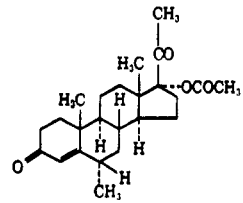
MEDROXYPROGESTERONE ACETATE

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	U.S.	1959
Farlutal	Carlo Erba	France	1962
Provest	Upjohn	U.S.	1964
Amen	Carnrick	U.S.	1975
Unison	Reid-Provident	U.S.	1978
Mepred	Savage	U.S.	1978
Curretab	Reid-Provident	U.S.	1979
Farlutal	Carlo Erba	U.K.	1982
Depcorlutin	O'Neal, Jones & Feldman	U.S.	–
Depo-Clinovir	Upjohn	W. Germany	–
Depo-Progevera	Alter	Spain	–
Depo-Provera	Upjohn	U.S.	–
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	U.S.	–
Progevera	Alter	Spain	–
Sodelut G	Sodex	Switz.	–

Raw Materials

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

fluxed 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,17α-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 2½ 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 U.S. Patent 3,147,290.

References

Merck Index 5614
Kleeman & Engel p. 546
PDR pp. 777, 1447, 1839, 1858
OCDS Vol. 1 pp. 180, 186 (1977) & 2, 165 (1980)
DOT 4 (1) 14 (1968)
I.N. p. 586
REM p. 992
Miramontes, L.E., Romero, M.A. and Farjat, F.A.; U.S. Patent 3,000,914; September 19, 1961; assigned to G.D. Searle & Co.

de Ruggieri, P. and Ferrari, C.; U.S. Patent 3,043,832; July 10, 1962; assigned to Ormoterapia Richter S.p.A., Italy
Camerino, B., Modelli, R., Patelli, B., Sala, G. and Baldratti, G.; U.S. Patent 3,061,616; October 30, 1962; assigned to Societa Farmaceutici Italia, Italy
Patchett, A.A. and Hoffman, F.G.; U.S. Patent 3,084,174; April 2, 1963; assigned to Merck & Co., Inc.
Beyler, R.E.; U.S. Patent 3,105,840; October 1, 1963; assigned to Merck & Co.
Spero, G.B.; U.S. Patent 3,147,290; September 1, 1964; assigned to The Upjohn Company

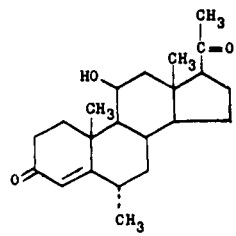
MEDRYSONE

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	U.S.	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, *J. 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-methylprogesterone 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 ml 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 U.S. Patent 2,864,837.

References

Merck Index 5616
Kleeman & 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.; U.S. Patent 2,864,837; assigned to The Upjohn Company
Spero, G.B. and Thompson, J.L.; U.S. Patent 2,968,655; January 17, 1961; assigned to The Upjohn Company

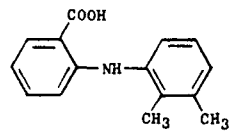
MEFENAMIC ACID

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	U.K.	1963
Ponalar	Parke Davis	W. Germany	1964

Trade Name	Manufacturer	Country	Year Introduced
Ponstyl	Parke Davis	France	1967
Ponstel	Parke Davis	U.S.	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 ml 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 & Engel p. 548
PDR p. 1383
OCDS Vol. 1 p. 110 (1977) & 2, 280 (1980)
DOT 1 (2) 59 (1965)
I.N. p. 31
REM p. 1118
Scherrer, R.A.; U.S. Patent 3,138,636; June 23, 1964; assigned to Parke, Davis & Company

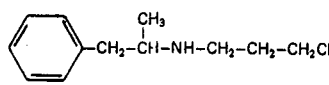
MEFENOREX HYDROCHLORIDE

Therapeutic Function: Anorexic

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

Common Name: —

Structural Formula:



(base)

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	U.S.	–
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 & 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.; U.S. Patent 3,485,926; December 23, 1969; assigned to Hoffmann-LaRoche, Inc.

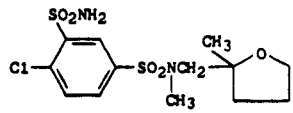
MEFRUSIDE

Therapeutic Function: Diuretic

Chemical Name: 4-chloro-N'-methyl-N'[tetrahydro-2-methyl-2-furanyl)methyl]-1,3-benzenedisulfonamide

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	U.K.	1971
Baycaron	Yoshitomi	Japan	1975
Bendigon	Bayer	W. Germany	–

Trade Name	Manufacturer	Country	Year Introduced
Caprinol	Bayer	W. Germany	–
Sali-Presinol	Bayer	W. Germany	–

Raw Materials

α-methyl-α-cyanotetrahydrofuran
Hydrogen
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 & 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.; U.S. Patent 3,356,692; December 5, 1967; assigned to Farbenfabriken Bayer AG

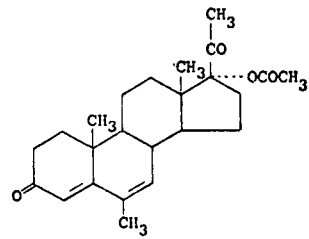
MEGESTROL ACETATE

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	U.K.	1967

Trade Name	Manufacturer	Country	Year Introduced
Megace	Mead Johnson	U.S.	1982
Pallace	Bristol	U.S.	1982
Megestat	Bristol	Switz.	1983
Megeron	Neofarma	Finland	–
Minigest	Novo	–	–
Niagestin	Novo	–	–
Ovarid	Glaxo	–	–
Volplan	B.D.H.	U.K.	–

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 U.S. Patent 3,356,573. 17α-Acetoxy-3β-hydroxy-6-methylpregn-5-en-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 & Engel p. 550
PDR p. 721
OCDS Vol. 1 p. 180 (1977)
DOT 4 (1) 17 (1968)
I.N. p. 588
REM p. 993
Dodson, R.M. and Sollman, P.B.; U.S. Patent 2,891,079; June 16, 1959; assigned to G.D. Searle & Co.
Kirk, D.N., Petrow, V. and Williamson, D.M.; U.S. Patent 3,356,573; December 5, 1967; assigned to The British Drug Houses Limited, England
Cross, A.D.; U.S. Patent 3,400,137; September 3, 1968; assigned to Syntex Corporation, Panama

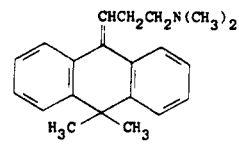
MELITRACEN

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)

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

Raw Materials

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

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

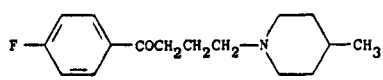
MELPERONE

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)

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

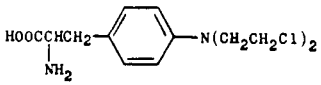
MELPHALAN

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	U.S.	1964
Alkeran	Wellcome	U.K.	1964
Alkeran	Wellcome	W. Germany	1965
Alkeran	Wellcome	France	1966
Alkeran	Wellcome	Italy	1968
Alkeran	Wellcome	Japan	1979

Raw Materials

Diethyl sodium phthalidomalonate
p-Nitrobenzoyl chloride
Cinchonidine
Hydrogen
Phosphorus oxychloride
Sodium carbonate
Acetic anhydride
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 diethyl-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 U.S. Patent 3,032,585.

Then, as described in U.S. 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 & 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.; U.S. Patent 3,032,584; May 1, 1962; assigned to National Research Development Corporation, England
Bergel, F. and Stock, J.A.; U.S. Patent 3,032,585; May 1, 1962; assigned to National Research Development Corporation, England

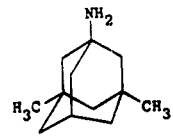
MEMANTINE

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.: –

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

Raw Materials

1,3-Dimethyladamantane
Acetonitrile
Sodium hydroxide
Bromine
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-acetamido-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.; U.S. Patent 3,391,142; July 2, 1968; assigned to Eli Lilly & Co.

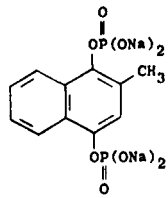
MENADIOL SODIUM DIPHOSPHATE

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	U.S.	1941
Analogue	Upjohn	U.S.	1951
Kappadione	Lilly	U.S.	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 extracte 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. Crys tals 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 & Engel p. 553
PDR p. 1502
I.N. p. 591
REM p. 1010
Solmssen, U.V.; U.S. Patent 2,345,690; April 4, 1944; assigned to Hoffmann-LaRoche, Inc.

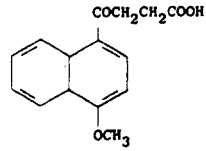
MENBUTONE

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
Aluminum chloride
Sodium carbonate
Succinic anhydride
Hydrogen chloride

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.; U.S. Patent 2,623,065; December 23, 1952; assigned to G.D. Searle & Co.

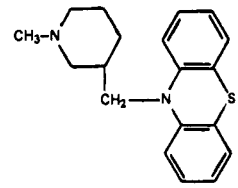
MEPAZINE

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)

Trade Name	Manufacturer	Country	Year Introduced
Pacatal	Warner Lambert	U.S.	1957
Pacatal	Promonta	W. Germany	–
Lacumin	Lundbeck	–	–
Ravenil	Caber	Italy	–

Raw Materials

1-Methyl-3-bromomethylpiperidine
Sodium amide
Phenothiazine
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 & Engel p. 689
I.N. p. 735
Schuler, W.A.; U.S. Patent 2,784,185; March 5, 1957; assigned to Chemische Fabrik Promonta GmbH

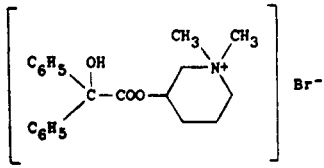
MEPENZOLATE BROMIDE

Therapeutic Function: Antispasmodic

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

Common Name: N-methyl-3-piperidyl benzilate methobromide

Structural Formula:



Chemical Abstracts Registry No.: 76-90-4

Trade Name	Manufacturer	Country	Year Introduced
Cantil	Merrell National	U.S.	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 & Engel p. 555
PDR p. 1223
I.N. p. 593
REM p. 916
Biel, J.H.; U.S. Patent 2,918,408; December 22, 1959; assigned to Lakeside Laboratories, Inc.

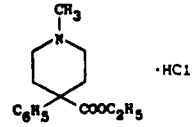
MEPERIDINE HYDROCHLORIDE

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	U.S.	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.	Neth.	—
Dolopethin	Gattiker	Switz.	—
Medfina	Carlo Erba	—	—
Pethidine Roche	Roche	U.K.	—
Supplosal	Specia	France	—

Raw Materials

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

Manufacturing Process

80 parts of finely pulverized sodium amide are added in portions each of about 1/5 of the entire quantity, while stirring and cooling in a suitable manner, to a mixture of 156 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 & Engel p. 707
PDR pp. 872, 1908, 1959, 1989
OCDS Vol. 1 p. 300 (1977); 2, 328 (1980) & 3, 116 (1984)
I.N. p. 750
REM p. 1108
Eisleb, O.; U.S. Patent 2,167,351; July 25, 1939; assigned to Winthrop Chemical Company, Inc.

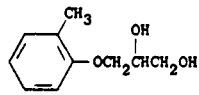
MEPHENESIN

Therapeutic Function: Skeletal 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	U.S.	1948
Oranixon	Organon	U.S.	1949
Avosyl	Schenley	U.S.	–
Curaresin	Kyoto	Japan	–
Decontractyl	Robert & Carriere	France	–
Glyotol	U.S. Standard	U.S.	–
Myanesin	B.D.H.	U.K.	–
Myanol	Chugai	Japan	–
Myocuran	Deutsch. Hydrierwerk	E. Germany	–
Myoserol	Sankyo	Japan	–
Myoxane	Ascher	U.S.	–
Noctynol	Moore	U.K.	–
Prolax	Cole	U.S.	–
Relaxar	Bouty	Italy	–
Rhex	Hobein	W. Germany	–
Spasmolyn	Heun	U.S.	–
Tolosate	Brewer	U.S.	–

Trade Name	Manufacturer	Country	Year Introduced
Tolulox	Miller	U.S.	–
Tolyspaz	Chicago Pharmacal	U.S.	–

Raw Materials

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

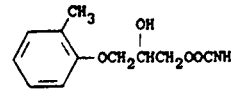
MEPHENESIN CARBAMATE

Therapeutic Function: Skeletal muscle relaxant

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

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 533-06-2; 59-47-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Tolseram	Squibb	U.S.	1954
Kinavosyl	Schenley	U.S.	–

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 ml 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 & Engel p. 556
OCDS Vol. 1 p. 118 (1977)
I.N. p. 593
Lott, W.A. and Pribyl, E.; U.S. Patent 2,609,386; September 2, 1952; assigned to E.R. Squibb & Sons

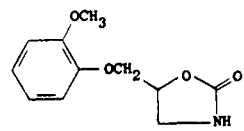
MEPHENOXALONE

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	U.S.	1961
Tranpoise	Robins	U.S.	1962
Lenetran	Lakeside	U.S.	1962
Xerene	Martinet	France	1964

Trade Name	Manufacturer	Country	Year Introduced
Control-Om	O.M.	Switz.	–
Dorsiflex	Syntex-Medial	Switz.	–
Placidex	Toraude	–	–
Riself	Gibipharma	Italy	–

Raw Materials

3-o-Methoxyphenoxy-2-hydroxy-1-propyl-carbamate
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°C 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.; U.S. Patent 2,895,960; July 21, 1959; assigned to A.H. Robins Co., Inc.

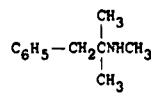
MEPHENTERMINE

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	U.S.	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.; U.S. Patent 2,597,445; May 28, 1952; assigned to Wyeth, Inc.

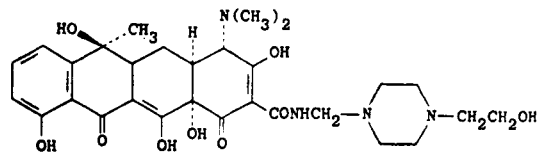
MEPICYCLINE

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

Structural Formula:



Chemical Abstracts Registry No.: 1110-80-1

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

Raw Materials

N-(β-Hydroxyethyl)diethylene diamine
p-Formaldehyde
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 Büchner 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.; U.S. Patent 3,149,114; September 15, 1964; assigned to Societe d'Etudes de Recherches et d'Applications Scientifiques et Medicales, France

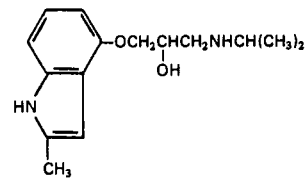
MEPINDOLOL

Therapeutic Function: β-Receptor blocker

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

Common Name: –

Structural Formula:



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

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

Raw Materials

4-Benzyloxy-2-dimethylamino-methylindole
Epichlorohydrin
Hydrogen
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 isopropyl amine, 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) & 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.

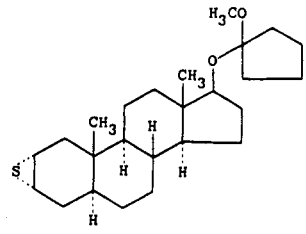
MEPITIOSTANE

Therapeutic Function: Antiestrogenic

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 & Engel p. 557
I.N. p. 594
Komeno, T.; U.S. Patent 3,567,713; March 2, 1971; assigned to Shionogi & Co.

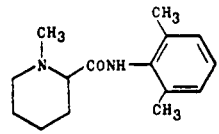
MEPIVACAINE

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)

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

Raw Materials

Ethyl bromide
N-Methylpipecolic acid ethyl ester
Magnesium
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 & 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.; U.S. Patent 2,799,679; July 16, 1957; assigned to AB Bofors, Sweden
Pettersson, B.G.; U.S. Patent 4,110,331; August 29, 1978; assigned to AB Bofors

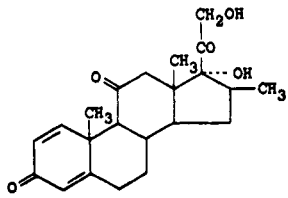
MEPREDNISONE

Therapeutic Function: Glucocorticoid

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

Common Name: 16β-methylprednisone

Structural Formula:



Chemical Abstracts Registry No.: 1247-42-3

Trade Name	Manufacturer	Country	Year Introduced
Betapar	Parke Davis	U.S.	1970
Betalone	Lepetit	France	–
Betapred	Schering	U.S.	–
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-methylprednisone. 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 g; sodium chloride, 8 g; 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 g; Bacto-peptone, 5 g; 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-methylcortisone in 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 & Engel p. 558
I.N. p. 595
Rausser, R. and Oliveto, E.P.; U.S. Patent 3,164,618; January 5, 1965; assigned to Schering Corporation

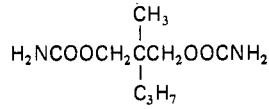
MEPROBAMATE

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	U.S.	1955
Miltown	Wallace	U.S.	1955
Meprotabs	Wallace	U.S.	1957
Meprospan	Wallace	U.S.	1958
Viobamate	Rowell	U.S.	1963
Meprocon	Consol. Midl. Co.	U.S.	1964
Canquil	Canfield	U.S.	1964
Klort	Lemmon	U.S.	1964
Equanil	Clin Midy	France	1967
SK-Bamate	SKF	U.S.	1971
Amepromamat	Arcana	Austria	–
Amosene	Ferndale	U.S.	–
Aneural	Wyeth	W. Germany	–
Ansietan	Italfarmaco	Italy	–
Ansiowas	Wassermann	Spain	–
Artolon	Roter	Neth.	–
Atraxin	Daiichi	Japan	–
Carb-A-Med	Chemieprodukte	Austria	–
Coprobate	Coastal	U.S.	–
Cyrpon	Tropon	W. Germany	–
Dabrobamat	Dabrowski	W. Germany	–
Dapaz	Alter	Spain	–
Deprol	Wallace	U.S.	–
Dormabrol	Kwizda	Austria	–
Dystoid	Makara	W. Germany	–
Ecuanil	Orfi	Spain	–
Edenal	Wassermann	Italy	–
Epikur	Agepha	Austria	–
Equagesic	Wyeth	U.S.	–
Erina	Sumitomo	Japan	–
Gene-Bamate	Franca	Canada	–
Harmonin	Yoshitomi	Japan	–
Kesso-Bamate	McKesson	U.S.	–
Lan-Dol	Bio-Chimique	Canada	–
Marbate	Mardale	U.S.	–
Meditran	Medic	Canada	–
Mepavlon	I.C.I.	U.K.	–
Meprate	DDSA	U.K.	–
Mepriam	Lennon	U.S.	–
Mepro	Rekah	Israel	–
Meproban	Draco	Sweden	–
Meprocon CMC	Consol. Midl. Co.	U.S.	–
Meprodil	Streuli	Switz.	–
Meprodiol	Pirri	Italy	–
Meprol	Lokman	Turkey	–
Mepron	Choseido	Japan	–
Mepron	Hamilton	Australia	–
Mepronel	Heather Drug	U.S.	–
Meprosa	Chemipharm	W. Germany	–
Meprotil	Brunner-Tillman	U.S.	–
Meriprobate	Meriot	Canada	–
Microbamat	Werfft	Austria	–
Midixin	Reid-Provident	U.S.	–
Miltaun	Mack	W. Germany	–
Misedant	Lemmon	U.S.	–
M.P. Trantabs	Martin-Phillips	U.S.	–

Trade Name	Manufacturer	Country	Year Introduced
My-Trans	Heather Drug	U.S.	–
Neo-Tran	Neo	Canada	–
Nervonus	Orion	Finland	–
Neuramate	Halsey	U.S.	–
Novamato	Torlan	Spain	–
Novomepro	Novopharm	Canada	–
Oasil	Simes	Italy	–
Paxin	Pierrel	Italy	–
Pensive	Norbrook	U.K.	–
Perequil	Lepetit	Italy	–
PMB Ayerst	Ayerst	U.S.	–
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	U.S.	–
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-n-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 & Engel p. 559
PDR pp. 634, 830, 1024, 1606, 1723, 1874, 1880, 1947, 1949
OCDS Vol. 1 p. 218 (1977) & 2, 21 (1980)
I.N. p. 595
REM p. 1072
Berger, F.M. and Ludwig, B.J.; U.S. Patent 2,724,720; November 22, 1955; assigned to Carter Products, Inc.