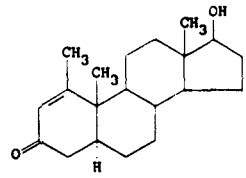
METHENOLONE ACETATE

Therapeutic Function: Anabolic

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

Common Name: –

Structural Formula:



(base)

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
Magnesium
$\Delta^{1,4,6}$-Androstatrien-17β-ol-3-one-17-acetate
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 0°C, 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-acetate obtained 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 & Engel p. 571
OCDS Vol. 1 p. 175 (1977)
I.N. p. 606
Schering A.G.; British Patent 977,082; *December* 2, 1944

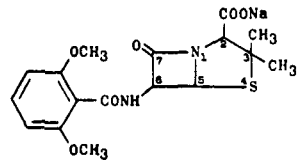
METHICILLIN SODIUM

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	U.K.	1960
Staphcillin	Bristol	U.S.	1960
Dimocillin	Squibb	U.S.	1961
Flabelline	Delagrange	France	1961
Celbenin	Beecham	U.S.	1973
Azapen	Pfizer	U.S.	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 & 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.; U.S. Patent 2,951,839; September 6, 1960

METHIONINE

Therapeutic Function: Lipotropic

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

Common Name: –

Structural Formula: $CH_3SCH_2CH_2CH(NH_2)COOH$

Chemical Abstracts Registry No.: 63-68-3

Trade Name	Manufacturer	Country	Year Introduced
Meonine	Ives	U.S.	1944
Lobamine	Opodex	France	1948

Trade Name	Manufacturer	Country	Year Introduced
Oradash	Lambda	U.S.	1955
Ammonil	Philips Roxane	U.S.	1957
Dyprin	Lincoln	U.S.	1958
Acimetion	Continental Pharm.	Belgium	–
Amino-Serv	Milex	U.S.	–
Amino-Plex	Tyson	U.S.	–
Antamon P.E.D.	Protea	S. Africa	–
Methnine	Medical Research	Australia	–
Monile	Cortunon	Canada	–
Ninol	Horner	Canada	–
Uracid	Wesley	U.S.	–
Unanap	N. Amer. Pharm.	U.S.	–
Urimeth	N. Amer. Pharm.	U.S.	–

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 U.S. Patent 2,584,496.

Then as described in U.S. 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 ammonium 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; U.S. Patent 2,584,496; February 5, 1952; assigned to Merck & Co., Inc.
Weiss, M.J.; U.S. Patent 2,732,400; January 24, 1956; assigned to American Cyanamid Company

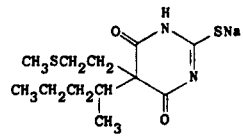
METHITURAL

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	U.S.	1956
Diogenal	Merck	—	—
Thiogenal	Merck	—	—

Raw Materials

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

Manufacturing Process

A solution of 69 g of sodium in 1,380 cc of absolute alcohol is mixed with 257.4 g of β-methyl-thioethyl-(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 230°C.

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 withdrawn 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.; U.S. Patent 2,802,827; August 13, 1957; assigned to Emanuel Merck (Germany)

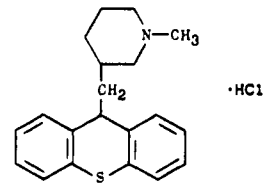
METHIXENE HYDROCHLORIDE

Therapeutic Function: Antispasmodic

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	U.K.	1963
Trest	Dorsey	U.S.	1965
Atosil	Teikoku	Japan	—
Cholinfall	Tokyo Tanabe	Japan	—
Dalpan	Grelan	Japan	—
Inoball	Sawai	Japan	—
Methixart	Fuso	Japan	—
Methyloxan	Nippon Shoji	Japan	—
Raunans	Kowa	Japan	—
Spasmenzyme	Salvoxyl-Wander	France	—
Thioperkin	Hokuriku	Japan	—

Raw Materials

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

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 & Engel p. 592
OCDS Vol. 1 p. 400 (1977) & 2, 413 (1980)
I.N. p. 628
REM p. 919
Schmutz, J.; U.S. Patent 2,905,590; September 22, 1959; assigned to The Wander Company

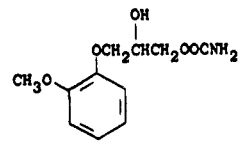
METHOCARBAMOL

Therapeutic Function: Skeletal 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	U.S.	1957
Lumirelax	Sarbach	France	1968
Robaxin	Brenner	W. Germany	1976
Carbametin	Uji	Japan	–
Carxin	Kanto	Japan	–
Delaxin	Ferndale	U.S.	–
Methocabal	Zeria	Japan	–

Trade Name	Manufacturer	Country	Year Introduced
Methocal	Daiko	Japan	–
Miowas	Wassermann	Italy	–
Myomethol	Abic	Israel	–
Parabaxin	Parmed	U.S.	–
Relax	Ion	Italy	–
Robamol	Cenci	Italy	–
Robaxisal	Robins	U.S.	–
Romethocarb	Robinson	U.S.	–
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 & 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.; U.S. Patent 2,770,649; November 13, 1956; assigned to A.H. Robins Company, Inc.

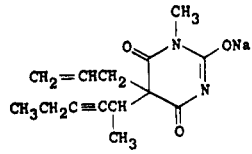
METHOHEXITAL SODIUM

Therapeutic Function: Anesthetic (intravenous)

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	U.S.	1960
Brietal	Lilly	U.K.	1961
Brevimytal	Lilly	W. Germany	1963
Brietal	Lilly	Italy	1963

Raw Materials

Ethyl acetylene (1-butyne)
Magnesium
Phosphorus tribromide
Sodium
Allyl bromide
Ethyl bromide
Acetaldehyde
Diethyl malonate
Ethanol
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 2-bromo-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 & Engel p. 578
PDR p. 1038
OCDS Vol. 1 p. 269 (1977)
I.N. p. 613
REM p. 1046
Doran, W.J.; U.S. Patent 2,872,448; February 3, 1959; assigned to Eli Lilly and Company

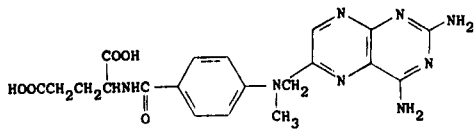
METHOTREXATE

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	U.S.	1955
Mexate	Bristol	U.S.	1979
Emtexate	Nordic	U.K.	1981
Folex	Adria	U.S.	1983
Abitrexate	Abic	Israel	—
Emthexate	Pharmachemie	Neth.	—
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°C 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 & Engel p. 579
PDR p. 1016
DOT 8 (11) 426 (1972) & 16 (5) 170 (1980)
I.N. p. 614
REM p. 1152
Wiecko, J.; U.S. Patent 4,057,548; November 8, 1977
Ellard, J.A.; U.S. Patent 4,080,325; March 21, 1978; assigned to U.S. Dept. of Health, Education and Welfare

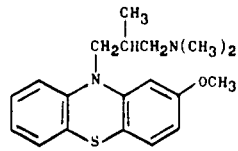
METHOTRIMEPRAZINE

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)

Trade Name	Manufacturer	Country	Year Introduced
Levoprome	Lederle	U.S.	1966
Hirnamin	Shionogi	Japan	–
Levaru	Mohan	Japan	–
Levomezine	Toho	Japan	–

Trade Name	Manufacturer	Country	Year Introduced
Levotomin	Shionogi	Japan	–
Nozinan	Farmalabor	Italy	–
Ronexine	Ikapharm	Israel	–
Sinogan	Rhodia Iberica	Spain	–
Sofmin	Dainippon	Japan	–
Veractil	May & Baker	U.S.	–

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

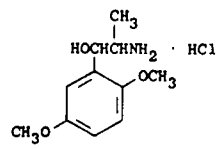
METHOXAMINE HYDROCHLORIDE

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	U.S.	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 & Engel p. 580
PDR p. 768
I.N. p. 614
REM p. 888
Baltzly, R., de Beer, E.J. and Buck, J.S.; U.S. Patent 2,359,707; October 3, 1944; assigned to Burroughs Wellcome & Co. (U.S.A.) Inc.

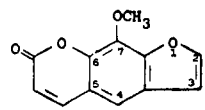
METHOXSALEN

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	Elder	U.S.	1955
Meloxine	Upjohn	U.S.	1958
Meladinine	Basoterm	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 & Engel.

References

Merck Index 5864
Kleeman & 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.; U.S. Patent 2,889,337; June 2, 1959; assigned to the U.S. Secretary of Agriculture
Glunz, L.J. and Dickson, D.E.; U.S. Patent 4,129,575; December 12, 1978; assigned to Thomas C. Elder, Inc.
Liebman, A.A. and Liu, Y.-Y.; U.S. Patent 4,147,703; April 3, 1979; assigned to Hoffmann-LaRoche, Inc.

METHOXYFLURANE

Therapeutic Function: Anesthetic (inhalation)

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

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

Structural Formula: $CH_3OCF_2CHCl_2$

Chemical Abstracts Registry No.: 76-38-0

Trade Name	Manufacturer	Country	Year Introduced
Penthrane	Abbott	U.S.	1962
Penthrane	Abbott	W. Germany	1962
Penthrane	Abbott	U.K.	1963
Anecotan	Spofa	Czechoslovakia	—
Methofane	Pitman-Moore	U.S.	—

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 U.S. 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 & Engel p. 581
PDR p. 547

I.N. p. 615
REM p. 1043
Larsen, E.R.; U.S. Patent 3,264,356; August 2, 1966; assigned to The Dow Chemical Company

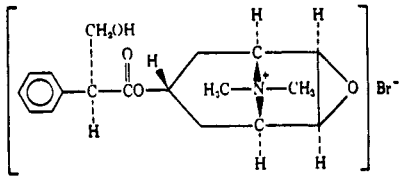
METHSCOPOLAMINE BROMIDE

Therapeutic Function: Antispasmodic

Chemical Name: 7-(3-hydroxy-1-oxo-2-phenylpropoxy)-9,9-dimethyl-3-oxa-9-azoniatricyclo-[3.3.1.$0^{2,4}$]nonane bromide

Common Name: Hyoscine methyl bromide

Structural Formula:



Chemical Abstracts Registry No.: 155-41-9

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

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 80 g (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 & Engel p. 582
PDR p. 1857
I.N. p. 508
REM p. 917
Visscher, F.E.; U.S. Patent 2,753,288; July 3, 1956; assigned to The Upjohn Company

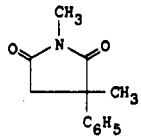
METHSUXIMIDE

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	U.S.	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 & 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.; U.S. Patent 2,643,257; June 23, 1953; assigned to Parke, Davis & Company

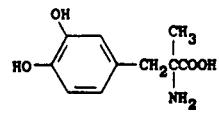
METHYLDOPA

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	U.K.	1962
Aldomet	MSD	Italy	1962
Aldomet	MSD	U.S.	1963
Aldomet	MSD-Chibret	France	1964
Adopal	Pharmacal	Finland	—
Aldomin	Teva	Israel	—
Aldoril	MSD	U.S.	—
Alphamex	Protea	S. Africa	—
Becanta	Kissei	Japan	—
Caprinol	Bayer	W. Germany	—
Dansul	Nippon Yakko	Japan	—
Desens	Nissin	Japan	—
Dimal	Protea	Australia	—
Domecin	Sankyo	Japan	—
Dopamet	Berk	U.S.	—
Dopamin	Hokuriku	Japan	—
Dopatec	Labatec	Switz.	—
Dopegyt	Gideon 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.	U.K.	—
Medopa	Kaigai	Japan	—
Medopal	A.L.	Norway	—

Trade Name	Manufacturer	Country	Year Introduced
Medopren	Dietopharma	Italy	–
Metholes	Taisho	Japan	–
Methoplain	Kowa	Japan	–
Nichidopa	Nichiiko	Japan	–
Novomedopa	Novopharm	Canada	–
Polinal	Boehr-Yamanouchi	Japan	–
Sembrina	Boehr. Mann.	Italy	–

Raw Materials

3-Hydroxy-4-methoxyphenylalanine
Hydrogen chloride

Manufacturing Process

The dl-α-methyl-3,4-dihydroxyphenylalanine may be made as described in U.S. Patent 2,868,818. Five-tenths of a gram of 3-hydroxy-4-methoxyphenylalanine was 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 U.S. 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 & Engel p. 583
PDR pp. 993, 1133
OCDS Vol. 1 p. 95 (1977)
DOT 10 (9) 323 (1974) & 19 (3) 170 (1983)
I.N. p. 618
REM p. 846
Pfister, K., III and Stein, G.A.; U.S. Patent 2,868,818; January 13, 1959; assigned to Merck & Co., Inc.
Jones, R.T., Krieger, K.H. and Lago, J.; U.S. Patent 3,158,648; November 24, 1964; assigned to Merck & Co., Inc.

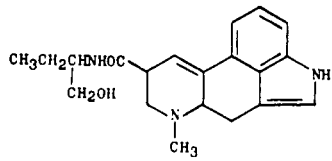
METHYLERGONOVINE MALEATE

Therapeutic Function: Oxytocic

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

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

Structural Formula:



(base)

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

Trade Name	Manufacturer	Country	Year Introduced
Methergine	Sandoz	U.S.	1948
Methergin	Sandoz	France	1953
Ergotrate	Lilly	U.S.	—
Levospan	Isei	Japan	—
Metenarin	Teikoku Zoki	Japan	—
Methylergobrevin	Arzneim. 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 ether 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 & Engel p. 584
PDR p. 1587
I.N. p. 619
REM p. 948
Stoll, A. and Hofmann, A.; U.S. Patent 2,265,207; December 9, 1941; assigned to Sandoz AG, Switzerland

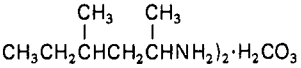
METHYLHEXANEAMINE CARBONATE

Therapeutic Function: Nasal decongestant

Chemical Name: 4-methyl-2-hexylamine carbonate

Common Name: —

Structural Formula:



$$(CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HNH_2)_2 \cdot H_2CO_3$$

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

Trade Name	Manufacturer	Country	Year Introduced
Forthane	Lilly	U.S.	1948

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 U.S. 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 con-

stant 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 U.S. Patent 2,386,273.

References

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

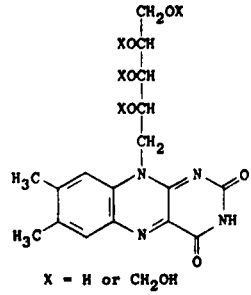
METHYLOL RIBOFLAVIN

Therapeutic Function: Enzyme Cofactor vitamin source

Chemical Name: See Structural Formula

Common Name: –

Structural Formula:



X = H or CH_2OH

Chemical Abstracts Registry No.: –

Trade Name	Manufacturer	Country	Year Introduced
Hyflavin	Endo	U.S.	1948

Raw Materials

Riboflavin
Formaldehyde

Manufacturing Process

100 g of riboflavin and 4 g 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.; U.S. Patent 2,587,533; February 26, 1952; assigned to Endo Products, Inc.

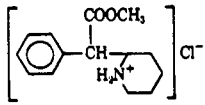
METHYLPHENIDATE HYDROCHLORIDE

Therapeutic Function: Psychostimulant

Chemical Name: α-phenyl-2-piperidineacetic acid methyl ester

Common Name: —

Structural Formula:



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

Trade Name	Manufacturer	Country	Year Introduced
Ritalin	Ciba	U.S.	1958
Rubifen	Rubio	Spain	—

Raw Materials

Phenyl acetonitrile
2-Chloropyridine
Methanol
Hydrogen
Sodium amide
Sulfuric acid
Hydrogen chloride

Manufacturing Process

As described in U.S. 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 ren-

dered alkaline with sodium carbonate. α-Phenyl-α-pyridyl-(2)-acetamide is precipitated thereby which melts at 134°C after recrystallization from ethyl acetate.

100 g 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 U.S. Patent 2,957,880.

References

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

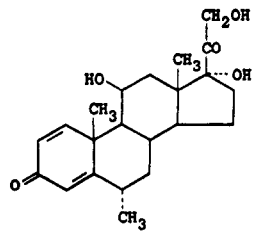
METHYLPREDNISOLONE

Therapeutic Function: Glucocorticoid

Chemical Name: 11β,17α,21-trihydroxy-6α-methyl-1,4-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	U.S.	1957
Medrol	Upjohn	France	1959
A-Methapred	Abbott	U.S.	1978
Solu-Medrol	Upjohn	Japan	1980
Caberdelta	Caber	Italy	—
Cortalfa	S.A.M.	Italy	—

Trade Name	Manufacturer	Country	Year Introduced
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	Gazeini	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
6-α-Methylhydrocortisone

Manufacturing Process

The following process description is taken from U.S. 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 & 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.; U.S. Patent 2,897,218; July 28, 1959; assigned to The Upjohn Company
Gould, D.H.; U.S. Patent 3,053,832; September 11, 1962; assigned to Schering Corporation

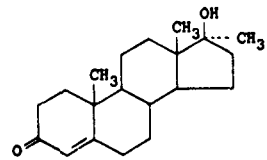
METHYLTESTOSTERONE

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	U.S.	1941
Oreton-M	Schering	U.S.	1941
Neo-Hombreol	Organon	U.S.	1941
Hormale	Key	U.S.	1958
Android-S	Brown	U.S.	–
Arcosterone	Arcum	U.S.	–
Climaterine	Lucien	France	–
Climatone	Paines & Byrne	U.K.	–
Dumone	Squibb	U.S.	–
Estan	Schering	U.S.	–
Gynosterone	Sam-On	Israel	–
Hormobin	Munir Sahin	Turkey	–
Malogen	Fellows-Testagar	U.S.	–
Orchisterone	Negroni	Italy	–
Seksfort	Uranium	Turkey	–
Steronyl	Kay	U.S.	–
Synandrets	Pfizer	U.S.	–
Testipron	Kwizda	Austria	–
Testomet	Protea	Australia	–
Testora	Alcon	U.S.	–
Testostelets	Barlow Cote	Canada	–
Testonic B	Sam-On	Israel	–
Testovis	Vister	Italy	–
Testred	I.C.N.	U.S.	–
Virilon	Star	U.S.	–

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 U.S. Patent 2,384,335.

References

Merck Index 6000
Kleeman & 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.; U.S. Patent 2,374,369; April 24, 1945; assigned to Ciba Pharmaceutical Products, Incorporated
Miescher, K. and Wettstein, A.; U.S. Patent 2,374,370; April 24, 1945; assigned to Ciba Pharmaceutical Products, Incorporated
Oppenauer, R.; U.S. Patent 2,384,335; September 4, 1945
Miescher, K.; U.S. Patent 2,386,331; October 9, 1945; assigned to Ciba Pharmaceutical Products, Incorporated
Miescher, K.; U.S. Patent 2,435,013; January 27, 1948; assigned to Ciba Pharmaceutical Products, Incorporated

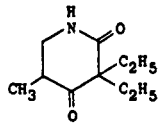
METHYPRYLON

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	U.S.	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-oxymethylene-piperidine 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-oxymethylene-piperidine 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 & Engel p. 590
PDR p. 1495
DOT 9 (6) 245 (1973)
I.N. p. 626
REM p. 1072
Frick, H. and Lutz, A.H.; U.S. Patent 2,680,116; June 1, 1954; assigned to Hoffmann-LaRoche Inc.

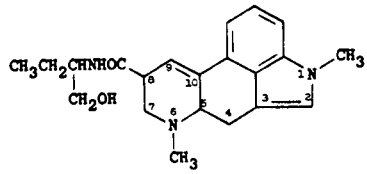
METHYSERGIDE MALEATE

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

Structural Formula:



(base)

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

Trade Name	Manufacturer	Country	Year Introduced
Sansert	Sandoz	U.S.	1962
Desernil	Sandoz	France	1962
Deseril	Sandoz	U.K.	1963

Raw Materials

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

Manufacturing Process

As described in U.S. 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 & 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.; U.S. Patent 3,113,133; December 3, 1963; assigned to Sandoz Ltd., Switzerland
Hofmann, A. and Troxler, F.; U.S. Patent 3,218,324; November 16, 1965; assigned to Sandoz Ltd., Switzerland

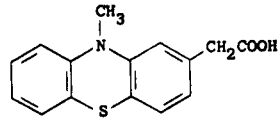
METIAZINIC ACID

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

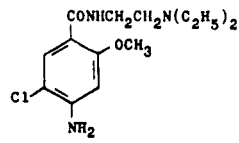
METOCLOPRAMIDE HCl

Therapeutic Function: Antiemetic

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

Common Name: –

Structural Formula:



(base)

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	U.K.	1967
Plasil	Richter	Italy	1967
Reglan	Robins	U.S.	1979
Metox	Steinhard	U.K.	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	Japan	–
Emesa	Mulda	Turkey	–
Emetisan	Phoenix	Argentina	–
Emperal	Neofarma	Finland	–
Gastronertron	Dolorgiet	W. Germany	–
Imperan	Bender	Austria	–
Kilozim	A.G.I.P.S.	Italy	–
Maxeran	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	Argentina	–
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	Teikoru Zoki	Japan	–
Viscal	Zoja	Italy	–

Raw Materials

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

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

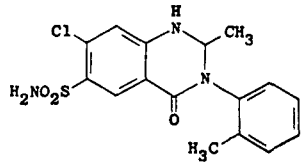
METOLAZONE

Therapeutic Function: Diuretic

Chemical Name: 7-chloro-1,2,3,4-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	U.K.	1973
Zaroxolyn	Pennwalt	U.S.	1974
Diulo	Searle	U.S.	1978
Zaroxolyn	Searle	W. Germany	1978
Zaroxolyn	Sandoz	Switz.	1978
Zaroxolyn	I.S.F.	Italy	1981
Normeran	Sankyo	Japan	1982
Metenix	Hoechst	U.K.	–
Oldren	Roemmers	Argentina	–

Raw Materials

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

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 ¾ 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 U.S. Patent 3,360,518.

References

Merck Index 6024
Kleeman & 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.; U.S. Patent 3,360,518; December 26, 1967; assigned to Wallace & Tiernan Inc.
Shetty, B.V.; U.S. Patent 3,557,111; January 19, 1971

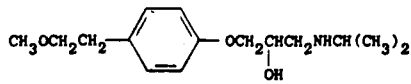
METOPROLOL TARTRATE

Therapeutic Function: Beta-adrenergic blocker

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

Common Name: –

Structural Formula:



(base)

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

Trade Name	Manufacturer	Country	Year Introduced
Betaloc	Astra	U.K.	1975
Lopressor	Geigy	U.K.	1975
Beloc	Astra	W. Germany	1976
Lopressor	Ciba-Geigy	W. Germany	1976
Lopressor	Ciba-Geigy	Italy	1978
Selomen	Bracco	Italy	1978
Lopressor	Ciba Geigy	U.S.	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
Sodium bicarbonate
Tartaric acid
p-(β-Methoxyethyl)phenol
Epichlorohydrin

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 0.35 mm Hg.

1,2-Epoxy-3-[p-(β-methoxyethyl)-phenoxy]-propane (16.7 g) 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 2N HCl. 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 & Engel p. 595
PDR p. 894
OCDS Vol. 2 p. 109 (1980)
DOT 11 (9) 360 (1975) & 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.; U.S. Patent 3,873,600; March 25, 1975

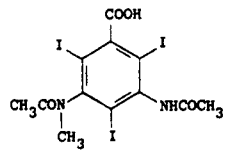
METRIZOIC ACID

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 Winthrop	U.S.	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), 5N 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 & Engel p. 597
I.N. p. 631
REM p. 1270
Holtermann, H., Haugen, L.G., Nordal, V. and Haavaldsen, J.L.; U.S. Patent 3,178,473; April 13, 1965; assigned to Nyegaard & Co. A/S (Norway)

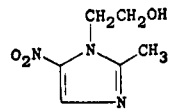
METRONIDAZOLE

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 & Baker	U.K.	1960
Flagyl	Rhone-Poulenc	W. Germany	1961
Flagyl	Farmitalia	Italy	1962
Flagyl	Searle	U.S.	1963
Satric	Savage	U.S.	1982
Metryl	Lemmon	U.S.	1982
Metro IV	McGaw	U.S.	1982
Protostat	Ortho	U.S.	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	–

Trade Name	Manufacturer	Country	Year Introduced
Klion	Kobanyai	Hungary	–
Kreucosan	Kreussler	W. Germany	–
Medazol	Belupo	Yugoslavia	–
Meronidal	Kissei	Japan	–
Metrajil	Mulda	Turkey	–
Metrogil	Ikapharm	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	–
Tricho Cordes	Icthyol	W. Germany	–
Tricho-Gynaedron	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.	U.K.	–
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 (30 mm 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 & Engel p. 597
PDR pp. 830, 872, 876, 993, 1034, 1305, 1605, 1670, 1723, 1999
OCDS Vol. 1 p. 240 (1977)
DOT 13 (4) 147 (1977) & 17 (1) 34 (1981)
I.N. p. 632
REM p. 1222
Jacob, R.M., Regnier, G.L. and Crisan, C.; U.S. Patent 2,944,061; July 5, 1960; assigned to Societe des Usines Chimiques Rhone-Poulenc, France

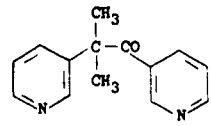
METYRAPONE

Therapeutic Function: Diagnostic aid (pituitary function)

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

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 54-36-4

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

Raw Materials

3-Acetylpyridine
Sulfuric acid
Hydrogen
Hydroxylamine sulfate

Manufacturing Process

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

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