried at 80°C in a vacuum, according to US Patent 3,360,518.

References

Merck Index 6024
Kleeman and Engel p. 594
PDR pp. 1401, 1668
OCDS Vol. 2 p. 384 (1980)
DOT 9 (12) 498 (1973)
I.N. p. 629
REM p. 940
Shetty, B.V.; US Patent 3,360,518; December 26, 1967; assigned to Wallace and Tiernan Inc.
Shetty, B.V.; US Patent 3,557,111; January 19, 1971

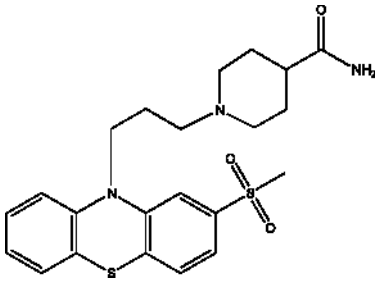
METOPIMAZINE

Therapeutic Function: Antiemetic

Chemical Name: 4-Piperidinecarboxamide, 1-(3-(2-(methylsulfonyl)-10H-phenothiazin-10-yl)propyl)-

Common Name: Metopimazine

Structural Formula:



Chemical Abstracts Registry No.: 14008-44-7

Trade Name	Manufacturer	Country	Year Introduced
Nortrip	Rhodia	-	-

Raw Materials

2-Methylsulfonylphenothiazine
1-Bromo-3-chloropropane
Piperidine-4-carboxylic acid amide
Sodium
Ammonia

Manufacturing Process

2-Methylsulfonyl-10-(3-chloropropyl)phenothiazine was prepared by condensation of 1-bromo-3-chloropropane and 2-methylsulfonyl phenothiazine in liquid ammonia in presence of obtained in situ sodium amide.

10 g 2-methylsulfonyl-10-(3-chloropropyl)-phenothiazine, 4 g piperidine-4-carboxylic acid amide, 3.5 g dry sodium carbonate in 200 ml of ethanol was heated to reflux for 24 hours. Than 1.75 g sodium carbonate was added and the mixture was heated another 8 hours. After that the new 1.75 g portion of sodium carbonate was added and heated for 16 hours. The solvent was removed in vacuum (20 mm Hg). The residue was stirred with 50 ml water and 150 ml ethyl acetate. The organic layer was separated and extracted with 200 ml 1 N hydrochloric acid. The water layer was made alkaline with 4 N sodium hydroxide, extracted with ethyl acetate and dried over sodium sulfate. The solvent was removed in vacuum (20 mm Hg) to dryness. The obtained residue 2-methylsulfonyl-10-(3-(4-carbamoylpiperidino)propyl)phenothiazine was recrystallized from ethyl acetate. Yield 6 g; MP: 170°-171°C.

References

Jacob R. et al.; D.B. Patent No. 1,092,476; April 14, 1959; Societe des Usines Chimiques Rhone-Poulenc, Paris

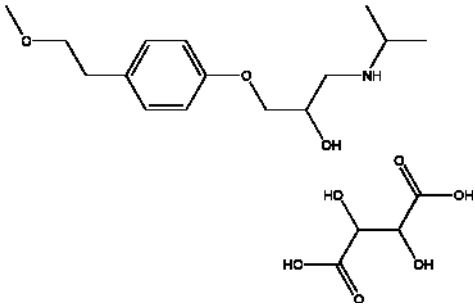
METOPROLOL TARTRATE

Therapeutic Function: Beta-adrenergic blocker

Chemical Name: 1-[4-(2-Methoxyethyl)phenoxy]-3-[(1-methylethyl)amino]-2-propanol tartrate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 56392-17-7; 37350-58-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Betaloc	Astra	UK	1975
Lopressor	Geigy	UK	1975
Beloc	Astra	W. Germany	1976
Lopressor	Ciba Geigy	W. Germany	1976
Lopressor	Ciba Geigy	Italy	1978
Selomen	Bracco	Italy	1978
Lopressor	Ciba Geigy	US	1978
Seloken	Searle	France	1980
Seloken	Fujisawa	Japan	1983
Lopresol	Takeda	Japan	1983
Lati 2	Unifa	Argentina	-
Neobloc	Unipharm	Israel	-
Prelis	Brunnengraber	W. Germany	-

Raw Materials

Isopropylamine
Tartaric acid
Epichlorohydrin
Sodium bicarbonate
p-(β-Methoxyethyl)phenol

Manufacturing Process

The starting material 1,2-epoxy-3-[p-(β-methoxyethyl)phenoxy]-propane was obtained from p-(β-methoxyethyl)-phenol which was reacted with epichlorohydrin whereafter the reaction product was distilled at 118°C to 128°C at a pressure of 0.35mm Hg.

1,2-Epoxy-3-[p-(β-methoxyethyl)-phenoxy]-propane (16.7g) was dissolved in 50 ml isopropanol and mixed with 20 ml isopropylamine. The mixture was heated in an autoclave on boiling water-bath overnight, whereafter it was evaporated and the remainder dissolved in 2 N HCI. The solution was extracted first with ether and thereafter with methylene chloride. After evaporating the methylene chloride phase, the hydrochloride of 1-isopropylamino-3-[p(β-methoxyethyl)-phenoxy] -propanol-2 was obtained which, after recrystallization from ethyl acetate, weighed 10.4 g. Melting point 83°C. Equivalent weight: found 304.0, calculated 303.8.

The hydrochloride is then converted to the tartrate.

References

Merck Index 6027
Kleeman and Engel p. 595
PDR p. 894
OCDS Vol. 2 p. 109 (1980)
DOT 11 (9) 360 (1975) and 17 (2) 65 (1981)
I.N. p. 630
REM p. 905
Brandstrom, A.E., Carlsson, P.A.E., Carlsson, S.A.I., Corrodi, H.R., Ek, L.and Ablad, B.A.H.; US Patent 3,873,600; March 25, 1975

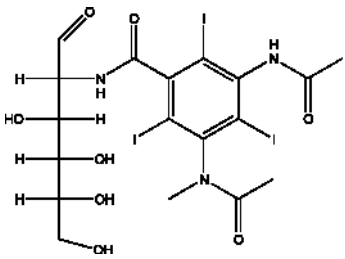
METRIZAMIDE

Therapeutic Function: Diagnostic aid

Chemical Name: D-Glucose, 2-((3-(acetylamino)-5-(acetylmethylamino)-2,4,6-triiodobenzoyl)amino)-2-deoxy-

Common Name: Metrizamide

Structural Formula:



Chemical Abstracts Registry No.: 31112-62-6

Trade Name	Manufacturer	Country	Year Introduced
Amipaque	Winthrop laboratories	-	-

Raw Materials

3-(Acetylmethylamino)-2,4,6-triiodo-5-methylamino-benzoic acid
Thionyl chloride
Glucosamine

Manufacturing Process

1 mole 3-(acetyl-methyl-amino)-2,4,6-triiodo-5-methylamino-benzoic acid was suspended in thionyl chloride and reacted by stirring at 70°C for 16 hours. Excess thionyl chloride was distilled off in vacuum, the residue dissolved in chloroform, cooled in the ice bath, washed with iced water (3x100 ml), saturated sodium bicarbonate solution (3 x 100 ml), 2 N sodium carbonate solution (2 x 100 ml) and finally with water (3 x 100 ml). After drying with $CaCl_2$ the chloroform distilled off and residue dried in vacuum. Yield of 3-acetylamino-5-(acetyl-methyl-amino)-2,4,6-triiodo-benzoyl chloride: 66%; MP: 238°-240°C (the re-crystallization from tetrahydrofuran).

It (0.02 mole) was dissolved in dioxan (120 ml). To the solution was added (25 ml) and $NaHCO_3$ (0.0022 mol). Glucosamine (0.022 mol) was added in portions and reaction mixture left by stirring at room temperature for 24 hours. The solution was evaporated to dryness in vacuum, the residue dissolved in water (500 ml), filtered clear and run through an Amberlite IR

120 H^+ ion exchange column. The effluent was evaporated to dryness in vacuum resulting in a white crystalline residue. The crude 3-acetylamino-5-N-methyl-acetylamino-2,4,6-triiodobenzoyl glucosamine was crystallised from isopropanol (charcoal-treated when in solution), dissolved in water and charcoal-treated at 100°C for 20 min. The water was distilled off in vacuum and the white residue dried in vacuum at 70°C. MP: 190°-195°C.

References

Almen T.H.O.; US Patent No. 3,701,771; Oct. 31, 1972; Assigned to Nyegaard and Co. A/S; Norway

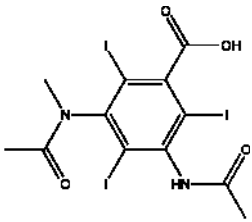
METRIZOIC ACID

Therapeutic Function: Diagnostic aid (radiopaque medium)

Chemical Name: 3-(Acetylamino)-5-(acetylmethylamino)-2,4,6-triiodobenzoic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 1949-45-7

Trade Name	Manufacturer	Country	Year Introduced
Isopaque	Winthrop	France	1973
Isopaque	Sterling	US	1975
Isopaque	Winthrop	Italy	1978
Ronpacon	Cilag Chemie	W. Germany	-

Raw Materials

Diatrizoic acid (diatrizoate)
Dimethyl sulfate

Manufacturing Process

3,5-Diacetamido-2,4,6-triiodobenzoic acid (diatrizoic acid) (see Diatrizoate

entry for synthesis) (10 g) is suspended in water (10 ml), 5 N potassium hydroxide (4.3 equivalent) is added and the mixture cooled to about 15°C. Dimethyl sulfate (0.5 equivalent) dissolved in an equal volume of acetone is added drop by drop while stirring. After the reaction mixture has been stirred for about 1 hour hydrochloric acid (1:1) is added, with stirring to pH about 0.5. The precipitate is filtered, washed and suspended moist in 4 parts of water, concentrated ammonia is added to pH about 7 and the ammonium salt solution is isomerized at 90°C to 100°C for about one-half hour whereafter additional ammonia is added to pH about 9 followed by solid ammonium chloride (about 10% weight/volume) and the solution stirred overnight and the excess of 3,5-diacetamide-2,4,6-triiodobenzoic acid recovered as ammonium salt on the filter. The filtrate is precipitated by means of hydrochloric acid (1:1) at pH about 0.5 and the N-methyl-3,5-diacetamido-2,4,6-triiodobenzoic acid collected on a filter, washed and dried.

References

Merck Index 6032
Kleeman and Engel p. 597
I.N. p. 631
REM p. 1270
Holtermann, H., Haugen, L.G., Nordal, V. and Haavaldsen, J.L.; US Patent 3,178,473; April 13, 1965; assigned to Nyegaard and Co. A/S (Norway)

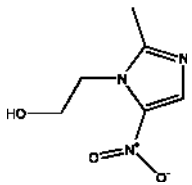
METRONIDAZOLE

Therapeutic Function: Antiprotozoal

Chemical Name: 2-Methyl-5-nitroimidazole-1-ethanol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 443-48-1

Trade Name	Manufacturer	Country	Year Introduced
Flagyl	Specia	France	1960
Flagyl	May and Baker	UK	1960
Flagyl	Rhone Poulenc	W. Germany	1961
Flagyl	Farmitalia	Italy	1962
Flagyl	Searle	US	1963

Trade Name	Manufacturer	Country	Year Introduced
Satric	Savage	US	1982
Metryl	Lemmon	US	1982
Metro IV	McGaw	US	1982
Protostat	Ortho	US	1983
Anaerobex	Gerot	Austria	-
Arilin	Wolff	W. Germany	-
Asuzol	Fuji	Japan	-
Clont	Bayer	W. Germany	-
Deflamon	SPA	Italy	-
Efloran	Krka	Yugoslavia	-
Elyzol	Dumex	Denmark	-
Entizol	Polfa	Poland	-
Flagemona	Phoenix	Argentina	-
Fossyol	Merckle	W. Germany	-
Gineflavir	Crosara	Italy	-
Klion	Kobanyai	Hungary	-
Kreucosan	Kreussler	W. Germany	-
Medazol	Belupo Ltd.	Yugoslavia	-
Meronidal	Kissei Pharmaceutical Co., Ltd.	Japan	-
Metrajil	Mulda	Turkey	-
Matrogil	Lkapharm	Israel	-
Metrolag	Lagap	Switz.	-
Monasin	Helvepharm	Switz.	-
Nalox	Omega	Argentina	-
Neo-Tric	Neo	Canada	-
Nida	Toyo Pharm.	Japan	-
Novonidazol	Novopharm	Canada	-
Orvagil	Galenika	Yugoslavia	-
Rathimed N	Pfleger	W. Germany	-
Rivozol	Rivopharm	Switz.	-
Rodogyl	Specia	France	-
Salandol	Sato	Japan	-
Sanatrichom	Godecke	W. Germany	-
Sawagyl	Sawai	Japan	-
Servizol	Servipharm	Switz.	-
Surimol	Labatec	Switz.	-
Takimetol	Nakataki	Japan	-
Tarozole	Taro	Israel	-
Tranoxa	Exa	Argentina	-
Trichazol	Will	Canada	-
Trichex	Gerot	Austria	-
Trichocide	Green Cross	Japan	-

Trade Name	Manufacturer	Country	Year Introduced
Tricho Cordes	Icthyol	W. Germany	-
TrichoGynaedron	Artesan	W. Germany	-
Trichomol	Gea	Denmark	-
Trichostop	Sigmapharm	Austria	-
Trichozole	Protea	Australia	-
Tricowas B	Wassermann	Spain	-
Trikamon	Elliott-Marion	Canada	-
Trikozol	Farmos	Finland	-
Trivazol	Vister	Italy	-
Vagilen	Farmigea	Italy	-
Vagimid	Apogepha	E. Germany	-
Vaginyl	D.D.S.A.	UK	-
Wagitran	Ono	Japan	-

Raw Materials

2-Methyl-5-nitroimidazole
Ethylene chlorohydrin

Manufacturing Process

2-Methyl-4(or 5)-nitroimidazole (127 g) is heated with ethylene chlorohydrin (795 g) for 18 hours at 128° to 130°C and the chlorohydrin (660 g) is then distilled under reduced pressure (30mm Hg). The residue is treated with water (300 cc) and filtered, and the filtrate is made alkaline by the addition of sodium hydroxide solution (d = 1.33, 100 cc). It is then extracted with chloroform (1,000 cc) and, after evaporation of the chloroform in vacuo, there is obtained a pasty mass (77 g) which is recrystallized from ethyl acetate (450 cc) in the presence of animal charcoal. There is thus obtained 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole (24 g) as a creamy white crystalline powder melting at 158° to 160°C.

References

Merck Index 6033
Kleeman and 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) 8117 (1) 34 (1981)
I.N. p. 632
REM p. 1222
Jacob, R.M., Regnier, G.L. and Crisan, C.; US Patent 2,944,061; July 5,1960; assigned to Societe des Usines Chimiques Rhone-Poulenc, France

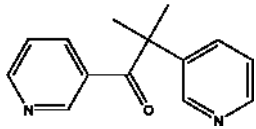
METYRAPONE

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	US	1961
Metopirone	Ciba	UK	1961
Metyrapone	Ciba	Switz.	1964
Metopiron	Ciba	W. Germany	1966

Raw Materials

3-Acetylpyridine
Sulfuric acid
Hydrogen
Hydroxylamine sulfate

Manufacturing Process

According to US 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
Kleernan and Engel p. 598
PDR p. 803
I.N. p. 633
REM p. 1276
Bencze, W.L. and Allen, M.J.; US Patent 2,923,710; February 2, 1960; assigned to Ciba Pharmaceutical Products, Inc.
Allen, M.J. and Bencze, W.L.; US Patent 2,966,493; December 27, 1960; assigned to Ciba Pharmaceutical Products, Inc.

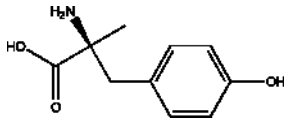
METYROSINE

Therapeutic Function: Tyrosine hydroxylase inhibitor

Chemical Name: α-Methyl-L-tyrosine

Common Name: Metirosine

Structural Formula:



Chemical Abstracts Registry No.: 672-87-7

Trade Name	Manufacturer	Country	Year Introduced
Demser	MSD	US	1979

Raw Materials

Hydrogen
Sulfuric acid
α-Methyl-N-dichloroacetyl-p-nitrophenylalanine
Sodium nitrite
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.; US Patent 2,868,818; January 13, 1959;assigned to Merck and Co., Inc.

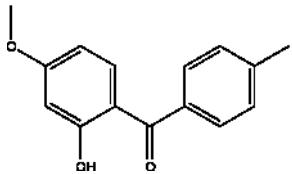
MEXENONE

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	UK	1960

Raw Materials

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

Manufacturing Process

p-Toluoyl 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 and Engel p. 598
OCDS Vol. 2 p. 175 (1980)
I.N. p. 633
Hardy. W.B. and Forster, W.S.; US Patent 2,773,903; December 11, 1956; assigned to American Cyanamid Company

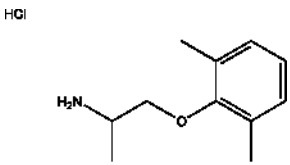
MEXILETINE HYDROCHLORIDE

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	Boehringer Ingelheim	US	1976
Mexitil	Boehringer Ingelheim	Switz.	1978
Mexitil	Boehringer Ingelheim	W. Germany	1979
Mexitil	Boehringer Ingelheim	France	1981
Mexitil	Boehringer Ingelheim	Italy	1982

Raw Materials

Dimethyl phenol
Hydrogen
Hydroxylamine
Chloroacetone
Sodium hydroxide

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-anino-propane hydrochloride.

References

Merck Index 6047
DFU 1 (4) 180 (1976)
Kleeman and 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.; US Patent 3,659,019; April 25,1972; assigned to Boehringer Ingelheim G.m.b.H. (W. Germany)

MEZLOCILLIN

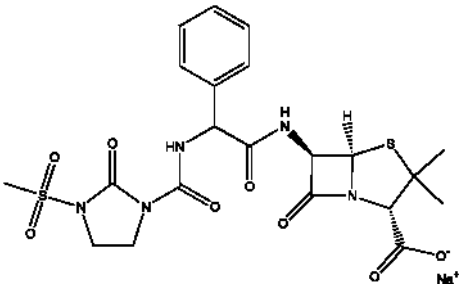
Therapeutic Function: Antibiotic

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

Common Name: -

Chemical Abstracts Registry No.: 51481-65-3

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Baypen	Bayer	W. Germany	1977
Baypen	Bayer	UK	1980
Baypen	Bayer	Switz.	1980
Baypen	Bayer	Italy	1981
Mezlin	Miles	US	1981
Baypen	Bayer Yakuhin	Japan	1982
Baypen	Bayer	France	1983
Baypen	Bayer	Sweden	1983
Baycipen	Bayer	-	-
Optocillin	Bayer	W. Germany	-

Raw Materials

Ampicillin
Methanesulfonyl 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-methylsulfonyl-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 methanesulfonyl 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-ethylhexanoate 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 precipitate, 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 and Engel p. 599
PDR p. 1254
OCDS Vol. 3 p. 206 (1984)
DOT 11 (11) 444 (1975) and 15 (2) 54 (1979)
I.N. p. 633
REM p. 1196
Konig, H.B., Schrock, W. and Metzger, K.G.; US 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

MIANSERIN

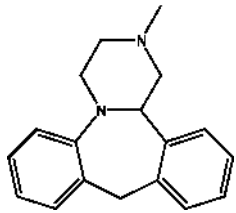
Therapeutic Function: Serotonin antagonist, Antihistaminic

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

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

Structural Formula:



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

Raw Materials

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

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 (31g) 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 and 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.; US Patent 3,534,041; October 13,1970; assigned to Organon Inc.

MIBEFRADIL HYDROCHLORIDE

Therapeutic Function: Coronary vasodilator

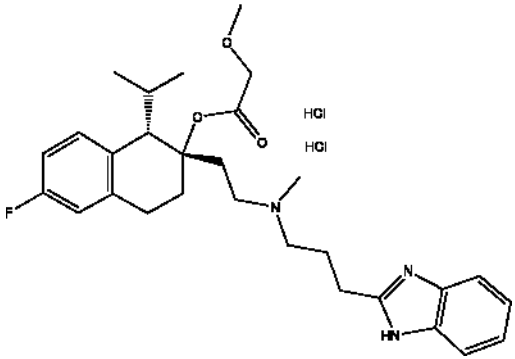
Chemical Name: Acetic acid, methoxy-, 2-(2-((3-(1H-benzimidazol-2-yl)propyl)methylamino)ethyl)-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride, (1S-cis)-

Common Name: Mibefradil hydrochloride

Chemical Abstracts Registry No.: 116666-63-8; 116644-53-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Posicor	Roche Pharmaceuticals	USA	-

Structural Formula:



Raw Materials

Butyl lithium
[3-(1H-Benzimidazol-2-yl)propyl]methylamine
Diisopropylamine
Isopropenyl acetate
Lithium chloride
Potassium hydroxide
Methoxyacetyl chloride
Sodium bis(2-methoxyethoxy)aluminum hydride
(S)-6-Fluoro-1-isopropyl-3,4-dihydro-1H-naphthalen-2-one

Manufacturing Process

To the solution of 5.35 g (28 mmol) [3-(1H-benzimidazol-2-yl)propyl]methylamine in 12.5 mL toluene was added by syringe 12.5 mL (11.42 g, 114 mmol) isopropenyl acetate. The reaction mixture was heated to reflux temperature, and stirred at that temperature for 1.75 hours, with reaction completion monitored by thin-layer chromatography (silica gel, eluting with 70% ethyl acetate/30% methanol). The product, N-[3-(1H-benzimidazol-2-yl)propyl]-N-methylacetamide, was obtained in quantitative yield.

Under a dry nitrogen atmosphere, a 2.5 molar solution of butyl lithium in hexane, 8.4 mL (21 mmol) was added by syringe to 20 mL pentane. The solution was cooled to 0°C and 2.75 mL (2.13 g, 21 mmol) diisopropylamine was added by syringe over six min. The solution was warmed to 25°C and stirred for three hours, then volatiles were removed in vacuo. THF, 20 mL, was added via syringe to the residue, and the resulting yellow solution cooled to 0°C. A solution of 2.42 g (10.5 mmol) N-[3-(1H-benzimidazol-2-yl)propyl]-N-methylacetamide in 10 mL THF was added by syringe over 9 min. The yellow solution was stirred for 15 min, then cooled to -78°C. (S)-6-Fluoro-1-isopropyl-3,4-dihydro-1H-naphthalen-2-one, 2.166 g, 87.2% pure (97.6:2.4 S:R), in 2 mL toluene was added by syringe over 12 min, and a further 2 mL toluene was used to complete the transfer. After stirring for two hours, the viscous yellow mixture was added to 50 mL water at less than 10°C. The suspension that formed was extracted with diethyl ether; and the extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford 3.74 g of impure (1S,2S)-N-[3-(1H-benzimidazol-2-yl)propyl]-2-(6-fluoro-2-hydroxy-1-isopropyl-1,2,3,4-tetrahydronaphthalen-2-yl)-N-

methylacetamide as a yellow foam. The foam was recrystallized from toluene, yield of a colorless solid 2.69 g, melting point 132-138°C. This material may be recrystallized a second time from toluene to remove residual (S)-6-fluoro-1-isopropyl-3,4-dihydro-1H-naphthalen-2-one if necessary.

(1S,2S)-N-[3-(1H-Benzimidazol-2-yl)propyl]-2-(6-fluoro-2-hydroxy-1-isopropyl-1,2,3,4-tetrahydronaphthalen-2-yl)-N-methylacetamidemay be synthesized by another method:

To the mixture 22.7 g (0.54 mol) dry lithium chloride and 100 mL THF at -15°C was added 160 mL 2 molar lithium diisopropylamide (0.32 mol) in heptane/THF/ethylbenzene was added. Then a solution of 36.6 g (0.16 mol) N-[3-(1H-benzimidazol-2-yl)-propyl]-N-methylacetamide in 140 mL toluene was added, the solution was stirred for 2 hours, and a further 155 mL toluene was added. (S)-6-Fluoro-1-isopropyl-3,4-dihydro-1H-naphthalen-2-one (29.9 g, 0.15 mol), in 15 mL toluene was added. After stirring at -10°C for 4 hours, the resulting solution was added to 200 mL ice water. The pH of the resulting mixture was adjusted to 7-8 by addition of a 71 g concentrated hydrochloric acid. The organic layer washed with water, then the solvents removed under reduced pressure to give 96 g of (1S,2S)-N-[3-(1H-benzimidazol-2-yl)propyl]-2-(6-fluoro-2-hydroxy-1-isopropyl-1,2,3,4-tetrahydronaphthalen-2-yl)-N-methylacetamide as a brown oil. The product was crystallysed from toluene, yield 45.3 g.

(1S,2S)-N-[3-(1H-Benzimidazol-2-yl)propyl]-2-(6-fluoro-2-hydroxy-1-isopropyl-1,2,3,4-tetrahydronaphthalen-2-yl)-N-methylacetamide,20.22 g (45.7 mmol), dissolved in 200 mL toluene at 40°C, was added by cannula over 40 min at 0°C to a suspension of sodium bis(2-methoxyethoxy)aluminum hydride in toluene, 40 mL (41.44 g suspension, 26.94 g sodium bis(2-methoxyethoxy)aluminum hydride, 133 mmol). The mixture was stirred at 0°C for 15 min, then at 35-40°C for 3 hours. The mixture was cooled to 25°C then added carefully to 70 g sodium hydroxide in 140 g ice. The resulting suspension was warmed to 25°C over 30 min, and the phases were separated. The aqueous phase was extracted with toluene; and the organic phase was washed twice with 10% aqueous sodium hydroxide, once with water, then once with saturated brine. The toluene phase was dried and concentrated in vacuo to afford 20.61 g of (1S,2S)-2-[2-{[3-(1H-benzimidazol-2-yl)propyl]methylmethylamino}ethyl]-6-fluoro-1-isopropyl-1,2,3,4-tetrahydronaphthalen-2-ol as a colorless foam.

To the mixture of 41.0 g (1S,2S)-2-[2-{[3-(1H-benzimidazol-2-yl)propyl]methylmethylamino}ethyl]-6-fluoro-1-isopropyl-1,2,3,4-tetrahydronaphthalen-2-ol, 240 mL water, and 240 mL toluene were added 22.4 g potassium hydroxide, and the mixture heated to 45-50°C for one hour. The resulting two-phase mixture was separated. To the organic phase was added 39.4 g (4.0 eq.) potassium carbonate sesquihydrate; then a solution of 21.0 g (17.7 mL, 3.25 eq.) methoxyacetyl chloride in 33 mL toluene was added over two hours at 25-30°C, and the resulting mixture stirred for an additional 30 min. Water, 200 mL, was added to quench the reaction. The organic phase, containing mibefradil as the free base was added an ethanol. To the stirred mixture of mibefradil and ethanol was added at 20°C a solution of 4.4 g of hydrogen chloride in 44.6 mL (35.0 g) ethanol. The mixture was heated to 50°C and 1.0 mL water was added, followed by a solution of 3.4 mL water in 332 mL methyl tert-butyl ether over one hour. The mixture was

stirred for 3 hours. Mibefradil dihydrochloride crystals was seeded. A solution of 0.6 mL water in 65 mL methyl tert-butyl ether was added over one hour, and the mixture aged for a further 1.5 hours. The mixture was then cooled, and the resulting slurry of mibefradil dihydrochloride was filtered; yield 95%.

References

Harrington P. J.; US Patent No. 5,892,055; April 6, 1999; Assigned to Roche Colorado Corporation (Boulder, CO)

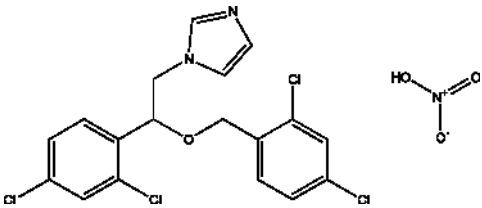
MICONAZOLE NITRATE

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	UK	1974
Daktar	Janssen	W. Germany	1974
Dermonistat	Ortho	UK	1974
Monistat	Ortho	US	1974
Daktarin	Le Brun	France	1975
Micatin	Johnson and Johnson	US	1976
Minostate	Janssen	US	1978
Andergin	Isom	Italy	1980
Frolid P	Mochida	Japan	1981
Aflorix	Gerardo Ramon	Argentina	-
Conofite	Pitman-Moore	US	-
Dektarin	Janssen	Italy	-
Deralbine	Andromaco	Argentina	-

Trade Name	Manufacturer	Country	Year Introduced
Epi-Monistat	Cilag	W. Germany	-
Florid	Mochida	Japan	-
Fungisdin	Esteve	Spain	-
Gyno-Daktarin	Le Brun	France	-
Gyno-Monistat	Cilag	W. Germany	-
Micatin	McNeil	US	-
Miconal	Ecobi	Italy	-
Micotef	Italfarmaco	Italy	-
Vodol	Andromaco	Brazil	-

Raw Materials

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

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

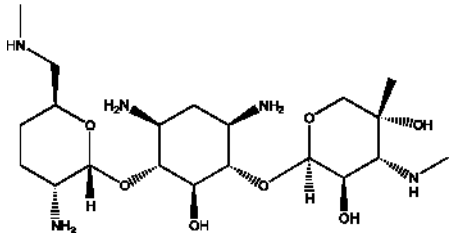
MICRONOMICIN

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 C_{1a}; Sagamicin

Structural Formula:



Chemical Abstracts Registry No.: 52093-21-7

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 extract	0.5
$CaCO_3$(pH: 7.2 before sterilization)	0.1

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
$CaCO_3$ (pH: 7.2 before sterilization)	0.7

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 6N 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 1N 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 6N 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 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 C1ais 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) and 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.; US Patent 4,045,298; August 30,1977; assigned to Abbott Laboratories

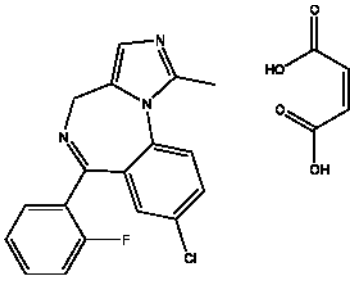
MIDAZOLAM MALEATE

Therapeutic Function: Anesthetic

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	-	-
Hypnovel	Roche	UK	-
Sorenor	Roche	-	-

Raw Materials

Acetic anhydride
Manganese dioxide
2-Aminomethyl-7-chloro-2,3-dihydro-5-(2-fluorophenyl)-1H-1,4-benzodiazepine
Polyphosphoric acid
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)-lH -l,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 and (7) 378 (1983)
I.N.p. 635

F. Hoffmann-La Roche and Co.; British Patent 1,527,131; October 4,1978

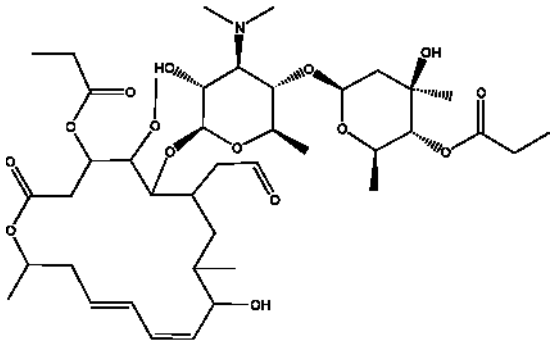
MIDECAMYCIN

Therapeutic Function: Antibacterial

Chemical Name: Leucomycin V, 3,4B-dipropanoate

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 mycsrofaciens*
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 5N 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 3N sodium hydroxide and then extracted with 800 rnl 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 and 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.; US Patent 3,761,588; September 25,1973; assigned to Meiji Seika Kaisha, Ltd. (Japan)

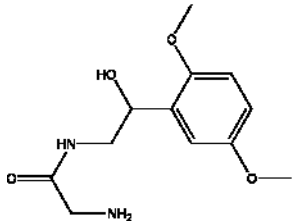
MIDODRINE

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 salt)

Trade Name	Manufacturer	Country	Year Introduced
Gutron	Hormonchemie	W. Germany	1977
Gutron	Chemie Linz	Italy	1981
Alphamine	Centerchem	US	-

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 and Engel.

References

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

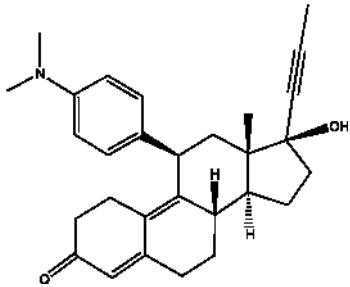
MIFEPRISTONE

Therapeutic Function: Antiprogesterone

Chemical Name: Estra-4,9-dien-3-one, 11-(4-(dimethylamino)phenyl)-17-hydroxy-17-(1-propynyl)-, (11β,17β)-

Common Name: Mifepristone

Structural Formula:



Chemical Abstracts Registry No.: 84371-65-3

Trade Name	Manufacturer	Country	Year Introduced
Mifegyne	HMR	-	-
Mifegyne	Exelgyn	-	-

Raw Materials

4-(N,N-Dimethylaminoethoxy)bromobenzene
1,2-Dibromoethane
Dimethylsulfide-cuprous bromide complex
3,3-[1,2-(Ethanediyl-bisoxy)]-5α,10α-epoxy-17α-prop-1-ynyl-$\delta^{(9(11))}$-estrene-17β-ol

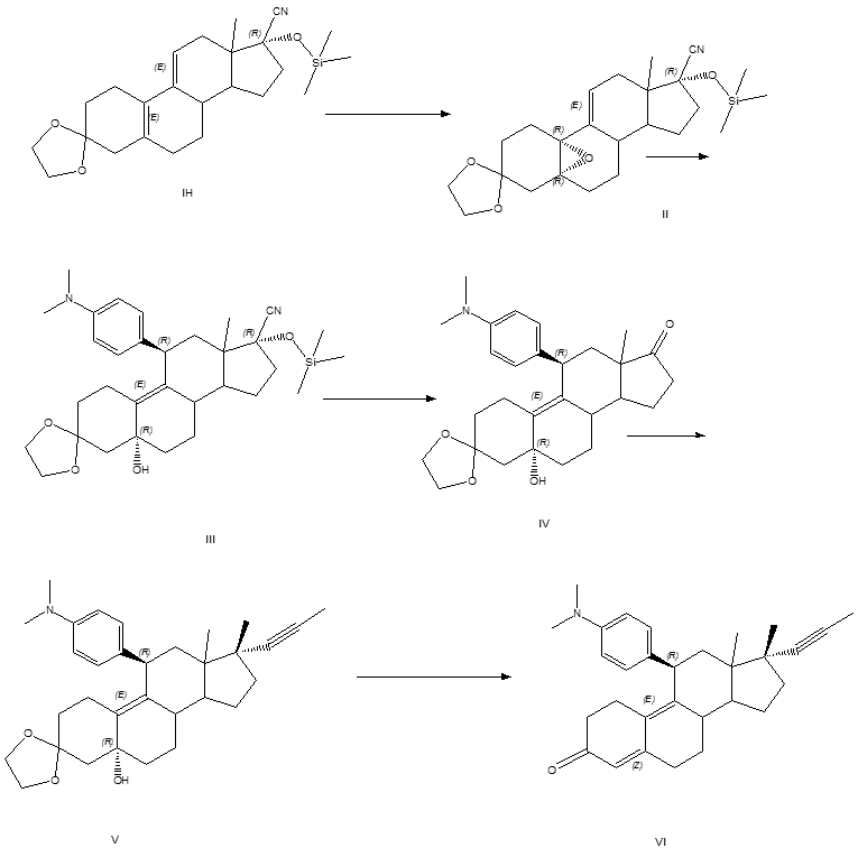
Manufacturing Process

1st method of synthesis of mifepristone:

A solution of 24 g of 4-(N,N-dimethylaminoethoxy)bromobenzene was added dropwise over 45 min to magnesium in 90 ml of anhydrous tetrahydrofuran. 2 ml of 1,2-dibromoethane were added as catalyst. After the addition, the mixture was stirred at 25°C for one hour to obtain a solution of 0.7 M of 4-(N,N-dimethylaminoethoxy)-benzene magnesium bromide which was then added to a solution of 6.16 g of dimethylsulfide-cuprous bromide complex in 20 ml of tetrahydrofuran. The mixture was stirred at room temperature for 20 min and a solution of 3.7 g of 3,3-[1,2-(ethanediyl-bisoxy)]-5α,10α-epoxy-17α-prop-1-ynyl-$\delta^{(9(11))}$-estrene-17β-ol in 50 ml of tetrahydrofuran was added thereto dropwise over a few minutes. The mixture was stirred under an inert atmosphere for one hour and was then poured into a solution of 15 g of ammonium chloride in 20 ml of iced water. The mixture was extracted with ether and the organic phase was washed with aqueous saturated sodium chloride solution, was dried and evaporated to dryness under reduced pressure. The 18.3 g of oil were chromatographed over silica gel and eluted with chloroform to obtain 4.5 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylaminoethoxy)phenyl]-17α-(prop-1-ynyl)-δ^{9}-estrene-5α,17β-diol with a specific rotation of $[\alpha]_D^{20}$ =-44(+/-)1.5° (c = 1% in chloroform).

9.5 ml of 2 N hydrochloric acid were added to a solution of 4.5 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylaminoethoxy)phenyl]-17α-(prop-1-ynyl)-δ^{9}-estrene-5α,17β-diol in 20 ml of methanol and the solution was stirred at room temperature for 2 hours. 260 ml of ether and 110 ml of an aqueous saturated sodium bicarbonate solution were added to the mixture which was stirred at room temperature for 15 min. The decanted aqueous phase was extracted with ether and the organic phase was dried and evaporated to dryness under reduced pressure. The 3.3 g of residue were chromatographed over silica gel and eluted with a 92.5/7.5 methylene chloride-methanol mixture to obtain 1.8 g of amorphous 11β-[4-(N,N-dimethylaminoethoxy) phenyl]-17α-(prop-1-ynyl)-$\delta^{4,9}$-estradiene-17β-ol-3-one with a specific rotation of $[\alpha]_D^{20}$ =+71° (c = 1% in chloroform).

2th method of synthesis of mifepristone (see scheme):



The oxidation of the diene I, which constitutes an intermediate for total synthesis of 19-nor steroids, with a reagent prepared from trifluoroacetic anhydride/hydrogen peroxide was obtained exclusively α-epoxide II. The condensation of II with the Grignard reagent from 4-bromo-N,N-dimethylaniline results in addition of the reagent at the 11β-position. This results in rearragement of the olefin to 9,10 and opening of the epoxide. The stereochemistry of the product obtained III is consistent with trans-opening of the oxirane, albeit at a remove of two carbon atoms. Mild hydrolysis removes the silyl cyanohydrin protecting group at the 17-position to give a ketone IV. Reaction of the ketone with propargyl lithium leads to V. Hydrolysis of that product under more strenuous condition results in removal of the acetal at 3; the resulting β-hydroxyketone then dehydrates to afford the 4,10(9)-dienone VI. Another name of VI is estra-4,9-dien-3-one, 11-(4-(dimethylamino) phenyl)-17-hydroxy-17-(1-propynyl)-, (11β,17β)- or mifepristone.

References

Merck Index, Monograph number: 6273, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.

Teutsch J.G. et al.; US Patent No. 4,386,085; May 31, 1983; Assigned to Roussell Uclaf, Paris, France
Velluz L. et al.; Compt. Rend., 257, 569 (1963)
Lednicer D.; Ed 'Chronicles of Drug Discovery', Vol. 3, p.1., ACS Books, Washington, DC, 1993, p.1

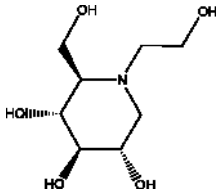
MIGLITOL

Therapeutic Function: Glucosidase inhibitor

Chemical Name: 3,4,5-Piperidinetriol, 1-(2-hydroxyethyl)-2-(hydroxymethyl)-, (2R-(2α,3β,4α,5β))-

Common Name: Glycet; Miglitol

Structural Formula:



Chemical Abstracts Registry No.: 72432-03-2

Trade Name	Manufacturer	Country	Year Introduced
Miglitol	SMS Pharmaceuticals Limited	-	-
Miglitol	ZYF Pharm Chemical	-	-
Diastabol	Sanofi-Synthelabo	-	-
Diastabol	Sanofi Aventis	-	-
Diastabol	Bayer Pharma	-	-
Glyset	Pharmacia and Upjohn	-	-

Raw Materials

Triethylamine
Sodium borohydride
Lewatit
6-Amino-6-desoxy-L-sorbose hydrochloride
Dimethylaminoborane
1,5-Didesoxy-1,5-imino-D-glucitol of 6-amino-6-desoxy-L-sorbose hydrochloride

Manufacturing Process

50 g (0.23 mole) of 6-amino-6-desoxy-L-sorbose hydrochloride were dissolved

in 500 ml of distilled water, and the solution was added in the course of one hour to a solution of 11.2 g of dimethylaminoborane in 500 ml of distilled water, whilst stirring at a temperature of 50°C. The mixture was stirred for one hour at room temperature and one hour at 50°C, 5 ml of triethylamine were added to it, and it was then poured over a column containing 800 ml of strongly basic ion exchanger ("Lewatit" MP 500 OH--form). The exchanger was washed with distilled water, and the runnings collected were concentrated to a syrup on a rotary evaporator. The concentrated syrup was crystallised at 50°C on addition of a large amount of ethanol. The suspension of crystals was cooled and filtered off under suction, and the crystalline product was dried in a vacuum drying cabinet. Yield: 30 g, 80% of theory. MP: 192°-193°C.

25 g (0.115 mole) 1,5-didesoxy-1,5-imino-D-glucitol of 6-amino-6-desoxy-L-sorbose hydrochloride were dissolved in 200 ml of distilled water, and the solution was added at 5°C to a mixture of 4.8 g of $NaBH_4$, 250 ml of ethanol/water 1:1 and 16.2 ml of triethylamine, whilst stirring. The mixture was further stirred for one hour at room temperature and one hour at 50°C., and the reaction mixture was poured over a column containing 400 ml of strongly basic ion exchanger ("Lewatit" MP 500 OH-form). The exchanger was washed with distilled water, and the eluate collected was concentrated to a syrup in a rotary evaporator. Th syrup was taken up with 200 ml of distilled water, and the mixture was poured over a column containing 400 ml of acid ion exchanger ("Lewatit" S 100 H+-form). The column was rinsed with distilled water, and the product was eluted with 10% strength ammonia water. The runnings, rendered alkaline with ammonia, were collected and were concentrated to a syrup in a rotary evaporator. The syrup was crystallized, whilst warm, with a large amount of ethanol, and the suspension of crystals was cooled and is filtered off under suction, and the crystalline product was dried in a vacuum drying cabinet. Yield of 1,5-dideoxy-1,5-((2-hydroxyethyl)imino)-D-glucitol 14 g, 74% of theory. MP: 192°-193°C.

References

Koebernick W.; US Patent No. 4,611,058; September 9, 1986; Assigned to Bayer Aktiengesellschaft (Leverkusen, DE)

MILRINONE LACTATE

Therapeutic Function: Cardiotonic

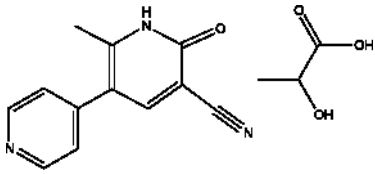
Chemical Name: Propanoic acid, 2-hydroxy-, compd. with 1,6-dihydro-2-methyl-6-oxo(3,4'-bipyridine)-5-carbonitrile

Common Name: Milrinone lactate

Chemical Abstracts Registry No.: 100286-97-3; 78415-72-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Primacor	Baxter Healthcare Corporation	-	-

Structural Formula:



Raw Materials

α-Cyanoacetamide
Sodium methoxide
Malononitrile
1-(4-Pyridinyl)-2-propanone
Dimethylformamide dimethyl acetal

Manufacturing Process

A mixture containing 20 g of 1-(4-pyridinyl)-2-propanone and 30 ml of hexamethylphosphoramide was diluted with 65 ml of dimethylformamide dimethyl acetal and the resulting mixture was refluxed for 30 min. TLC analysis showed a single spot, thereby indicating completion of the reaction (in another run, the reaction appeared to be complete after 30 min at room temperature). The mixture was evaporated under reduced pressure and a pressure, thereby resulting in a crystalline residue weighing 24 g. The residue was purified by continuous chromatographic extraction on alumina (about 150 g) using refluxing chloroform as eluant. After 90 min, the extract was heated in vacuo to remove the chloroform, thereby leaving, as a light yellow crystalline material, 23.2 g of 1-(4-pyridinyl)-2-(dimethylamino)ethenyl methyl ketone, alternatively named 4-dimethylamino-2-(4-pyridinyl)-3-buten-2-one.

To a mixture containing 23 g of 1-(4-pyridinyl)-2-(dimethylamino)ethenyl methyl ketone and 11 g of α-cyanoacetamide dissolved in 400 ml of dimethylformamide was added with stirring 14 g of sodium methoxide and the resulting reaction mixture was heated in an oil bath under gentle reflux for one hour. TLC analysis showed no starting material in the reaction mixture which was then concentrated in vacuo on a rotary evaporator to a volume of about 80 ml. The concentrate was treated with about 160 ml of acetonitrile and the resulting mixture was stirred on a rotary evaporator with warming until homogenous and then cooled. The crystalline product was collected, rinsed successively with acetonitrile and ether, and dried overnight at 55°C to yield 28 g of crystalline product, namely, sodium salt of 1,2-dihydro-6-methyl-2-oxo-5-(4-pyridinyl)nicotinonitrile, the presence of cyano being confirmed by IR analysis. An 8 g portion of said sodium salt was dissolved in 75 ml of hot water, the aqueous solution treated with decolorizing charcoal, filtered, the filtrate again treated with decolorizing charcoal and filtered, and the filtrate acidified with 6 N hydrochloric acid by dropwise addition to a pH of 3. The acidic mixture was diluted with ethanol and cooled. The crystalline product was collected, dried, recrystallized from dimethylformamide-water and dried to produce 3.75 g of 1,2-dihydro-6-methyl-2-oxo-5-(4-pyridinyl)nicotinonitrile, m.p. >300°C.

Another method of preparation of 1,2-dihydro-6-methyl-2-oxo-5-(4-

pyridinyl)nicotinonitrile (Patent US 4,413,127)

A 69.5 g portion of 1-ethoxy-2-(4-pyridinyl)ethenyl methyl ketone was dissolved in 300 ml of ethanol and to the solution was added 13.2 g of malononitrile. The resulting mixture was refluxed for 5 hours, crystals starting to separate after about 30 min of refluxing. The reaction mixture was allowed to cool to room temperature and, the precipitate of fine needles was filtered, washed with ethanol and dried in a vacuum at 90°C to yield 25.4 g of 1,2-dihydro-6-methyl-2-oxo-5-(4-pyridinyl)-nicotinonitrile, m.p. >300°C. Concentration of the mother liquor provided another 2.1 g of product, m.p. >300°C.

To a aqueous solution of 1,2-dihydro-6-methyl-2-oxo-5-(4-pyridinyl) nicotinonitrile was added one molar equivalent of lactic acid to prepare the monolactate of 1,2-dihydro-6-methyl-2-oxo-5-(4-pyridinyl)nicotinonitrile.

References

Lesher G. Y. et al.; US Patent No. 4,413,127; Feb. 2, 1982; Assigned to Sterling Drug Inc. (New York, NY)
Lesher G.Y. et al.; US Patent No. 4,313,951; Feb. 2, 1982; Assigneed to Sterling Drug Inc. (New York, NY)

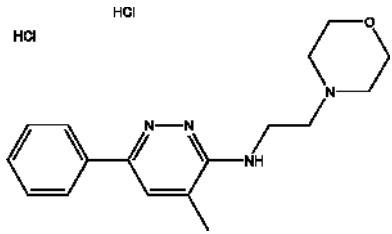
MINAPRINE

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 salt)

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 and Engel p. 602
I.N. p. 637
Laborit, H.; British Patent 1,345,880; Feb. 6, 1974; and US 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.)

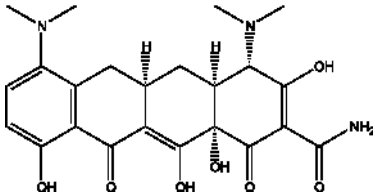
MINOCYCLINE

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 salt)

Trade Name	Manufacturer	Country	Year Introduced
Minocin	Lederle	US	1971
Minomycin	Lederle	Japan	1971
Klinomycin	Lederle	W. Germany	1972
Minocin	Lederle	Italy	1972
Minomycin	Takeda	Japan	1972
Vectrin	Parke Davis	US	1973
Minocin	Lederle	UK	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 US Patent 3,483,251.

References

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

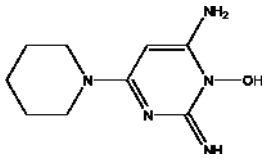
MINOXIDIL

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

Raw Materials

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

Trade Name	Manufacturer	Country	Year Introduced
Loniten	Upjohn	US	1979
Loniten	Upjohn	UK	1980
Loniten	Upjohn	Switz.	1981
Loniten	Upjohn	W. Germany	1982
Loniten	Upjohn	Italy	1983
Prexidil	Bioindustria	Italy	1983

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-diaminopyritnidine.

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 193 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-4-chloro-1,2-dihydro-1-hydroxy-2-iminopyrimidine, melting point 248°C, decomposition at 259°C to 261°C.

References

Merck Index 6069
DFU 2 (6) 383 (1977)
Kleeman and Engel p. 604
PDR p. 1848
OCDS Vol. 1 p. 262 (1977)
DOT8 (7) 277 (1972) and 16 (9) 298 (1980)
I.N.p. 638
REM p. 848
Anthony, W.C. and Ursprung, J.J.; US Patents 3,382,247; May 7,1968 and 3,382,248; May 7,1968; both assigned to The Upjohn Co.
Anthony, W.C.; US Patent 3,644,364; February 22,1972; assigned to The Upjohn Co.

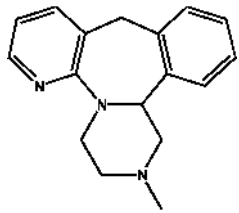
MIRTAZAPINE

Therapeutic Function: Antidepressant, Antihistaminic, Antidiuretic

Chemical Name: Pyrazino[2,1-a]pyrido[2,3-c](2)benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl-

Common Name: Azamiaserin; Mepirzapin; Mirtazapine

Structural Formula:



Chemical Abstracts Registry No.: 61337-67-5

Trade Name	Manufacturer	Country	Year Introduced
Mirazep	Syncro (A Div. of Microlabs)	India	-
Mirt	Panacea Biotec Ltd.	India	-
Mirtaz	Sun Pharmaceuticals Industries Ltd.	India	-
Remeron	Organon	Netherlands	-
Zispin	Triton	-	-

Raw Materials

Potassium fluoride
2-Chloronicotinonitrile
Sulfuric acid
1-Methyl-3-phenylpiperazine
Lithium aluminum hydride

Manufacturing Process

1) 1-(3-Cyanopyridyl-2)-2-phenyl-4-methylpiperazine

17.43 g (0.3 mol) potassium fluoride is added to a solution of 13.85 g (0.1 mol) 2-chloronicotinonitrile and 17.62 g (0.1 mol) 1-methyl-3-phenylpiperazine in 250 ml dry DMF and the suspension is heated at 140°C under a nitrogen atmosphere for 20 hours. After cooling, the reaction mixture is poured into 1,250 ml water. The aqueous phase is extracted four times with ethyl acetate the combined organic extracts are washed with 100 ml water. After drying, the extracts are evaporated. The crude oil may be used as such for the following step. The nitrile obtained may however also be purified by column chromatography on SiO_2, with hexane-acetone (95:5). In this way, 21.9 g (79%) pure 1-(3-cyanopyridyl-2)-4-methyl-2-phenylpiperazine is obtained; the substance crystallizes from petroleum ether; melting point 66.5-67.5°C.

2) 1-(3-Carboxypyridyl-2)-2-phenyl-4-methylpiperazine

The solution of 19.5 g (0.07 mol) 1-(3-cyanopyridyl-2)-4-methyl-2-phenylpiperazine in 390 ml of a solution of 25 g KOH/ 100 ml ethanol is heated at 100°C for 24 hours. After cooling, water (390 ml) is added. The alcohol is evaporated under vacuum and the cloudy solution remaining is extracted twice with 100 ml methylene chloride. The residual aqueous phase is cooled and the pH is adjusted to 7 with 2 N HCl, after which it is extracted with chloroform. After drying the chloroform extract, it is evaporated and 16.2 g 1-(3-carboxypyridyl-2)-4-methyl-2-phenylpiperazine is obtained as a colourless oil. Crystallization from ethanol gives a crystalline substance with a melting point of 161-162°C.

3) 1-(3-Hydroxymethylpyridyl-2)-2-phenyl-4-methylpiperazine

20.4 g (0.07 mol) 1-(3-carboxypyridyl-2)-2-phenyl-4-methylpiperazine is dissolved in 300 ml dry THF and gradually added to a boiling suspension of 20.4 g LiAlH4in 600 ml dry THF under a nitrogen atmosphere. The mixture is boiled for 4 hours, after which it is cooled in an ice-bath and decomposed by adding 81.6 ml water. The inorganic salts are filtered off. The filtrate is dried and solvent is removed by evaporation, giving a yield of 18.39 g (93%) 1-(3-hydroxymethylpyridyl-2)-2-phenyl-4-methylpiperazine. Recrystallization from ether gives a crystalline product (white needles) of melting point 124-126°C.

4)2-Methyl-1,2,3,4,10,14b-hexahydro-benzo[c]pyrazino-[1,2-a]-pyrido[2,3-c]azepine(Mirtazapine)

6.5 ml concentrated sulfuric acid is added dropwise at room temperature to 3.25 g of 1-(3-hydroxymethylpyridyl-2)-2-phenyl-4-methylpiperazine. During the addition, the temperature rises to 35°C. The whole is subsequently stirred for a few hours, after which 60 g ice is added and the mixture is made alkaline with concentrated ammonia (22 ml). The reaction mixture is then extracted with chloroform. The chloroform extracts are dried and concentrated. The crude reaction product crystallizes when ether is added, and the solid obtained is recrystallized from petroleum ether. Yield of 2-methyl-1,2,3,4,10,14b-hexahydro-benzo[c]pyrazino-[1,2-a]-pyrido[2,3-c]azepine 2.43 g; melting point: 114-116°C.

References

Maeda, et al.; US Patent No. 6,660,730; Dec. 9, 2003; Assigned to Sumika Fine Chemicals Co., Ltd.

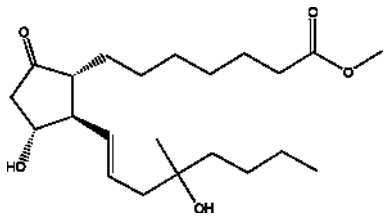
MISOPROSTOL

Therapeutic Function: Antiulcer

Chemical Name: Prost-13-en-1-oic acid, 11,16-dihydroxy-16-methyl-9-oxo-, methyl ester, (11α,13E)-(+-)-

Common Name: Misoprostol

Structural Formula:



Chemical Abstracts Registry No.: 59122-46-2; 62015-39-8

Trade Name	Manufacturer	Country	Year Introduced
Cytotec	Searle, division of Monsanto plc.	UK	-
Misoprost	Cipla Limited	India	-
Misoprostol	IVAX	-	-
Misoprostol	G.D. Searle and Co.	USA	-

Raw Materials

(E)-Trimethyl[[1-methyl-1-[3-(tributylstannyl)-2-propenyl]pentyl]oxy]silane
Copper (I) iodide
Methyllithium
Methyl-5-oxo-3-[(triethylsilyl)oxy]-1-cyclopentene-1-heptanoate

Manufacturing Process

1 method of synthesis

To a 1000 ml dried flask under a nitrogen atmosphere was added 74.6 g of (E)-trimethyl-[[1-methyl-1-[3-(tributylstannyl)-2-propenyl]pentyl]oxy]silane, 125 ml anhydrous THF and 24.2 g of copper (I) iodide. The mixture was stirred at room temperature for 30 minutes and then it was cooled to -25 to -30°C. 98.8 ml of methyllithium (2.86 M) in DEM was added dropwise and the resultant solution was stirred at -15°C for 2 hours. Then the reaction mixture was cooled to -78°C and 25 g of methyl-5-oxo-3-[(triethylsilyl)oxy]-1-cyclopentene-1-heptanoate in 100 ml of THF was added rapidly. After stirring the mixture for 5 min at -78°C, it was quenched into a mixture of 750 ml of aqueous ammonium chloride solution and 200 ml of ammonium hydroxide. The resulting mixture was warmed to room temperature and stirred until a deep blue aqueous layer was obtained. Ethyl acetate (250 ml) was used for extraction. Then the combined organic layers were washed with brine and subsequently dried over magnesium sulfate. After a filtration and concentration under reduced pressure, an oil (105 g) was obtained. This oil containing the protected prostaglandin was subjected to acidic deprotection (cat. PPTS, acetone and water) and purification (chromatography on silica gel) to provide 15.8 g (60%) of misoprostol was identical.

2 method of synthesis

To a 300 ml dried flask under a nitrogen atmosphere was added 4.45 g of copper (I) iodide and 60 ml of anhydrous THF. The mixture was cooled to 0°C 35 ml of 1.4 M methyllithium in diethyl ether was added dropwise and the resultant solution was stirred at 0°C for 30 min. 13.7 g of (E)-trimethyl-[[1-methyl-1-[3-(tributylstannyl)-2-propenyl]pentyl]oxy]silane in 5 ml of THF was added and then the mixture was stirred at 0°C for 30 min. Then an additional 1.5 ml of 1.4 M methyllithium in diethyl ether was added and the mixture was stirred for another 30 min. The reaction mixture was cooled to -78°C and 10 g of methyl 5-oxo-3-[(triethylsilyl)oxy]-1-cyclopentene-1-heptanoate in 10 ml of THF was added rapidly. After stirring the mixture for 5 min at -78°C, it was quenched into 210 ml of basic aqueous ammonium chloride solution. The resulting mixture was warmed to room temperature and stirred until a deep blue aqueous layer was obtained. Ethyl acetate was used for extraction. Then the combined organic layers were washed with water (10 ml), then with brine (25 ml) and subsequently dried over magnesium sulfate. After a filtration and concentration under reduced pressure, an oil (21 g) was obtained. This oil containing the protected prostaglandin was subjected to acidic deprotection (cat. PPTS, acetone and water) and purification (chromatography on silica gel) to provide 4.2 g (40%) misoprostol.

References

Li Y.-F. et al.; US Patent No. 5,684,177; Nov. 4, 1997; Assigned to Torcan Chemical Ltd.
"Organometallics in Synthesis: A Manual", Chapter 4, page 283-382; B. H. Lipshutz, Edited by M Schlosser, John Wiley and Sons, 1994
Lipshutz B.H., Synthesis, 325 (1987)

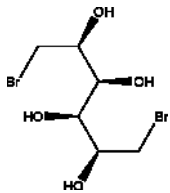
MITOBRONITOL

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	Hormonchemie	W. Germany	1967
Myelobromol	Berk	UK	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 to1 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 and Engel p. 604
I.N. p. 639
REM p. 1156
Chinoin Gyogyszeres Vegyeszeti Termekek Gyarart; British Patent 959,407; June 3,1964

MITOMYCIN

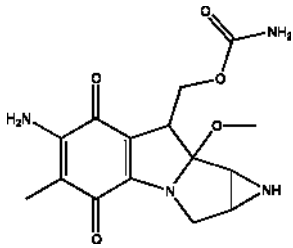
Therapeutic Function: Cancer chemotherapy

Chemical Name: Azirino(2',3':3,4)pyrrolo(1,2-a)indole-4,7-dione, 6-amino-8-(((aminocarbonyl)oxy)methyl)-1,1a,2,8,8a,8b-hexahydro-8a-methoxy-5-methyl-, (1aS,8S,8aR,8bS)-

Common Name: -

Chemical Abstracts Registry No.: 50-07-7

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Mitomycin	Medac	W. Germany	1960
Mitomycin C	Kyowa	Italy	1961
Ametycine	Choay	France	1970
Mitamycin	Bristol	US	1974
Mitomycin C	Kyowa	Japan	1980
Mitamycin	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 US 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 and Engel p. 604
PDR p. 724
I.N. p.640
REM p. 1156
Gourevitch, A., Chertow, B. and Lein, J.; US Patent 3,042,582; July 3,1962; assigned to Bristol-Myers Company

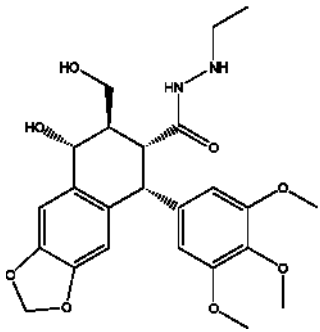
MITOPODOZIDE

Therapeutic Function: Antineoplastic

Chemical Name: 5,6,7,8-Tetrahydro-8-hydroxy-7-(hydroxymethyl)-5-(3,4,5-trimethoxyphenyl)naphtho[2,3d]-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 toa 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 and Engel p. 605
I.N. p. 640
Rutschmann, J.; US Patent 3,054,802; September 18, 1962; assigned to Sandoz Ltd. (Switzerland)

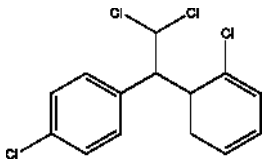
MITOTANE

Therapeutic Function: Antineoplastic

Chemical Name: Ethane, 2-(o-chlorophenyl)-2-(p-chlorophenyl)-1,1-dichloro-

Common Name: Mitotane

Structural Formula:



Chemical Abstracts Registry No.: 53-19-0

Trade Name	Manufacturer	Country	Year Introduced
Lysodren	Bristol Labs, Division of Bristol-Myers Squibb Canada Inc.	Canada	-

Raw Materials

Dichloroacetaldehyde
2-Chlorphenylmagnesiumbromide

Manufacturing Process

From dichloroacetaldehyde and 2-chlorphenylmagnesiumbromide was prepared 1-(2-chlorphenyl-2,2-dichloroethanol. By action of H_2SO_4 on 1-(2-chlorphenyl)-2,2-dichloroethanol in chlorobenzene was prepared 1,1-dichloro-2,2-bis(2,4'-dichlorophenyl)ethane.

References

Haller B.L. et al.; JACS 1945, 67, 1591

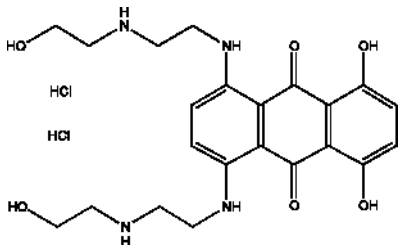
MITOXANTRONE DIHYDROCHLORIDE

Therapeutic Function: Antineoplastic

Chemical Name: 9,10-Anthraquinone, 5,8-bis((2-((2-hydroxyethyl)amino) ethyl)amino)-1,4-dihydroxy-, dihydrochloride

Common Name: Mitoxantrone hydrochloride; Mitozantrone hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 70476-82-3; 65271-80-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Novantrone	Immunex Corporation	-	-
Oncotrone	Baxter Oncology GmbH	Germany	-

Raw Materials

2-(2-Aminoethylamino)ethanol
N,N,N',N'-Tetramethylethylenediamine
Leuco-1,4,5,8-tetrahydroxyanthraquinone
Chloranil

Manufacturing Process

A suspension of 12.5 g of 2-(2-aminoethylamino)ethanol in 40 ml of N,N,N',N'-tetramethylethylenediamine is stirred and de-aerated by bubbling nitrogen in for 15 min. A 10.97 g of leuco-1,4,5,8-tetrahydroxyanthraquinone is gradually added with stirring. The suspension is heated and stirred under nitrogen at 50-52°C for 5 hours. The mixture is allowed to stand and cool under nitrogen for 12 hours. The solid is collected by decantation, macerated in ethanol, collected and washed with ethanol giving 15.06 g of the desired product leuco-1,4-bis[2-(2-hydroxyethylamino)ethylamino]-5,8-dihydroxyanthraquinone as a green-gray solid, melting point 129-131°C.

Chloranil oxidation. To 17.86 g of a suspension of the leuco-1,4-bis[2-(2-hydroxyethylamino)ethylamino]-5,8-dihydroxyanthraquinone (0.03 mole) in 2-methoxyethanol was added gradually with stirring 15 ml of 8 N ethanolic hydrogen chloride. The system was chilled with an ice bath and stirred as 7.50 g (0.0305 mole) of chloranil powder was gradually added. The mixture was stirred overnight at room temperature and diluted with 600 ml of ether. The solid was collected and washed with tetrahydrofuran. Yield of 1,4-bis[2-(2-hydroxyethylamino)ethylamino]-5,8-dihydroxyanthraquinone dihydrochloride 21.34 g, melting point 203-205°C (without recrystallisation).

References

Murdock K.C., Durr F.E.; US Patent No. 4,197,249; April 8, 1980; Assigned: American Cyanamid Company

MIVACURIUM CHLORIDE

Therapeutic Function: Muscle relaxant

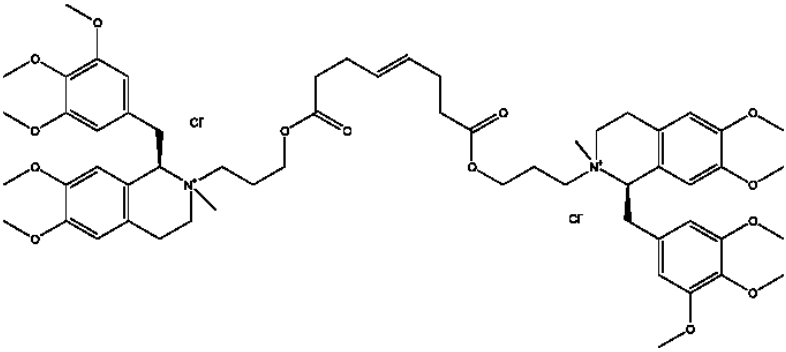
Chemical Name: Isoquinolinium, 2,2'-((1,8-dioxo-4-octene-1,8-diyl)bis(oxy-3,1-propanediyl))bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-((3,4,5-trimethoxyphenyl)methyl)-, dichloride, (R-(R*,R*-(E)))-

Common Name: Mivacurium chloride

Chemical Abstracts Registry No.: 106861-44-3; 133814-19-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Mivacron	GlaxoSmithKline S.p.A.	Italy	-
Mivacron	Abbott Laboratories	-	-

Structural Formula:



Raw Materials

3-Chloropropanol
Sodium iodide
Tartaric acid, dibenzoate, (-)-, monohydrate
(E)-4-Octene-1,8-dioic acid chloride
(+/-)-5'-Methoxylaudanosine
Sodium carbonate
Tartaric acid, dibenzoate, (+)-, monohydrate

Manufacturing Process

To ()-5'-methoxylaudanosine (46.4 g) in methanol (240 mL) was added (-)-dibenzoyltartaric acid monohydrate (45.2 g). The mixture was heated to boiling, cooled at 5°C for 16 h and the (S)-(-)-5'-methoxylaudanosinium dibenzoyltartrate salt (35.6 g, 80%) was filtered and discarded. The mother liquors were made basic with concentrated aqueous NaOH and evaporated under vacuum. The solid residue was partitioned between H_2O and diethyl ether. The ether phase was dried and evaporated to an oil (24.9 g). To the oil in methanol (128 mL) was added (+)-dibenzoyltartaric acid monohydrate (26.6 g). The mixture was heated to boiling and cooled at 5°C for 16 h. Crystals were collected and recrystallized from methanol until a constant specific rotation of $[\alpha]_D^{20}$=+17.7° (1% EtOH) had been achieved. The yield of (R)-(+)-5'-methoxylaudanosinium dibenzoyltartrate as white crystals was 29.4 g (66%). A portion of the salt (15.0 g) in methanol (200 mL) was made basic with concentrated aqueous NaOH. The mixture was evaporated under vacuum and the residue was partitioned between H_2O and diethyl ether. The combined ether layers were dried and evaporated under vacuum to yield 7.2 g (92%) of (R)-(-)-5'-methoxylaudanosine as an oil.

(R)-(-)-5'-Methoxylaudanosine (7.2 g), 3-chloropropanol (3.5 g), sodium iodide (5.6 g) and sodium carbonate (0.5 g) were refluxed in 2-butanone (125 mL) for 16 h. The white suspension was filtered hot and solvent removed from the filtrate under vacuum. The residual gum was trituated with hot ethyl acetate to remove excess 3-iodopropanol, dissolved in 200 mL methanol and passed through a column packed with Dowex RTM.1-X8 ion exchange resin (60 g chloride form). The eluant was stripped of solvent under vacuum to give N-3-hydroxypropyl-1-(R)-5'-methoxylaudanosinium chloride (8.4 g) as an amophous solid. The material was assayed by HPLC as a 2.3/1 mixture of the

trans/cis diastereomers.

N-3-Hydroxypropyl-1-(R)-5'-methoxylaudanosinium chloride (2.3/1, trans/cis by HPLC, 2.5 g) was dissolved in 60 mL 1,2-dichloroethane at about 70°C. (E)-4-Octene-1,8-dioic acid chloride (0.5 g) (K. Sisido, K. Sei, and H. Nozaki, J. Org. Chem., 1962, 27, 2681) was added and the mixture was stirred at ambient temperature for 19 h. Solvent was removed under vacuum to give an amorphous solid which was dissolved in chloroform (25 mL) and washed with 5% aqueous sodium chloride solution to remove unreacted quaternary salts. The chloroform layer was dried and evaporated under vacuum to give an amorphous solid. The acid ester impurities were substantially removed by washing with hot 2-butanone. Residual solvent was evaporated under vacuum and the resulting amorphous solid was dissolved in methanol, filtered and lyophilized to give 1.9 g of (E)-(1R,1'R)-2,2'-[4-octenedioylbis (oxytrimethylene)]bis[1,2,4,3-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium] dichloride, which was assayed by HPLC as 44.6% RS-RS (trans-trans) diester, 42.4% RR-RS (cis-trans) diester, 7.5% RR-RR(cis-cis) diester, 4.0% RS (trans) acid ester and 1.5% RR (cis) (E)-(1R,1'R)-2,2'-[4-Octenedioylbis(oxytrimethylene)]bis[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium]dichloride acid ester, $[\alpha]_D^{20}$=-62.7° (1.9% in water).

References

Swaririgen R.A. et al.; US Patent No. 4,761,418; Aug. 2; Assigned to Burroughs Weiicome Co., Research Triangle Park, N.C.; Boston, Mass.

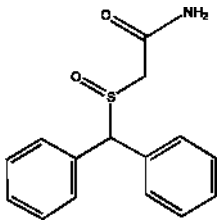
MODAFINIL

Therapeutic Function: Psychostimulant

Chemical Name: Acetamide, 2-((diphenylmethyl)sulfinyl)-

Common Name: Modafinil

Structural Formula:



Chemical Abstracts Registry No.: 68693-11-8

Trade Name	Manufacturer	Country	Year Introduced
Modafinil	Cephalon, Inc.	USA	-
Modafinil	Merckle GmbH	Germany	-

Trade Name	Manufacturer	Country	Year Introduced
Modavigil	CSL LTD	-	-
Provigil	Aetna Inc.	-	-
Provigil	Cephalon, Inc.	-	-

Raw Materials

Thionyl chloride	Benzhydrylthioacetic acid
Ammonia	Acetic acid
Thiourea	Hydrobromic acid
Benzhydrol	Chloroacetic acid
Hydrogen peroxide	Dimethyl sulfate

Manufacturing Process

To 19.5 g (0.076 mol) of benzhydrylthioacetic acid in 110 ml of benzene was added drop by drop 19 ml of thionyl chloride. The mixture was refluxed 1 hour, benzene and the excess thionyl chloride was evaporated. A clear orange oil of benzhydrylthioacetyl chloride is obtained.

The benzhydrylthioacetyl chloride in 100 ml of methylene chloride was added drop by drop to 35 ml of ammonia in 40 ml of water. Once the addition is complete, the organic phase is washed with a dilute solution of soda and dried over Na_2SO_4, the solvent is evaporated and the residue is taken up in diisopropyl ether, the benzhydrylthioacetamide is crystallised. 16.8 g of product (yield 86%) are obtained. Melting point 110°C.

14.39 g (0.056) of benzhydrylthioacetamide are placed in a balloon flask and 60 ml of acetic acid and 5.6 ml of H_2O_2 are added. The mixture is left for one night at 40°C and about 200 ml of water are then added; the CRL 40476 crystallises. By recrystallisation from methanol 11.2 g of benzhydrylsulphinylacetamide are obtained. Yield: 73%, melting point 164-166°C.

The synthesis of benzhydrylsulphinylacetamide (CRL 40476) on an industrial scale.

1.003 kg of thiourea is dissolved in 5.72 L of 48% hydrobromic acid and 0.880 L of water in a 20 L reaction vessel. The mixture is heated to 60°C and 2.024 kg of benzhydrol are introduced. The temperature is increased to 95°C and the contents of the vessel are allowed to cool to room temperature. The crystals are filtered off and washed with water. They are made into a paste again in 5.5 L of water and this is introduced into a 20 L reaction vessel with 3.5 L of soda lye (d = 1.33). The mixture is heated to 70°C and 1144 g of chloroacetic acid dissolved in 2.2 L of water are passed in slowly. After cooling the benzhydrylthioacetic acid is obtained, but is not isolated.

1.430 L of hydrogen peroxide are passed in over 3 hours at 30°C into the above reaction mixture. 22 L of water are then passed in, the insoluble material is filtered off and acidification is carried out with hydrochloric acid (d = 1.18). Filtration, washing with water to reform a paste and drying without heat are carried out. In this way, the benzhydrylsulphinylacetic acid is obtained.

The above acid is placed in a 20 L reaction vessel with 6 L of water. 1.1 liters of soda lye (d = 1.33) and 1.848 kg of sodium bicarbonate are added. 2.1 L of dimethyl sulfate are added. After one hour, crystallisation is induced. Filtration, drying without heat and washing are carried out. Methyl benzhydrylsulphinylacetate is obtained.

1 kg of methyl benzhydrylsulphinylacetate is dissolved in 3.5 liters of anhydrous methanol in a 10-liter balloon flask. NH_3 is bubbled in at a high rate of flow for 1 hour, and then left in contact for 4 hours. Filtration, drying without heat and washing with water are then carried out. By recrystallisation from a mixture of water and methanol (4:1) and then from a mixture of water and methanol (9:1) and drying under reduced pressure, CRL 40476 is obtained in the form of a white crystalline powder; melting point 164-166°C. Total yield (calculated from the benzhydrol): 41%.

References

Lafon L.; US Patent No. 4,177,290; Dec. 4, 1989; Assigned to Laboratoire L. Lafon

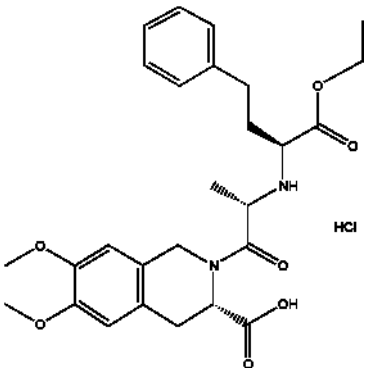
MOEXIPRIL HYDROCHLORIDE

Therapeutic Function: Antihypertensive

Chemical Name: 3-Isoquinolinecarboxylic acid, 1,2,3,4-tetrahydro-6,7-dimethoxy-2-(2-((1-(ethoxycarbonyl)-3-phenylpropyl)amino)-1-oxopropyl)-, monohydrochloride, (3S-(2(R*(R*)),3R*))-

Common Name: Moexipril hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 82586-52-5; 103775-10-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Moexipril Hydrochloride	Schwarz Pharma	Germany	-
Perdix	Schwarz Pharma	Germany	-
Primox Tablets	Minipharm	-	-
Univasc	Teva Pharmaceuticals	USA	-
Univasc	Schwarz Pharma	USA	-

Raw Materials

t-Butyl alanine
Triethylamine
1-Hydroxybenzotriazole
Diclohexylcarbodiimide
Ethyl 2-bromo-4-phenylbutanoate
1,2,3,4-Tetrahydro-3-isoquinolinecarboxylic acid (S-form)

Manufacturing Process

1) A solution of 2.0 g of t-butyl alanine (S-form) and 3.78 g of ethyl 2-bromo-4-phenylbutanoate in 25 ml of DMF was treated with 1.8 ml of triethylamine and the solution was heated at 70°C for 18 hours. The solvent was removed at reduced pressure and the residue was mixed with water and extracted with ethyl ether. The organic layer was washed with water and dried over magnesium sulfate. Concentration of the solvent at reduced pressure gave the oily ethyl-α-[(1-carboxyethyl)amino]benzene-t-butanoate.

A solution of 143.7 g of this t-butyl ester in 630 ml of trifluoroacetic acid was stirred at room temperature for one hour. The solvent was removed at reduced pressure and the residue was dissolved in ethyl ether and again evaporated. This operation was repeated. Then the ether solution was treated dropwise with a solution of hydrogen chloride gas in ethyl ether until precipitation ceased. The solid, collected by filtration, was a mixture of diastereoisomers of ethyl-α-[(1-carboxyethyl)amino]benzenebutanoate hydrochloride, melting point 153-165°C; $[\alpha]_D^{23}$ = +3.6° (1% MeOH).

The free amino acid (S,S-form) was prepared by treatment of an aqueous solution of the hydrochloride with saturated sodium acetate. The product was filtered, washed efficiently with cold water and recrystallized from ethyl acetate; melting point 149-151°C; $[\alpha]_D^{23}$ = +29.7°.

2) A stirred solution of 0.0158 mole of ethyl-α-[(1-carboxyethyl)amino] benzenebutanoate hydrochloride in 200 ml of methylene chloride was treated successively with 1.60 g (0.0158 mole) of triethylamine, 0.0158 mole of 1-hydroxybenzotriazole, 0.0158 mole of 1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid and then with 0.0158 mole of dicyclohexylcarbodiimide in 10 ml of methylene dichloride. Dicyclohexylurea gradually separated. The mixture was allowed to stand at room temperature overnight. Hexane (300 ml) was added and the urea was filtered. The filtrate was washed with 250 ml of saturated sodium bicarbonate, dried over sodium sulfate and concentrated to remove solvent. The viscous residue was triturated with 50 ml of ether and filtered to remove insolubles. The filtrate was concentrated to give 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid.

After addition of hydrochloric acid was obtained 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, hydrochloride.

References

Hoefle M.L., Klutchko S.; US Patent No. 4,344,949; August 17, 1982; Assigned: Warner-Lambert Company
O'Reilly N. J., Lin H. C.; US Patent No. 4,912,221; March 27, 1990; Assigned: Occidental Chemical Corporation
Wang Z.-X., Horne S.E.; US Patent No. 6,642,384; Nov. 4, 2003; Assigned: Brantford Chemicals Inc.

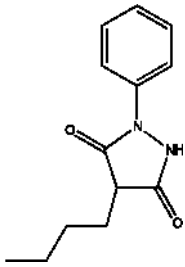
MOFEBUTAZONE

Therapeutic Function: Antirheumatic, Analgesic, Antiinflammatory

Chemical Name: 3,5-Pyrazolidinedione, 4-butyl-1-phenyl-

Common Name: Mofebutazone; Monophenylbutazone; Mophebutazonum

Structural Formula:



Chemical Abstracts Registry No.: 2210-63-1

Trade Name	Manufacturer	Country	Year Introduced
Butaphen	Wiedenmann	-	-
Ecasil	Laquifa	-	-
Metrogyl	Benzon	-	-
Monofen	Star	-	-

Raw Materials

Phenyl hydrazine
n-Butylmalonic acid

Manufacturing Process

A mixture comprising 108 g of phenyl hydrazine and 216 g of the diethyl ester of n-butylmalonic acid is heated on an oil bath at 170°-180°C for 12 hours. The residue is taken up with water in which an alkaline compound has been dissolved and acetic acid is added to precipitate 4-n-butyl-2-phenyl-pyrazolidine-3,5-dione. The product is a white crystalline solid having a MP: 103°C. It is soluble in acetone and benzene, soluble in hot condition in methanol and ethanol and insoluble in water.

References

Commissionara Farmaceutica Milaneze, an Italian Company, Milan Italy; G.B. Patent No. 839,057; Nov. 28, 1956

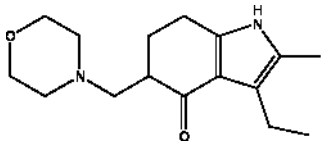
MOLINDONE

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 salt)

Trade Name	Manufacturer	Country	Year Introduced
Moban	Endo	US	1974
Lidone	Abbott	US	1977

Raw Materials

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

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 1N 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-4-oxoindole, melting point 180°C to 181°C.

References

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

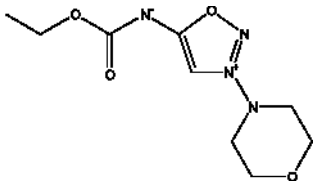
MOLSIDOMINE

Therapeutic Function: Coronary vasodilator

Chemical Name: Sydnone imine, N-carboxy-3-morpholino-, ethyl ester

Common Name: Molsidomine; Morsydomine

Structural Formula:



Chemical Abstracts Registry No.: 25717-80-0

Trade Name	Manufacturer	Country	Year Introduced
Corvasal	Hoechst	-	-

Raw Materials

3-Morpholinosydnonimine hydrochloride
Ethyl chloroformate
Pyridine

Manufacturing Process

1.6 parts by volume of ethyl chloroformate is stirred dropwise into a suspension of 1.0 part by weight of 3-morpholinosydnonimine hydrochloride in 5 parts by volume of pyridine, and the mixture is agitated for a while to allow reaction to take place. Pyridine is removed from the reaction mixture by evaporation, and the residue is dissolved in a small amount of water and extracted with chloroform several times. The extract is dehydrated by adding anhydrous magnesium sulfate and subjected to filtration. Chloroform is removed from the filtrate by distillation, crude crystals being obtained. Recrystallization of the crude crystals from toluene gives 0.6 part by weight of 3-morpholino-N-carboethoxysydnonimine having a melting point of 140°-141°C. Yield 51%.

References

Masuda K. et al.; US Patent No. 3,812,128; May 21, 1974; Assigned to Takeda Chemical Industries, Ltd., Osaka, Japan

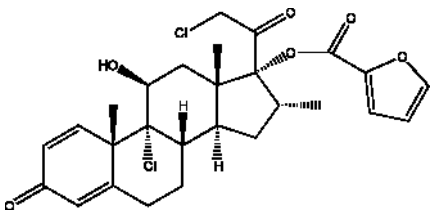
MOMETASONE FUROATE

Therapeutic Function: Glucocorticoid

Chemical Name: Pregna-1,4-diene-3,20-dione, 9,21-dichloro-17-((2-furanylcarbonyl)oxy)-11-hydroxy-16-methyl-, (11β,16α)-

Common Name: Mometasone furoate

Structural Formula:



Chemical Abstracts Registry No.: 83919-23-7

Trade Name	Manufacturer	Country	Year Introduced
Asmanex	Novartis Communications	Switz.	-
Asmanex Twisthaler	Schering-Plough	Belgium	-
Cutizone-T	Crosland Research Laboratories	India	-
Elocon	Fulford GALT (India) Ltd.	India	-
Elocon	Schering-Plough	Belgium	-
Nasonex	Schering-Plough	Belgium	-

Raw Materials

9β,11β-Epoxy-17α,21-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione
Mesyl chloride
2-Furoyl chloride
4-Dimethylaminopyridine
1,3-Dichloro-5,5-dimethylhydantoinyl

Manufacturing Process

METHOD I (Patent U.S. 4,472,393)

A. 21-Chloro-9β,11β-epoxy-17α-hydroxy-16α-methyl-1,4-pregnadiene-3,20-dione

Prepare a solution of 5.0 g. of 9β,11β-epoxy-17α,21-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione in 20 ml of dry pyridine. Cool on an ice bath; to the stirred solution under nitrogen, add dropwise 1.1 ml of mesyl chloride. Remove the ice bath and continue stirring at room temperature for 30 min. Add 2.0 g of lithium chloride and continue stirring for a further 150 min. Add to a mixture of 150 ml ethyl acetate and 100 ml distilled water. Wash the organic phase with dilute 3% aqueous hydrochloric acid, then saturated aqueous sodium chloride solution and finally saturated sodium bicarbonate solution. Dry the organic phase over magnesium sulfate, filter and remove the solvent to give 4.62 g of 21-chloro-9β,11β-epoxy-17α-hydroxy-16α-methyl-1,4-pregnadiene-3,20-dione.

B. 21-Chloro-9β,11β-epoxy-17α-hydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 17-(2'-furoate)

Prepare under argon a solution of 8 g of 4-dimethylaminopyridine in 250 ml of dry methylene chloride. Cool on an ice bath and add to the stirred solution 6.0 ml of 2-furoyl chloride. Remove from the ice bath, allow the temperature to rise to room temperature and then add 11.5 g of the 21-chloro-9β,11β-epoxy-17α-hydroxy-16α-methyl-1,4-pregnadiene-3,20-dione. After 24 hours add 500 ml of ethyl acetate saturated with water. Filter off the precipitate and then evaporate off the solvent to give the crude 21-chloro-9β,11β-epoxy-17α-hydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 17-(2'-furoate).

C. 9α,21-Dichloro-11β,17α-hydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 17-(2'-furoate)

To the crude 21-chloro-9β,11β-epoxy-17α-hydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 17-(2'-furoate) add 50 ml of glacial acetic acid, then

add a solution of 3.5 g of anhydrous hydrogen chloride in 125 ml of glacial acetic acid. Stir for 15 minutes and then quench with 500 ml of distilled water. Filter off the solids, recrystallise from methanol:water, dry for 24 hours under vacuum to give 12.6 g 9α,21-dichloro-11β,17α-hydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 17-(2'-furoate) (yield 83% of theory).

Prepare under nitrogen a solution of 1.80 g of 21-chloro-17α-hydroxy-16α-methyl-1,4,9(11)-pregnatriene-3,20-dione 17-(2'-furoate). Add, with stirring, a solution of 1.15 ml of 70% perchloric acid in 2.53 ml of distilled water, and immediately thereafter 604 mg of 1,3-dichloro-5,5-dimethylhydantoin. Stir the reaction mixture for twenty minutes and then raise the temperature to ambient temperature. Monitor the consumption of starting material by thin layer chromatography of aliquots using chloroform:1,3-dichloro-5,5-dimethylhydantoinyl acetate (9:1) and hexane:ethyl acetate (1:1). When the starting material is consumed, pour the reaction mixture into 500 ml of distilled water containing the 1,3-dichloro-5,5-dimethylhydantoin and 7 g of sodium bisulphite. Add sodium chloride until the solution is saturated. Filter the precipitated solid, wash and dry at 50°C under vacuum. Purify the resulting crude product by preparative chromatography on 1000 micron silica gel plates using chloroform: ethyl acetate (19:1). Elute the desired band with ethyl acetate, filter the eluate and evaporate at room temperature to give crude product (1.3 g). Recrystallize the product by dissolving in refluxing methylene chloride, filtering and then replacing the methylene chloride at reflux with methanol and then the methanol with distilled water. Cool the suspension to room temperature, filter and dry under vacuum at 50°C to give the pure pregna-1,4-diene-3,20-dione, 9,21-dichloro-17-((2-furanylcarbonyl)oxy)-11-hydroxy-16-methyl-, (11β-,16α)-.

METHOD II

The present invention (Patent U.S. 6,177,560) refers to a new process for the preparation of mometasone furoate carried out by esterifiication of the 17 hydroxy group of mometasone without prior protection of the 11 hydroxy group. Mometasone (30 g) was suspended in methylene chloride (300 ml) and the resulting suspension was cooled to 0-5°C. At this temperature triethylamine (57 ml) was added. 2-Furoyl chloride (24 ml) was then added slowly. The mixture was then stirred at 8-12°C until the level of mometasone present was lower than 0.2% by HPLC. The reaction solution was then cooled to between -5-5°C and water (120 ml) was added with stirring. After stirring for 1 hour at 10-15°C the mixture was cooled to between 0-5°C and concentrated hydrochloric acid was added to adjust the pH of the aqueous layer between 1 and 2.

The phases were separated and the aqueous layer was extracted with methylene chloride (60 ml). To the combined organic layers concentrated hydrochloric acid (90 ml) and acetic acid (30 ml) was added at a temperature 15-25°C. Then the two phase reaction mixture was stirred until less than 0.1% of the side products remained as monitored by HPLC. The reaction mixture was cooled to 0-5°C and water (120 ml) was added. The lower organic layer was separated, water (120 ml) and 8 N aqueous sodium hydroxide solution (about 30 ml) were added to adjust the pH to between 5 and 6. After stirring for 2 hours the organic layer was separated and washed with water (120 ml). The organic solution [containing the mometasone 17-(2-furoate)] was concentrated by distillation to a volume of 120 ml. Further

methanol (120 ml) was added and the mixture was concentrated to 120 ml. This procedure was repeated twice more. The reaction mixture was slowly cooled to 0-5°C and stirred for 2 hours. The crude mometasone 17-(2-furoate) was then filtered off and washed with cold methanol.

Purification of mometasone 17-(2-furoate)

The wet cake was dissolved in acetone (395 ml) and charcoal (3 g) was added. After 24 hours, the charcoal was filtered off and washed with acetone (90 ml). Charcoal (3 g) was added to the solution and the solution stirred for at least 24 hours at between 15-25°C. The charcoal was then filtered off and washed with acetone (75 ml). The solution was concentrated by distillation to a volume of 120 ml. During this concentration the mometasone 17-(2-furoate) started to crystallise. Methanol (120 ml) was added and the solution was again concentrated to 120 ml. This procedure was repeated twice. The suspension was cooled slowly to 0-5°C and stirred for about 2 hours at this temperature. The pure mometasone 17-(2-furoate) was then filtered off and washed with cold methanol. The product was dried at 60-70°C. A yield of 29.92 g was obtained.

References

Shapiro E.L.; US Patent No. 4,472,393; Sep. 18, 1984; Assigned: Schering Corporation (Kenilworth, NJ)

Heggie W., Bandarra J.; US Patent No. 6,177,560; Jan. 23, 2001; Assigned to Hovione Inter Ltd.

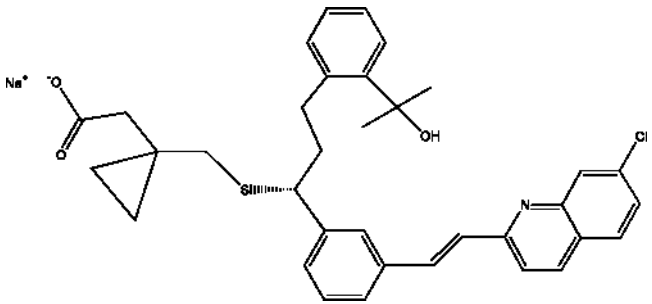
MONTELUKAST SODIUM

Therapeutic Function: Anti-asthmatic

Chemical Name: Cyclopropaneacetic acid, 1-((((1R)-1-(3-((1E)-2-(7-chloro-2-quinolinyl)ethenyl)phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl) propyl)thio)methyl)-, monosodium salt

Common Name: Montelukast sodium

Structural Formula:



Chemical Abstracts Registry No.: 151767-02-1; 158966-92-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Singulair	Merck Pharmaceutical Corporation	Canada	-

Raw Materials

Crotonaldehyde
4-Chloroaniline
Chloranil
Palladium (II) acetate
Cerium (III) chloride
Thionyl chloride
Sodium cyanide
Triethylamine
Potassium t-butoxide
Methyl 2-(2-iodophenyl)propanoate
Tetrabutylammonium chloride
Diethyl 1,1-cyclopropanedicarboxylate
Vinyl magnesium bromide
Methyl magnesium chloride
Borane-tetrahydrofuran complex
Diisopropylethylamine
Methanesulfonyl chloride

Manufacturing Process

Crotonaldehyde (3.23 mol) in 100 mL of 2-butanol was added dropwise to a refluxing solution of 4-chloroaniline (3.23 mol), p-chloranil (3.23 mol) and HCl conc. (808 mL) in 5.4 L of 2-butanol. After 2 hours of heating 2.7 L of solvent was removed under vacuum at 60°C. Then 2 L of toluene was added to the reaction mixture followed by removal of 2.5-3 L of solvent until a very pasty solid formed. THF (2 L) was added and the mixture heated 30 min after which it was cooled to 0°C. The solid was collected and washed with THF until pure by tlc. The solid was then dissolved in aq. K_2CO_3/EtOAc and the organic phase separated. The aqueous phase was extracted with EtOAc and the organic phases combined, dried over $MgSO_4$ and the solvent removed. The product was crystallized in the minimum amount of EtOAc to give 328.08 g (57%) of 4-chloro-2-methylquinolin.

4-Chloro-2-methylquinalin was converted into 3-(2-(7-chloro)-2-quinolinyl)ethenyl)benzaldehyde. Reaction was carried out according to a method described in U.S. Pat. No. 4,851,409

To a degassed suspension of 3-(2-(7-chloro-2-quinolinyl)ethenyl)benzaldehyde (0.34 mol) in toluene (700 mL) at 0°C was added 1.0 M vinylmagnesium bromide in toluene/THF (370 mL). After stirring for 1 hour at 0°C, the reaction was quenched by the addition of saturated NH_4Cl solution (150 ml), followed by H_2O (500 mL) and HOAc (50 mL). The product was extracted with EtOAc and the two-phase system was filtered through celite to remove an insoluble precipitate. The aqueous phase was then re-extracted with EtOAc (100 mL) and the combined organic layer was washed with H_2O, followed by brine. The solution was dried ($MgSO_4$), and evaporated to give a dark yellow residue which was purified by flash chromatography (EtOAc:hexane 1:5, then 1:3). The product was filtered from the column fractions to give a solid of 1-(3-(2-(7-chloro-2-quinolinyl)ethenyl)phenyl)-2-propen-1-ol (melting point = 110-112°C). The filtrate was concentrated and the resulting residue was recrystallized from EtOAc/hexane 1:4 to give a second crop of 15.1 g.

A degassed suspension of 1-(3-(2-(7-chloro-2-quinolinyl)ethenyl)phenyl)-2-

propen-1-ol (46.6 mmol), n-Bu_4NCl (93 mmol), $LiOAcH_2O$ (115 mmol), LiCl (93 mmol), Pd(OAc)2 (1.4 mmol) and methyl 2-(2-iodophenyl)propanoate in DMF (90 mL) was stirred for 2 hours at 100°C. The dark red solution was then cooled to 0°C and poured into saturated $NaHCO_3$ solution (500 mL). The product was extracted with EtOAc and the organic layer was washed with H_2O followed by brine. The solvent was removed under vacuum and the residue was purified by flash chromatography (EtOAc:hexane 1:10, 1:5 and 3:10) to give a pale yellow foam of ethyl 2-(3(S)-(3-(2-(7-chloro-2-quinolinyl)ethenyl) phenyl)-3-hydroxy-propyl)benzoate (18.9 g).

A mixture of anhydrous $CeCl_3$ (164 mmol) in THF (500 mL) was refluxed overnight using a Dean Stark trap filled with activated molecular sieves. Methyl magnesium chloride (3.0 Molar solution in THF, 790 mmol) was added dropwise over 30 min to the $CeCl_3$ slurry at 0°C. After stirring 2 hours, the mixture was cooled to -5°C and a toluene (600 mL) solution of the ethyl 2-(3(S)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)phenyl)-3-hydroxy-propyl)benzoate (152 mmol) was added dropwise over 1 hour. The reaction mixture was stirred another hour before the addition of 2 M HOAc (600 mL) and toluene (600 mL). The organic layer was washed with saturated aq. $NaHCO_3$ and with brine. Concentration in vacuo and purification of the residue by flash chromatography (30% EtOAc in toluene) gave 63.48 g (91%) of the 2-(2-(3(S)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)phenyl)-3-hydroxypropyl)phenyl)-2-propanol.

To a solution of BH_3THF complex (1 M in THF, 262 mL) was added diethyl 1,1-cyclopropanedicarboxylate (134 mmol) at 25°C under N_2. The solution was heated at reflux for 6 hours, cooled to r.t., and MeOH (300 mL) was cautiously added. The solution was stirred for 1 hour and then concentrated to an oil. The crude 2-(2-(3(S)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)phenyl)-3-hydroxypropyl)phenyl)-2-propanol was dissolved in CH_2Cl_2 (234 mL) and $SOCl_2$ (15.9 g, 134 mmol) was added dropwise over a period of 15 min at 25°C. After stirring for another 15 min, the mixture was washed with aqueous $NaHCO_3$. The organic extract was dried over Na_2SO_4, filtered and concentrated to give quantitatively the 1,1-cyclopropanedimethanol cyclic sulfite.

To a solution of the 1,1-cyclopropanedimethanol cyclic sulfite (99 mmol) in DMF (83 mL) was added NaCN (199 mmol). The mixture was heated to 90°C for 20 hours. Upon cooling, EtOAc (400 mL) was added and the solution was washed with saturated $NaHCO_3$ solution (55 mL), H_2O (4 times 55 mL), saturated NaCl solution and dried over Na_2SO_4. The solution was concentrated to give 7.1 g (65%) of 1-(hydroxymethyl)cyclopropaneacetonitrile.

To a solution of 1-(hydroxymethyl)cyclopropaneacetonitrile (42 g, 378 mmol) in dry CH_2Cl_2 (450 mL) at -30°C was added Et_3N (741 mmol) followed by CH_3SO_2Cl (562 mmol) dropwise. The mixture was warmed to 25°C, washed with $NaHCO_3$, dried over Na_2SO_4 and concentrated in vacuo to give the corresponding mesylate. The mesylate was then dissolved in DMF (450 mL) and cooled to 0°C. Potassium thioacetate (55.4 g, 485 mmol) was added, and the mixture was stirred at 25°C for 18 hours. EtOAc (1.5 L) was added, the solution was washed with $NaHCO_3$, dried over Na_2SO_4 and concentrated in vacuo to give 45 g (70%) of 1-(acetythiomethyl)cyclopropaneacetonitrile.

To a solution of the 1-(acetythiomethyl)cyclopropaneacetonitrile (266 mmol) in MeOH (1.36 L) was added H_2O (84 mL) and conc. H_2SO_4(168 mL). The mixture was heated to reflux for 20 hours, cooled to 25°C, H_2O (1 L) was added and the product was extracted with CH_2Cl_2. The organic extract was washed with H_2O and dried over Na_2SO_4. Concentration of the organic solution gave 36 g (93%) of the methyl 1-(thiomethyl)cyclopropaneacetate.

To a solution of 2-(2-(3(S)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)phenyl)-3-hydroxypropyl)phenyl)-2-propanol in THF was dissolved in THF (1 mL) and DMF (1 mL) at -40°C was added diisopropylethylamine (2.2 mmol) and then methanesulfonyl chloride (2.2 mmol). The mixture was stirred 2 hours with slow warming to -30°C. The methyl 1-(thiomethyl)cyclopropaneacetate (2.3 mmol) was added to the cloudy reaction mixture followed by dropwise addition of potassium tert-butoxide/THF solution (4.4 mmol). The reaction mixture was stirred at -30°C for 3.5 hours before quenching it with 25% aq NH4OAc. Extraction with EtOAc, washing the organic layer with brine and evaporation of the solvents left a residue that was purified by flash chromatography (5%-10% EtOAc in toluene) giving 658 mg (53%) of methyl 1-((((R)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)phenyl)-3-(2-(2-hydroxy-2-propyl)phenyl)propyl)thio)methyl)cyclopropaneacetate.

Following the hydrolysis the methyl 1-((((R)-(3-(2-(7-chloro-2-quinolinyl) ethenyl)phenyl)-3-(2-(2-hydroxy-2-propyl)phenyl)propyl)thio)methyl) cyclopropaneacetate with NaOH was obtained the free acid: 4-((1(R)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)phenyl)-3-(2-(2-hydroxy-2-propyl)-phenyl)propyl) thio)methyl)cyclopropaneacetic acid or sodium 1-(((1(R)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)phenyl)-3-(2-(2-hydroxy-2-propyl)phenyl)propyl)thio) methyl) cyclopropaneacetate.

References

Zamboni R. et al.; US Patent No. 5,270,324; Dec. 14, 1993; Assigned to Merck Frosst Canada, Inc.

MOPERONE HYDROCHLORIDE

Therapeutic Function: Neuroleptic

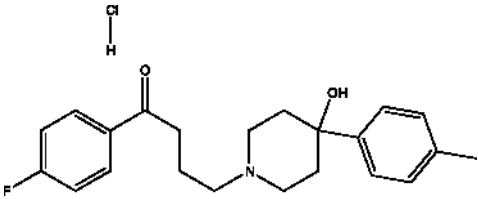
Chemical Name: 4'-Fluoro-4-(4-hydroxy-4-p-tolylpiperidino)butyrophenone hydrochloride

Common Name: Moperone hydrochloride; Methylperidol

Chemical Abstracts Registry No.: 3871-82-7

Trade Name	Manufacturer	Country	Year Introduced
Luvatren	Cilag	-	-
Moperone hydrochloride	Janssen Pharmaceutica	-	-

Structural Formula:



Raw Materials

Methyl bromide
Magnesium

Manufacturing Process

A solution of 95 parts of methyl bromide in 356 parts of ether was added portionwise to a refluxing suspension of 24 parts of magnesium in 214 parts of ether. The mixture was refluxed for 2 hours, and 92 parts of 4-methylacetophenone were added in the course of 90 minutes. The refluxing was continued for 3 hours, and the mixture was stirred for 24 hours at room temperature. The Grignard complex was destroyed by the addition of ammonium chloride and 10% hydrochloric acid. The mixture was extracted with ether and the ether extracts were washed with 10% sulfuric acid and then with water. Then extracts were dried over anhydrous calcium chloride, filtered, and concentrated in vacuum to remove the solvent. About 0.5 part of hydroquinone was added to the residue, which was then heated to a temperature of 100-110°C at 50 mm. The distillate was extracted with ether and the ether extracts were dried over anhydrous calcium chloride and filtered. A small quantity of hydroquinone was added to the ether. The solution was fractionated by distillation to yield 4-methyl-α-methylstyrene boiling at about 72-74°C at 80 mm.

A mixture of 856 parts of ammonium chloride and 3000 parts of 36% formaldehyde was stirred and heated to about 60°C. With cooling to maintain this temperature, 944 parts of 4-methyl-α-methylstyrene were added slowly. After the addition was completed, the mixture was stirred at room temperature until the temperature of the reaction mixture dropped to about 40°C. After 2000 parts of methanol were added, the stirring was continued for 20 hours. The methanol was removed in vacuum and the residue was diluted with 3000 parts of concentrated hydrochloric acid. For 4 hours, the mixture was heated with stirring at a temperature of 100°C. The mixture was cooled, diluted with 2000 parts of water, and made alkaline with 15 N sodium hydroxide solution. The reaction mixture was extracted with benzene, and the benzene extracts were dried over anhydrous potassium carbonate and filtered. The benzene was removed from the filtrate. The remaining residue was distilled in vacuum to yield 4-(p-tolyl)-1,2,3,6-tetrahydropyridine. This base was dissolved in benzene. Dry, gaseous hydrogen chloride was passed through the solution, whereupon there precipitated the hydrochloride, which was collected on a filter. The 4-(p-tolyl)-1,2,3,6-tetrahydropyridine hydrochloride boiling at about 162-170°C/10 mm Hg.

While the temperature was being maintained at about 10-20°C, anhydrous hydrogen bromide gas was passed for 7 hours through a solution of 160 parts of 4-(p-tolyl)-1,2,3,6-tetrahydropyridine in 500 parts of acetic acid. The mixture was stirred during the addition of the hydrogen bromide gas. The mixture was then allowed to stand at room temperature of 16 hours. The acetic acid and the excess hydrogen bromide were removed in vacuum at a bath temperature of less than 40°C. The residue was treated with ether. This solution was cooled, and the product was collected on a filter to give the 4-(p-tolyl)-4-bromopiperidine hydrobromide. A solution of 160 parts of above prepared hydrobromide in 3000 parts of water was treated with 100 parts of 20% sodium hydroxide solution. The resulting precipitate was recovered by filtration and washed with water. The precipitate was then dissolved in toluene, and the solution was dried over anhydrous potassium carbonate and filtered. The filtrate was cooled to 0°C. The crystalline product thus obtained was collected on a filter to yield 4-(p-tolyl)-piperidin-4-ol; MP: 136-137°C.

To a suspension of 341 parts of aluminium chloride in 1740 parts of carbon disulphide were added 96 parts of fluorobenzene with stirring and cooling. While the temperature was maintained at about 10°C, 141 parts of γ-chlorobutyryl chloride were added. After the addition was completed, the cooling bath was removed and the stirring was continued for 2 hours. The reaction mixture was poured into ice water. The organic layer was separated, washed with water, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure and the residue was distilled to yield γ-chloro-p-fluorobutyrophenone. BP: at about 136-142°C/6 mm Hg. 3.7 parts by weight of it, 14.16 parts of 4-(p-tolyl)-piperidin-4-ol, 0.1 parts KI and 150 parts by volume of toluene was treated in the pressure vessel at 140-150°C for 72 hours. On cooling to room temperature the reaction mixture was filtered. The solid residue was treated with mixture of water and ether and ethereal layer added to filtrate from original with water and pressed as dry as possible on the filter. It was then dissolved in 1500 parts by volume of boiling toluene to which anhydrous potassium carbonate was added to remove the remaining water. The mixture was filtered and the filtrate cooled to 0°C. The was p-fluoro-4-(4-hydroxy-4-p-tolyl-piperidino)butyrophenone. MP of chlorohydrate: 216-218°C.

References

PAUL ADRIAAN JAN JANSSEN; GB Patent No. 881,893; Nov. 8, 1961; N.V. Research Laboratorim Dr.C. Janssen, a Belgium Limited Liability Company, Belgium

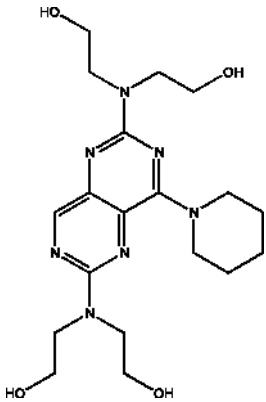
MOPIDAMOL

Therapeutic Function: 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 tetrahydropyrimido[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 and Engel p. 608
DOT 17 (3) 89 (1981)
I.N. p. 644
Roch, J. and Scheffler, H.; US Patent 3,322,755; May 30,1967;assigned to Boehringer Ingelheim GmbH

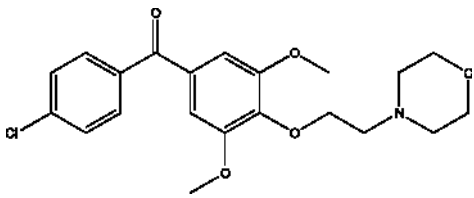
MORCLOFONE

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 salt)

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 140C, 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 and Engel p. 609
DOT 12 (7) 269 (1976)
I.N. p. 645
Lauria, F., Vecchietti, V. and Logemann, W.; US Patent 3,708,482; January 2, 1973; assigned to Carlo Erba SpA (Italy)

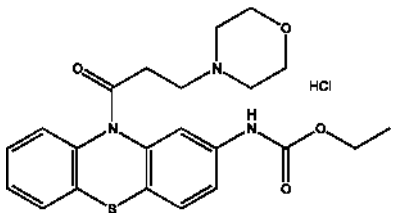
MORICIZINE HYDROCHLORIDE

Therapeutic Function: Antiarrhythmic

Chemical Name: Carbamic acid, (10-(3-(4-morpholinyl)-1-oxopropyl)-10H-phenothiazin-2-yl)-, ethyl ester, hydrochloride

Common Name: Moracizine hydrochloride; Moricizine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 29560-58-5 ; 31883-05-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Ethmozine	Bristol-Myers Squibb	-	-

Raw Materials

Ethyl phenthiazine-2-carbamate
3-Chloropropionyl chloride
Morpholine hydrochloride

Manufacturing Process

To a solution of 10 g (0.035 mole) of ethyl phenthiazine-2-carbamate in 30 ml of anhydrous toluene is added dropwise 5.3 g (0.042 mole) of 3-chloropropionyl chloride, and the mixture is refluxed at 110-120°C for 4 hours, followed by clarifying the mixture with activated carbon and cooling it to room temperature. A precipitate of ethyl 10-(3-chloropropionyl)-phenthiazine-2-carbamate is removed by filtration. The yield is 10.2 g (77.5% of the theoretical amount), M.P. 169-170°C.

10.2 g of ethyl 10-(3-chloropropionyl)-phenthiazine-2-carbamate ester is dissolved in 50 ml of toluene, 4.72 g of morpholine is added thereto, and the mixture is refluxed at 110-120°C for a period of 3 hours. A precipitate of morpholine hydrochloride is removed by filtration, and the filtrate is washed with water in order to remove excess morpholine, followed by acidulating with dilute hydrochloric acid to adjust the pH of the filtrate is adjusted at 3. The acidic aqueous layer is separated, clarified by treatment with activated carbon and made alkaline until the pH equals 8-9. This procedure yields the free base of ethyl 10-(β-morpholylpropionyl)-phenthiazine-2-carbamate, M.P. 156-157°C.

The free base thus obtained is extracted with toluene, the extract is dried over magnesium sulphate and to the anhydrous toluene solution is added an anhydrous ethereal solution of hydrogen chloride until the precipitation of the target compound is complete. This procedure yields 9.53 g (76.2% of the theoretical amount) of ethyl 10-(β-morpholylpropionyl)-phenthiazine-2-carbamate hydrochloride. After recrystallization from dichloroethane, the target compound melts at 189°C. (decomp.).

References

Merck Index, Monograph number: 6351, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Page G.O.; US Patent No. 5,202,435; April 13, 1993; Assigned to Du Pont Merck Pharmaceutical Company (Wilmington, DE)
Gritsenko A. et al.; US Patent No. 3,864,487; Feb. 4, 1975

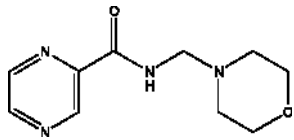
MORINAMIDE

Therapeutic Function: Antitubercular

Chemical Name: Pyrazinecarboxamide, N-(morpholinomethyl)-

Common Name: Morfazinamida; Morinamide; Morinammide; Morphazinamide

Structural Formula:



Chemical Abstracts Registry No.: 952-54-5

Trade Name	Manufacturer	Country	Year Introduced
Morinamide	Bracco Industria Chimica S.p.A.	-	-

Raw Materials

2-Pyrazinecarboxamide
Diethylamine
Formaldehyde
Morpholine

Manufacturing Process

98.5 parts by weight 2-pyrazinecarboxamide was mixed with 260 parts by volume of diethylamine. 91 parts by weight of 37% formaldehyde was added to above mixture by stirring for 30 minutes. The reaction mixture was spontaneously heated to 50°C. Then it heated to reflux for 5 hours on water bath. After that it was distilled to dryness at temperature between 40°-50°C. The residue was dissolved with about 200 parts by volume of ligroin (B.P. 60°C) by heating. The solution was filtered hot for removing the not reacted 2-pyrazinecarboxamide. Then it was cooled to -10°C and desired N-(diethylaminomethyl)-pyrazinecarboxylic acid amide discharged. It was filtered off and recrystallized from light petrol ester. Yield about 90%, MP: 47°-50°C.

500 parts by weight of N-(diethylaminomethyl)pyrazinecarboxylic acid amide and 2500 parts by volume of was mixed and heated by stirring to temperature 140°-150°C. At 60°-100°C a distillation begun and ended at 127°C (a boiling point of morpholine). The distillate consisted from diethylamine and morpholine. After 30-60 minutes the mixture was cooled to 50°C and distilled in vacuum to dryness. The residue was recrystallized from 400 parts by volume of benzene to give N-(morpholinomethyl)pyrazinecarboxamide, yield 92%, MP: 114°-117°C.

References

Felder E., Tiepolo U.; D.B. Patent No. 1,129,492; June 23, 1960; Bracco Industria Chimica S.p.A., Mailand (Italien)

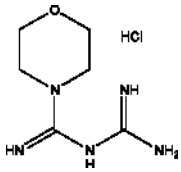
MOROXYDINE HYDROCHLORIDE

Therapeutic Function: Antiviral

Chemical Name: 4-Morpholinecarboximidoylguanidine, hydrochloride

Common Name: Abitilguanide; Moroxydine hydrochloride; Morpholinobiguanide hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 3160-91-6; 3731-59-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Grippe	Nissin	-	-
Tamaxin	Sawai	-	-
Virobis	S.C.S.	-	-
Virustat	Delagrange	-	-

Raw Materials

Morpholine
Dicyandiamide

Manufacturing Process

43.5 g morpholine, 41.7 ml concentrated hydrochloric acid, 40 ml of water, and 42 g dicyandiamide are refluxed for 48 hours, whereupon the reaction mixture is cooled to +5°C and filtered. The filtrate is evaporated to dryness and extracted and extracted with boiling ethanol. Yield: 50 g. The formed 4-morpholinecarboximidoylguanidine hydrochloride is purified by recrystallization from methanol. The salt may be converted into the base by adding equivalent of any basic compound (triethylamine, sodium bicarbonate and so on).

In practice it is usually used as hydrochloride.

References

Aktiebolaget Kabi, a Swedish Body corporate, of Stockholm 30, Sweden; G.B. Patent No. 776,176; Sept. 15, 1953

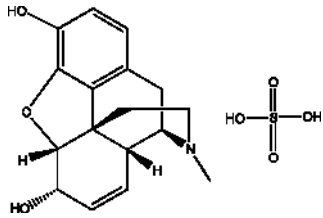
MORPHINE SULFATE

Therapeutic Function: Narcotic analgesic, Sedative

Chemical Name: Morphinan-3,6-α-diol, 7,8-didehydro-4, 5-α-epoxy-17-methyl-, sulfate (2:1) (salt)

Common Name: Morphine sulfate

Structural Formula:



Chemical Abstracts Registry No.: 64-31-3; 57-27-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Avinza	Aetna Inc.	-	-
Continus	Napp	-	-
Dolcontin	Kabipharmacia	-	-
Dolcontin	Norsk Ph.	-	-
Duramor	Biological E. Limited	India	-
Doloral	Atlas	-	-
Duralgin	Ethypharm	-	-
Kadian	Alpharma USHP	-	-
Kapanol	GlaxoSmithKline	Australia	-
M-Eslon	Grunenthal	Germany	-
Morcontin	Modi-Mundi Pharma Limited	India	-
Morphine Sulfate SR	Pharmascience	USA	-
MST Continus	Mundipharma	Austria	-
Oblioser	Serono	-	-
Oramorph SR	Roxane Laboratories	-	-
RMS	Upsher-Smith	-	-
Skenan	UPSA	France	-
Substitol	Mundipharma	-	-

Raw Materials

Plant vegetable
Methanol or the aqueous solution of potassium pyrosulfate

Manufacturing Process

Morphin was extracted from the plant vegetable (the poppy) by the mixture of water and methanol or the aqueous solution of potassium pyrosulfate. The precipitation of the morphin was carried out by addition to the extract the aqueous solution of sodium carbonate.

Morphin can be obtained from the extract by using the cation exchanger.

Free base of morphin was transformated to the sulfate salt.

References

Pharmazeutische Wirkstoffe, 610-611, p.610
Heropolitanski R. et al.; DE Patent No. 2,905,468, 13.02.1979
DE Patent No. 2,726,925, 13.02.1979

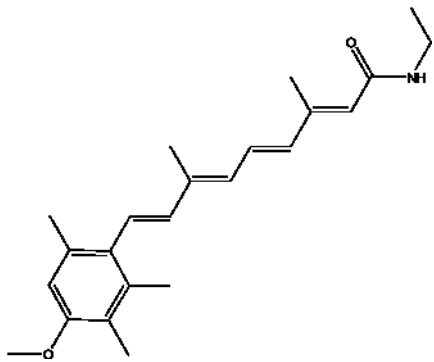
MOTRETINIDE

Therapeutic Function: Antipsoriatic

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

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

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-trimethyl-phenyl)-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-2,3,6-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-dimethylnona-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.; US Patents 4,105,681; August 8,1978; and 4,215,215; July 29,1980; both assigned to Hoffmann-LaRoche, Inc.

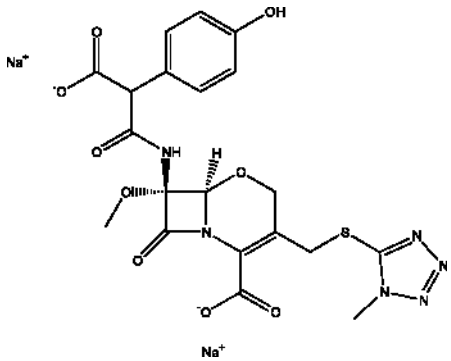
MOXALACTAM DISODIUM

Therapeutic Function: Antiinfective

Chemical Name: 7-[[Carboxy(4-hydroxyphenyl)acetyl]amino]-7-methoxy-3-[[(1-methyl-1H-tetrazole-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:



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

Trade Name	Manufacturer	Country	Year Introduced
Moxam	Lilly	US	1981
Moxalactam	Lilly	W. Germany	1981
Festamoxin	Shionogi	W. Germany	1981
Moxalactam	Lilly	France	1981
Moxalactam	Lilly	UK	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 l) and oxalyl chloride (26 l) 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 l), 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-5yl)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-oxycarbonil-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)thiomethyl1-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)thiomethyl1-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)thiomethyl1-oxadethia-3-cephem-4-carboxylic acid (342 mg). Yield: 888%. 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.; US Patent 4,138,486; February 6,1979; assigned to Shionogi and Co., Ltd. (Japan)

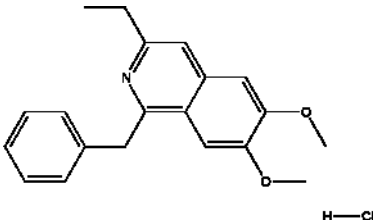
MOXAVERINE HYDROCHLORIDE

Therapeutic Function: Spasmolytic

Chemical Name: 1-Benzyl-3-ethyl-6,7-dimethoxyisoquinoline hydrochloride

Common Name: Moxaverine hydrochloride; Meteverine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 1163-37-7

Trade Name	Manufacturer	Country	Year Introduced
Paverin	Bracco	-	-

Raw Materials

1-Nitropropane
Sodium
Zinc
Phosphorous oxychloride
3,4-Dimethoxybenzaldehyde
Formic acid
Phenylacetic acid chloride

Manufacturing Process

166 g (1 mol) of 3,4-dimethoxybenzaldehyde were stirred for several hours (8 to 10 hours) with 180 g (2.02 mols.) of 1-nitropropane in 300 ml of methanol, in which 12 g of metallic sodium had previously been dissolved, the stirring taking place while heating to 45-50°C. After usual working up of the reaction

mixture, there were obtained 155 g of a white, crystalline product, which constituted the 1-(3,4-dimethoxyphenyl)-2-nitro-1-butanol and melted after recrystallization from isopropanol at 93-94°C (uncorrected). The composition was confirmed by elementary analysis and an infra-red spectrogram.

204 g (0.8 mol) of the above nitro alcohol were reduced at 30-35°C in 1250 g of 44% formic acid with 320 g of powdered zinc (about 4.9 at.). After working up, the base 1-(3,4-dimethoxyphenyl)-2-amino-1-butanol was obtained as a white crystalline product. After recrystallization from ethyl acetate, it melted at 91-93°C and the yield was 168 g, i.e. 93.3% of the theoretical.

90 g (0.4 mol) of the above amino alcohol are reacted at 45-50°C in 400 ml of chloroform in the presence of 95 g (1.2 mols) of pyridine by means of 139 g (0.9 mol) of phenylacetic acid chloride. After working up the reaction mixture, a yellowish-crystalline product was isolated (183.5 g, theoretical: 184.6 g), which melted at 123-125°C. After recrystallization from ethyl acetate, it yielded minute, white crystals, which melted at 129 -131°C (uncorrected). The composition of the product was confirmed by elementary analysis.

217 g of the above 1-(3,4-dimethoxyphenyl)-2-(phenylacetamido)-butanol-1-phenyl acetate (0.47 mol) were stirred in 80 1300 ml of xylene with 145 g of phosphorous oxychloride at 100-105°C. After some hours, when the evolution of hydrochloric acid gas had ceased, the reaction mixture was poured on to ice and stirred while cold until the crystallization was completed. After filtering, 144 g (89%) of the formed 1-benzyl-6,7-dimethoxy-3-ethyl isoquinoline hydrochloride were obtained in the form of yellowish crystals, which melted at 198-202°C with decomposition. From the separated aqueous mother liquors, the remainder of the formed isoquinoline base was obtained after treatment with ammonia and extraction with ether, the said base being isolated by way of the sparingly soluble and readily crystallisable acid sulfate. The salt represented a yellowish crystal powder, which melted at 239-243°C and weighed 21 g (11%). Thus, the yield of crude isoquinoline salt was almost the theoretical yield. The crude hydrochloride acid salt yielded white, lustrous prisms after recrystallisation from 96% ethanol, the said prisms melting at 208-210°C with decomposition. 1-Benzyl-6,7 -dimethoxy-3-ethyl isoquinoline may be prepared as a base from its salt by adding of equivalent of triethyl amine or any other base.

References

Orgamol S. A., a Swiss Body Corporate of Postfach, Switzerland; G.B. Patent No. 1,030,022; June 16, 1966

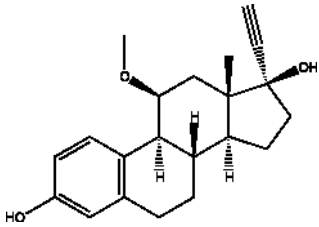
MOXESTROL

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-17a-ethynylestradiol

Structural Formula:



Chemical Abstracts Registry No.: 34816-55-2

Trade Name	Manufacturer	Country	Year Introduced
Surestryl	Roussel	France	1974

Raw Materials

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

Manufacturing Process

(A) Preparation of 11β-Methoxy-$\Delta^{4,9}$-Estradiene-3,17-Dione: 0.5 g of $\Delta^{4,9}$-estradiene-11β-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 11β-methoxy-$\Delta^{4,9}$-estradiene-3,17-dione having a MP of 140°C.

(B) Preparation of 11β-Methoxy-$\Delta^{1,3,5(10)}$-Estradiene-3-ol-17-one: 12.3 g of 11β-methoxy-$\Delta^{4,9}$-estradiene-3,17-dionewere 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 11β-methoxy-$\Delta^{1,3,5(10)}$-estradiene-3-ol-17-one having a MP of 264°C.

(C)Preparation of 11β-Methoxy-17α-Ethynyl-$\Delta^{1,3,5(10)}$-Estradiene-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 11β-methoxy-$\Delta^{1,3,5(10)}$-estradiene-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 17α-ethynyl derivative, which was purified by dissolution in ethyl acetate at reflux and by icing to obtain 2.33 g (yield = 77%) of 11β-methoxy-17α-ethynyl-$\Delta^{1,3,5(10)}$-estradiene-3,17β-diol, having a MP of 280°C.

References

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

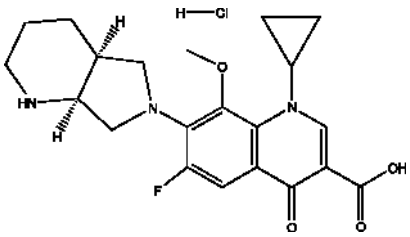
MOXIFLOXACIN HYDROCHLORIDE

Therapeutic Function: Antibacterial

Chemical Name: 3-Quinolinecarboxylic acid, 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-((4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-4-oxo-, monohydrochloride

Common Name: Moxifloxacin hydrochloride; Proflox

Structural Formula:



Chemical Abstracts Registry No.: 151096-09-2 (Base); 186826-86-8

Trade Name	Manufacturer	Country	Year Introduced
Avelox	Bayer	-	-
Actira	Bayer	-	-
Octegra	Lilly	-	-
Octegra	Bayer	-	-
Proflox	Div. Sigma	-	-

Raw Materials

Hydrogen
Potassium hydroxide
Copper cyanide
Hydrochloric acid
Sulfuric acid
Thionyl chloride
Diethyl malonate
Acetic anhydride
Sodium fluoride
Ethyl orthoformate
Acetic acid
Pyridine-2,3-dicarboxylic acid
N-Methyl-2-pyrrolidone
Ferric chloride hexahydrate
Glycol monomethyl ether
Lithium aluminum hydride
Ruthenium on charcoal
Magnesium ethoxide
4-Toluenesulfonic acid
Sodium bicarbonate
1,2,3,4-Tetrafluorobenzene
Palladium on charcoal
Cyclopropylamine
N-benzylimide

Manufacturing Process

Synthesis of intermidate octahydropyrrolo[3,4-b]pyridine (2,8-diazabicyclo[4.3.0]nonane):

47.6 g (0.2 mol) of pyridine-2,3-dicarboxylic acid N-benzylimide (British Patent No. 1,086,637; Chem. Abstr. 68, 95695w) are hydrogenated in 400 ml of glycol monomethyl ether over 15 g of ruthenium-on-active charcoal (5% strength) at 90°C under 100 bar until the calculated amount of hydrogen has been taken up. The catalyst is then filtered off and the filtrate is concentrated on a rotary evaporator 44 g of an oily crude product are obtained.

The corresponding hydrogenation with palladium-on-active charcoal (5% strength) gives a quantitative yield of a pure 6-benzyl-5,7-dioxo-octahydropyrrolo[3,4-b]pyridine of melting point 67°-69°C.

1.52 g (40 mmol) of lithium aluminium hydride are initially introduced into 30 ml of anhydrous tetrahydrofuran, and 44 g (about 0.18 mol) of crude or pure 6-benzyl-5,7-dioxo-octahydropyrrolo[3,4-b]pyridine are added dropwise as a solution in 15 ml of anhydrous tetrahydrofuran. The mixture is then subsequently stirred at the boiling point for 10 h. 1.5 ml of water, 1.5 ml of 15% strength potassium hydroxide solution and 4.5 ml of water are added dropwise in succession to the batch and the precipitate is then filtered off with suction and washed with tetrahydrofuran. The filtrate is concentrated on a rotary evaporator and the residue is distilled. 24.4 g of a colorless oil of 6-benzyl-octahydropyrrolo[3,4-b]pyridine having a boiling point of 93°-95°C/0.06 mbar are obtained on distillation.

69 g (0.32 mol) of 6-benzyl-octahydropyrrolo[3,4-b]pyridine are hydrogenated in 450 ml of methanol over 7 g of palladium-on-active charcoal (5% strength)

at 90°C/90 bar in the course of 3 h. The catalyst is then filtered off, the filtrate is concentrated and the residue is distilled. 33.8 g (84% of theory) of a colorless solid of octahydropyrrolo[3,4-b]pyridine (2,8-diazabicyclo[4.3.0] nonane) having a melting point of 65°-67° C and a boiling point of 78°C/9 mbar are obtained.

Synthesis of intermidate 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid:

According to the method by Bardon et al. (Tetrahedron, 22, 2541 (1966)), 1,2,3,4-tetrafluorobenzene (50 g) was brominated and methoxylated to give 1-bromo-3-methoxy-2,4,5-trifluorobenzene (22.2 g) as colorless oil.

A mixture of the oily product (22 g), cuprous cyanide (10 g) and N-methyl-2-pyrrolidone (37 ml) in sealed tube was heated for 4.5 h at 140° to 150°C. After cooling, a solution of ferric chloride hexahydrate (44 g) and concentrated hydrochloric acid (11 ml) in water (60 ml) was added to the reaction mixture and then stirred at 50° to 60°C for 20 min. The reaction mixture was extracted with ether and the organic layer was washed with dilute aqueous hydrochloric acid, with water and with saturated saline solution successively, and dried over anhydrous sodium sulfate and then concentrated. The residue was purified by distillation under reduced pressure to give 3-methoxy-2,4,5-trifluorobenzonitrile (14.25 g) as colorless oil, boiling point 94°C/8 mm Hg.

To oily product thus obtained (14.2 g) were added concentrated sulfuric acid (8.5 ml) and water (40 ml) and the mixture was stirred for 1 h at 110°C. After cooling, the reaction mixture was poured into ice water (50 ml) and the resulting precipitate was collected by filtration, washed with water, and recrystallized from a solution of dichloromethane-n-hexane to give 3-methoxy-2,4,5-trifluorobenzamide (11.59 g) as white needle, melting point 130°-133°C.

Then, to these crystals were added 18 N sulfuric acid (150 ml) and the mixture was heated for 3.5 h at 100°C. After cooling, water (400 ml) was added to the mixture and the resulting crystals were recrystallized from n-hexane to give the 3-methoxy-2,4,5-trifluorobenzoic acid (9.61 g) as colorless needle, melting point 98°-101°C.

To 3-methoxy-2,4,5-trifluorobenzoic acid (9.4 g) was added thionyl chloride (50 ml), the mixture was refluxed for 3 h and then concentrated. The residue was purified by distillation under reduced pressure to give 3-methoxy-2,4,5-trifluorobenzoyl chloride (8.86 g) as yellow oil, boiling point 108°-112°C/20 mm Hg.

To magnesium ethoxide (5.9 g) was added diethyl malonate (7 g) in anhydrous toluene (35 ml) dropwise and the mixture was warmed for 2 h at 50° to 60°C and then cooled to -10°C. To the mixture was added a solution of the acid chloride (8.86 g) in anhydrous toluene (10 ml) dropwise over 15 min. After stirring for 1 h at -5° to 0°C, ice water (30 ml) containing concentrated sulfuric acid (8 ml) was added to the mixture and the organic layer was separated. The organic layer was washed with saturated saline solution, dried over anhydrous sodium sulfate and then concentrated to give diethyl 3-methoxy-2,4,5-trifluorobenzoylmalonate (13.64 g) as brown oil.

To oily product, the diethyl 3-methoxy-2,4,5-trifluorobenzoylmalonate (13.55 g) were added water (20 ml) and p-toluenesulfonic acid (14 mg), and the mixture was refluxed for 9 h. After cooling, the reaction mixture was extracted with dichloromethane and the organic layer was washed with 7% aqueous sodium bicarbonate solution and with saturated saline solution successively, dried over anhydrous sodium sulfate and then concentrated to give ethyl 3-methoxy-2,4,5-trifluorobenzoylacetate (10.29 g).

To the ethyl 3-methoxy-2,4,5-trifluorobenzoylacetate (9.79 g) were added acetic anhydride (9.6 g) and ethyl orthoformate added cyclopropylamine (8.4 g), and the mixture was refluxed for 3 h. After supplemented further acetic anhydride (3.2 g) and ethyl orthoformate (8.8 g), the mixture was refluxed for 8 h, and then concentrated to give ethyl 2-(3-methoxy-2,4,5-trifluorobenzoyl)-3-ethoxyacrylate (9.73 g) as brown oil.

To a solution of the ethyl 2-(3-methoxy-2,4,5-trifluorobenzoyl)-3-ethoxyacrylate (9.73 g) in ethanol (20 ml) cyclopropylamine (2.0 g) was added dropwise under cooling. After stirring for 2 h at room temperature, the reaction mixture was concentrated and the residue was purified by silica gel column chromatography eluting with n-hexane-ethyl acetate (5:1) to give ethyl 2-(3-methoxy-2,4,5-trifluorobenzoyl)-3-cyclopropylaminoacrylate (7.52 g) as yellowish white crystals, melting point 56°-58°C.

The mixture of the ethyl 2-(3-methoxy-2,4,5-trifluorobenzoyl)-3-cyclopropylaminoacrylate (6.68 g), sodium fluoride (1.31 g) and anhydrous dimethylformamide (26 ml) was refluxed for 5 h. After cooling, the reaction mixture was poured into ice water (100 ml) and the resulting precipitate was collected by filtration, washed with water and recrystallized from ethyl acetate to give ethyl 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylate (4.53 g) as colorless needle, melting point 178°-180°C.

To the ethyl 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylate (4.5 g) was added a mixed solution of acetic acid (30 ml), concentrated sulfuric acid (4 ml) and water (22 ml), and the mixture was refluxed for 1 h. After cooling, ice water (100 ml) was added and the resulting precipitate was collected by filtration, washed with water and then dried to give 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid (4 g) as colorless powder, melting point 185°-186°C.

Syntesis of 1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid hydrochloride (moxifloxacin hydrochloride):

A mixture of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid, 2,8-diazabicyclo[4.3.0]nonane, DBU (1,8-diazobicyclo[5.4.-0]undec-7-ene and anhydrous acetonitrile was refluxed. After cooling, the resulting precipitate was collected by filtration and recrystallized from methanol to give the 1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid.

The 1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid are dissolved in half-concentrated hydrochloric acid by heating, the solution is concentrated and the residue is

stirred with ethanol. The undissolved precipitate of 1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid hydrochloride is filtered off with suction, washed with ethanol and dried at 100°C in vacuo.

References

Masuzawa K. et al.; US Patent No. 5,043,450; August 27, 1991; Assigned: Kyorin Pharmaceutical Co., Ltd., Tokuo, Japan
Petersen U. et al.; US Patent No. 4,990,517; February 5, 1991; Assigned: Bayer Aktiengesellschaft, Leverkusen, Fed. Rep. of Germany

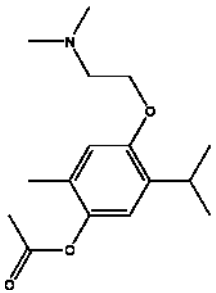
MOXISYLYTE

Therapeutic Function: 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
Sodium
Sulfuric acid
Acetic anhydride
Hydrogen chloride
Hydrogen sulfide
Dimethylaminoethyl chloride
Sodium nitrite
Ethanol

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 600cc 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 and Engel p. 612
OCDS Vol. 1 p. 116 (1977)
I.N. p. 647
Veritas Drug Co., Ltd; British Patent 745,070; February 22,1956

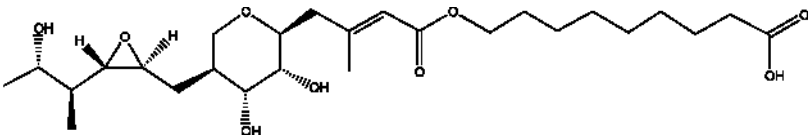
MUPIROCIN

Therapeutic Function: Antibiotic

Chemical Name: Nonanoic acid, 9-((3-methyl-1-oxo-4-(tetrahydro-3,4-dihydroxy-5-((3-(2-hydroxy-1-methylpropyl)oxiranyl)methyl)-2H-pyran-2-yl)-2-butenyl)oxy)-, (2S-(2-α(E),3-β,4-β,5-α(2R*,3R*(1R*,2R*))))-

Common Name: Acidum pseudomonicum; Mupirocin; Pseudomonic acid A

Structural Formula:



Chemical Abstracts Registry No.: 12650-69-0

Trade Name	Manufacturer	Country	Year Introduced
Bactroban	GlaxoSmithKline	UK	-
Bactroban	SmithKline Beecham	-	-
Bactroban Nasal	Beecham	-	-
Bactoderm	Pharmco Puerto Rico, Inc.	-	-
Bactoderm	Beecham	-	-
Eismycin	GlaxoSmithKline	Germany	-

Raw Materials

Pseudomonas fluorescens, strain NCIB 10586

Manufacturing Process

Production and recovery of Antibacterially active pseudomonic acid and Pseudomonic acid A

Pseudomonas fluorescens, strain NCIB 10586 was grown in submerged culture at 30°C in a medium containing 1% corn steep liquor and 0.5% glucose in a basic salts solution. The maximum yield of the antibiotic occurred after 24 hours and all of the detectable activity was in the culture fluid. After the addition of barium chloride (0.5%) the cells and precipitated non-active contaminant material were removed by centrifugation. The activity was progressively concentrated by partitioning into isobutylmethyl ketone (IBMK) (0.2 vol) at pH 4.5 water (0.8 vol) at pH 8.5, and then IBMK (0.25 vol) at pH 4.5 followed by evaporation to a small volume under reduced pressure. After a further partition into water at pH 8.5 and then adjustment to pH 7-8 the aqueous solution was freeze dried to give the sodium salt which could be stored at 0°C for several months, without loss of activity. The antibiotic extract was stable within the range pH 4-9 at 37°C for 24 hours. Outside these limits rapid loss of activity occurred. The sodium salt showed a broad

antibacterial spectrum against Gram positive and Gram negative bacteria, showed low toxicity and was bacteriostatic against S. aureus (N.C.T.C. 6571) and E. coli (M.R.E. 600).

Further purification of the crude acid was effected by chromatography on Amberlite XAD-2 polystyrene resin with a linear gradient produced by adding 0.1 N methanolic ammonia, to 0.01 N aqueous ammonia. A series of low molecular weight acids was eluted first, followed by a fraction (30-60% elution) that possessed the major part of the antibacterial (biological) activity.

Purification of Pseudomonic acid and Pseudomonic Acid A

The produced biologically active material upon methylation with diazomethane in ether showed two spots by thin layer chromatography corresponding to methyl pseudomonate as the major component and a minor amount of component methyl pseudomonate-A (ratio ca 9:1 by wt.).

Methyl pseudomonate was separated from methyl pseudomonate-A by preparative layer silica gel (GF245) chromatography on development with chloroform/isopropanol (9:1). 50% of methyl pseudomonate was recovered from the impure residue by crystallization from benzene/petroleum ether to give colorless needles of m.p. 76.5-78°C.

Acetylation of the methyl ester with pyridine/acetic anhydride affords a triacetate. Reduction of the methyl ester with $LiAlH_4$ in THF afforded 1,9-dihydroxynonanoate, m.p. 46°C.

References

Barrow K. D., Mellows G.; US Patent No. 4,289,703; Sep. 15, 1981; Assigned: Beecham Group Limited

O'Hanlon P. J. et al.; US Patent No. 4,222,942; Sep. 16, 1980; Assigned: Beecham Group Limited

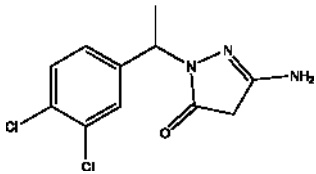
MUZOLIMINE

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 2 N 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) and 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.; US Patent 4,018,890; April 19, 1977; assigned to Bayer AG

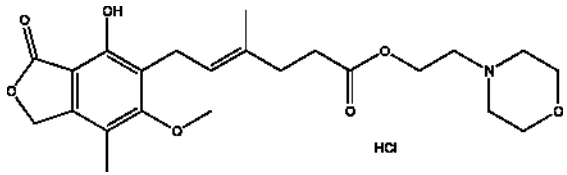
MYCOPHENOLATE MOFETIL HYDROCHLORIDE

Therapeutic Function: Antiarthritic, Immunosuppressive

Chemical Name: 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, (4E)-, hydrochloride

Common Name: Mycophenolate mofetil hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 116680-01-4; 128794-94-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
CellCept	Pharmacia	Italy	-
CellCept	Roche	Italy	-
CellCept	Syntex	-	-

Raw Materials

Sodium diethylmalonate	3-Methylpent-3-en-2-on
Diazomethane	Ammonium hydroxide
t-Butylhypochlorite	Hydroiodic acid
Phosphorus	Silver oxide
Thionyl chloride	Morpholinoethanol

Manufacturing Process

The synthesis of Mycophenolic acid (Canonica L. Et al., Tetrahedron Letters, 1971, N 28, p.2691-2692)

By condensation of sodium diethylmalonate and 3-methylpent-3-en-2-on in ethanol was obtained 2,3-dimethyl-4,6-dioxocyclohexanecarboxilic acid ethyl ester, which was aromatised to 4,6-dihydroxy-2,3-dimethylbenzoic acid ethyl ester (melting point 115-116°C). By treatment with diazomethane or with CH_3I and K_2CO_3 this compound was transformed into 2,4-dimethoxy-5,6-dimethylbenzoic acid ethyl ester (melting point 62-63°C). The hydrolysis of the ester group furnished the 2,4-dimethoxy-5,6-dimethylbenzoic acid (melting point 208-210°C), which was converted into the amide: carbamic acid 3-methoxy-4,5,6-trimethylphenyl ester (melting point 225-229°C). Treatment of the amide with t-butylhypochlorite in methylene dichloride yielded the corresponding N-chloroamide which was photolysed to the intermediate iminolactone and was immediately hydrolized to 5,7-dimethoxy-4-methyl-3H-isobenzofuran-1-one.

This compound with hydriodic acid in acetic acid in the presence of red phosphorous at reflux yielded 5,7-dihydroxy-4-methyl-3H-isobenzofuran-1-one. Condensation of 6-bromo-4-methylhex-4-enoic acid methyl ester and 5,7-dihydroxy-4-methyl-3H-isobenzofuran-1-one with silver oxide in dioxane at room temperature yielded 6-(4,6-dihydroxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-4-methylhex-4-enoic acid methyl ester (36% yield). At last, monomethylation with diazomethane yield 6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-4-methylhex-4-enoic acid

methyl ester, which was hydrolysed with aqueous sodium hydroxide to 6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-isobenzofuran-5-yl)-4-methylhex-4-enoic acid (Mycophenolic acid).

Mycophenolic acid may be obtained by the fermentation broth of Pennicillium brevicompactum. The synthesis of Mycophenolate mofetil (Patent U.S. 4,753,935). The mixture of Mycophenolic acid (32.0 g), thionyl chloride (25.0 ml) and DMF (0.3 ml) in dichloromethane (250 ml) was stirred at room temperature for 3 hours, after which the volatile components were removed under vacuum to afford mycophenolic acid chloride as an oil. The mycophenolic acid chloride oil was dissolved in dichloromethane (50.0 ml) and added to the chilled solution of morpholinoethanol (30.5 ml) in dichloromethane (250 ml). After stirring for 90 min at 4°C, the reaction mixture was washed with water and then with aqueous sodium bicarbonate. The organic solution was dried with sodium sulfate and evaporated to yield Mycophenolate mofetil: morpholinoethyl E-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate (melting point 93-94°C).

The product (38.0 g) was dissolved in isopropanol (200 ml) and the solution was added to a solution of hydrogen chloride (10.0 g) in isopropanol (150 ml). The hydrochloride of Mycophenolate mofetil was collected by filtration and dried under vacuum (melting point 154-155°C).

References

Nelson P. et al.; US Patent No. 4,753,935; Jun. 28, 1988; Assigned to Syntex (USA) Inc.
Pharmazeutische Wirkstoffe, S. 613
Kida T. et al.; US Patent No. 4,452,891; June 5, 1984; Assigned: Ajinomoto Company Incorporated (Tokyo, JP)
Queener S.W. et al.; US Patent No. 4,115,197; Sep. 19, 1978; Assigned: Eli Lilly and Company (Indianapolis, IN)
Canonica L. et al.; Tetrahedron Letters, 1971, N 28, p.2691-2692

MYRTECAINE

Therapeutic Function: Local anesthetic, Spasmolytic

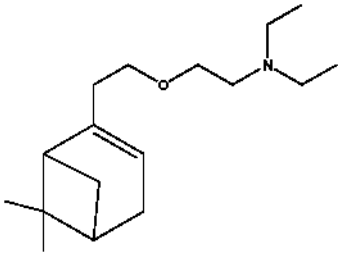
Chemical Name: Ethanamine, 2-(2-(6,6-dimethylbicyclo(3.1.1)hept-2-en-2-yl)ethoxy)-N,N-diethyl-

Common Name: Myrtecaine; Nopoxamine

Chemical Abstracts Registry No.: 7712-50-7

Trade Name	Manufacturer	Country	Year Introduced
Myrtecaine	Chemical Land21	-	-
Nopoxamine	Desynth	-	-
Nopoxamine	Bio Sidus	-	-

Structural Formula:



Raw Materials

Homomyrtenol
Sodium amide
Diethylaminochloroethane

Manufacturing Process

60 g (1.5 mol) of powdered sodium amide are put in suspension in 800 ml of toluene. The mixture is heated to 60°C and 166 g of homomyrtenol (1 mol) are added little by little. The reaction is continued for several hours until the homomyrtenol is entirely converted into sodium derivative. It is allowed to stand and the excess amide is filtered. The reaction is followed by titration on a sample of the decanted liquid after having removed the ammonia.

Added to the solution of the sodium derivative of the terpenic alcohol (1 mol) is a toluenic solution of 138 g (1.02 mol) diethylaminochloroethane in toluene. This mixture is refluxed in a nitrogen atmosphere for 12 hours. A precipitate of sodium chloride is formed which is dissolved in water. Two modes of extraction of the base myrtecaine are possible:

A) The toluenic solution is extracted with two times 200 ml of concentrated hydrochloric acid diluted to 20%. In this way there is obtained an aqueous solution of the hydrochloride, when the required amino base is salted out by addition of potassium carbonate. The amino ether-oxide is finally rectified under a vacuum. The fraction boiling between 135° and 140°C under 2 to 3 mm is collected; n_D^{20} = 1.477.

B) The toluenic solution is dried on potassium carbonate and then rectified. There is collected the toluene, then between 120° and 130°C under 2 mm the homomyrtenol which has not reacted, and then between 130° and 145°C a fraction which is again fractionated. The pure product is collected at 135°-140°C/2-3mm Hg.

References

Gaudin O.P.; G.B. Patent No. 861,900; Aug. 6, 1959