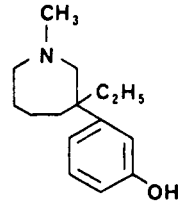
MEPTAZINOL

Therapeutic Function: Analgesic

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

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: —

Trade Name	Manufacturer	Country	Year Introduced
Meptid	Wyeth	U.K.	1983

Raw Materials

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

Manufacturing Process

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

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

The azepinone (9.1 g) in dry tetrahydrofuran (50 ml) and ether (50 ml) was added dropwise to a stirred suspension of aluminum lithium hydride (7.5 g) in dry ether (50 ml). After heating under reflux for 3 hours the reaction mixture was worked up and distilled yielding 7.66 g of a compound which was a colorless oil, BP 108°C to 110°C/0.01 mm.

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

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

References

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

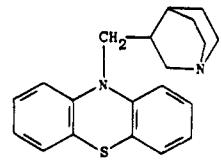
MEQUITAZINE

Therapeutic Function: Antihistaminic

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

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 29216-28-2

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

Raw Materials

Phenothiazine
Sodium amide
3-Chloromethyl quinuclidine HCl

Manufacturing Process

30 g of phenothiazine were added, all at once, to a suspension of 6 g of sodium amide in 240 ml of anhydrous xylene. The mixture was agitated and heated to reflux. When evolution of ammonia ceased (5 hours), 15 g of 3-chloromethyl-quinuclidine hydrochloride were added portionwise over a period of 50 minutes and reflux was then maintained for 22 hours. After cooling to room temperature, 250 ml of distilled water and 250 ml of ethyl acetate were added to the reaction mixture. The aqueous phase was decanted and extracted twice with a total of 250 ml of methyl acetate. The combined organic extracts were extracted three

times with a total of 750 ml of a 10% aqueous solution of tartaric acid. The combined acid solutions were treated with 5 g of animal charcoal, filtered and rendered alkaline on an ice bath with 96 ml of 10 N aqueous caustic soda. The oil which separated was extracted three times with a total of 1,500 ml of ethyl acetate. The combined organic extracts were washed to neutrality by washing twice with a total of 1 liter of distilled water, dried over anhydrous magnesium sulfate and evaporated under reduced pressure on a water bath at 45°C. 17 g of oil were obtained which was purified by chromatography on an inert alumina column. 13.3 g of crystallized product were obtained. 10-(3-Quinuclidinyl-methyl)-phenothiazine having a MP of 130°C to 131°C was obtained by recrystallization in boiling acetonitrile.

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

References

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

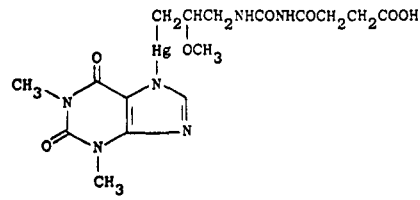
MERALLURIDE

Therapeutic Function: Diuretic

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

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

Structural Formula:



Chemical Abstracts Registry No.: 8069-64-5

Trade Name	Manufacturer	Country	Year Introduced
Mercuhydrin	Merrell National	U.S.	1943
Mercardac	Parke Davis	U.S.	–
Mercadon	Parke Davis	U.S.	–

Raw Materials

Allyl carbamide
Mercury acetate
Succinic anhydride
Theophylline

Manufacturing Process

First, to produce the mercury component, a pulverized mixture of 50 g of allylcarbamide and 50 g of succinic anhydride is heated for 30 minutes at 110°C. After cooling the fused

mass is ground with 50 cc of cold water and the crystalline mass after quick filtering from the liquid is recrystallized from hot water. The white crystalline needles having a MP of 142° to 144°C are allyl-succinyl-carbamide. In order to produce a mercury compound thereof a mixture of 20 g of the allyl-succinyl-carbamide and 30 g of mercury acetate is shaken for 3 hours with methanol. The scarcely soluble precipitate of the mercury compound after filtration is washed with methanol and with water and dried in vacuum. The white powder melts at 185° to 186°C under decomposition. Then, condensation with an equimolar proportion of theophylline yields meralluride.

References

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

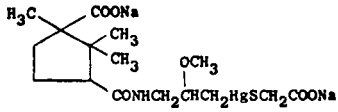
MERCAPTOMERIN SODIUM

Therapeutic Function: Diuretic

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

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 21259-76-7

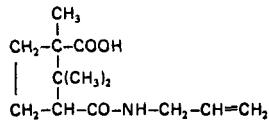
Trade Name	Manufacturer	Country	Year Introduced
Thiomerin	Wyeth	U.S.	1949
Diucardyn	Ayerst	–	–
Thio-Novurit	Chinoin	Hungary	–

Raw Materials

dl-N-Allyl-camphoramic acid
Sodium methylate
Mercuric acetate
Thioglycolic acid

Manufacturing Process

(A) Preparation of dl-N-(γ-Chloromercuri-β-Methoxy)-Propylcamphoramic Acid: A suspension of 31.9 g (= 0.10 M) of mercuric acetate in 25 ml of methanol is stirred for 30 minutes at room temperature in a 4-necked flask equipped with stirrer, dropping funnel, drying tube and thermometer. To this suspension is added dropwise and with stirring, a solution of 23.9 g (= 0.10 M) of dl-N-allyl-camphoramic acid



in 65 ml of methanol over a period of 30 minutes. The temperature of the reaction mixture should not rise over 30°C. The stirring is continued for one hour. The reaction mixture is allowed to stand at room temperature overnight in the dark to complete the reaction. A solution of 5.9 g (= 0.10 M) of sodium chloride in 25 ml of water is added and the stirring is continued for four hours. The small amount of gray precipitate produced is removed by centrifuging. The colorless, clear supernatant is concentrated to about half of its original volume and then dropped into 300 ml of water with stirring.

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

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

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

To 50 cc of a carefully purified aqueous solution of the sodium salt of N(γ-chloromercuri-β-methoxy-propyl)-d-α-camphoramic acid containing 40 mg of mercury per cc is added 10 cc of a solution containing 1.14 g (1 mol equivalent) of sodium thioglycollate and the mixture is then evaporated to dryness at room temperature and reduced pressure in the presence of a desiccant. The product is an amorphous white powder which decomposes at 156° to 158°C (uncorr.), and which was found on analysis to have a mercury content of 33.0%, according to U.S. Patent 2,576,349.

References

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

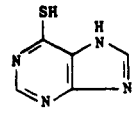
MERCAPTOPURINE

Therapeutic Function: Cancer chemotherapy

Chemical Name: 6-purinethiol

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 50-44-2

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

Raw Materials

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

Manufacturing Process

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

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

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

References

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

MESNA

Therapeutic Function: Mucolytic

Chemical Name: 2-Mercaptoethane sulfonic acid sodium salt

Common Name: –

Structural Formula: $[HSCH_2CH_2SO_3]^-Na^+$

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

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

Raw Materials

β-S-Thiuronium ethanesulfonate
Ammonia

Manufacturing Process

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

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

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

Although the preparation of β-mercaptoethanesulfonic acid through the ammonolysis reaction is the preferred method, it is also possible to prepare the sulfonic acid by the sodium hydroxide hydrolysis of β-S-thiuronium ethanesulfonate followed by the ion exchange treatment. The resulting acid, however, is generally not as satisfactory as that prepared by the ammonolysis reaction.

References

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

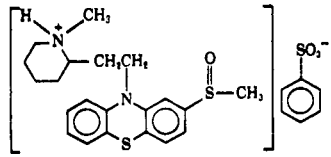
MESORIDAZINE BESYLATE

Therapeutic Function: Tranquilizer

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

Common Name: –

Structural Formula:



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

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

Raw Materials

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

Manufacturing Process

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

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

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

of benzene, 20 cc of concentrated caustic soda are added until the phenolphthalein reaction is alkaline, and the separated oily base is taken up in a total of 150 cc of benzene.

After having been washed with 50 cc of water the benzene layer is dried over potassium carbonate, filtered, allowed to stand over 10 g of alumina for about 1½ hours for partial decolorization, filtered again and concentrated under reduced pressure. The oily base which remains as a residue is directly converted into the tartrate. A solution cooled to 0°C, of 6.50 g of the free base in 100 cc of acetic acid ethyl ester is thoroughly shaken and poured into an ice cold solution of 2.66 g of tartaric acid in 410 cc of acetic acid ethyl ester. The precipitated, analytically pure, tartrate of 3-methylsulfinyl-10-[2'-N-methyl-piperidyl-2'')-ethyl-1'] -phenothiazine melts at 115° to 120°C (foam formation) and sinters above 80°C. The base is reacted with benzene sulfonic acid in a suitable solvent to give the besylate.

References

Merck Index 5755
Kleeman & Engel p. 564
PDR p. 681
OCDS Vol. 1 p. 389 (1977)
DOT 6 (6) 211 (1970) & 9 (6) 227 (1973)
I.N. p. 601
REM p. 1089
Renz, J., Bourquin, J.-P. and Schwarb, G.; U.S. Patent 3,084,161; April 2, 1963; assigned to Sandoz Ltd., Switzerland

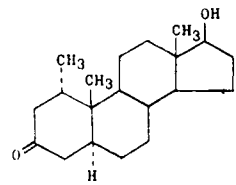
MESTEROLONE

Therapeutic Function: Androgen

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

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 1424-00-6

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

Raw Materials

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

Manufacturing Process

500 mg of 1α-methyl-androstan-17β-ol-3-one-17-acetate are heated under reflux for 90 minutes in a nitrogen atmosphere in 5 ml of 4% methanolic sodium hydroxide solution. The reaction mixture is then stirred into ice water, the precipitated product filtered with suction and recrystallized from isopropyl ether. 1α-Methyl-androstan-17β-ol-3-one melts at 203.5° to 205°C.

References

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

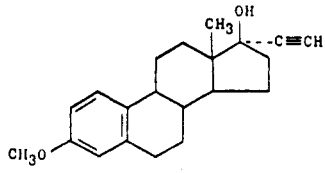
MESTRANOL

Therapeutic Function: Estrogen

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

Common Name: 17α-ethynylestradiol 3-methyl ether

Structural Formula:



Chemical Abstracts Registry No.: 72-33-3

Trade Name	Manufacturer	Country	Year Introduced
Enovid	Searle	U.S.	1957
Ortho-Novum	Ortho	U.S.	1963
Enovid-E	Searle	U.S.	1964
Norinyl	Syntex	U.S.	1964
C-Quens	Lilly	U.S.	1965
Ovulen	Searle	U.S.	1966
Conceplan	Gruenenthal	W. Germany	–
Conovid	Searle	U.K.	–
Enavid	Dainippon	Japan	–
Estalor	Lilly	U.S.	–
Gestamestrol	Hermal	W. Germany	–
Lutedione	Teikoku Zoki	Japan	–
Lyndiol	Organon-Sankyo	Japan	–
Metrulen	Searle	U.K.	–
Noracycline	Ciba Geigy	France	–
Noriday	Syntex	U.S.	–
Norinyl	Syntex	U.S.	–
Norluten	Shionogi	Japan	–

Trade Name	Manufacturer	Country	Year Introduced
Norquen	Syntex	U.S.	–
Nuriphasic	Noury Pharma	W. Germany	–
Orgaluton	Organon	U.K.	–
O.V. 28	Biosedra	France	–
Ovanon	Organon	U.K.	–
Ovastol	Rendell	U.K.	–

Raw Materials

3-Methoxy-$\Delta^{1,3,5}$-estratrien-17-one
Acetylene

Manufacturing Process

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

References

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

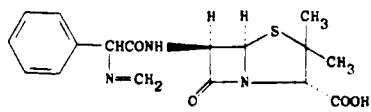
METAMPICILLIN SODIUM

Therapeutic Function: Antibacterial

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

Common Name: –

Structural Formula:



(base)

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

Trade Name	Manufacturer	Country	Year Introduced
Magnipen	Clin-Comar-Byla	Italy	1969
Magnipen	Clin Midy	France	1970

Trade Name	Manufacturer	Country	Year Introduced
Actuapen	Larma	Spain	–
Ampilprats	Prats	Spain	–
Apliopenil	Miluy	Spain	–
Co-Metampicil	Sanchez-Covisa	Spain	–
Daniven	Aldon	Spain	–
Doctamicina	Aristegui	Spain	–
Dompil	Spyfarma	Spain	–
Durmetan	Durban	Spain	–
Fedacilina	Fedal	Spain	–
Janopen	Janovich	Spain	–
Madecilina	Made	Spain	–
Maipen	Maipe	Spain	–
Mempil	Kairon	Spain	–
Metabacter	Rubio	Spain	–
Metacidan	Cidan	Spain	–
Meta-Ferran	Ferran	Spain	–
Metakes	Kessler	Spain	–
Metambac	Wolner	Spain	–
Metampicef	Cecef	Spain	–
Metamplimedix	Medix	Spain	–
Metiskia	Iskia	Spain	–
Ocelina	Roux-Ocefa	Argentina	–
Pluriespec	Vir	Spain	–
Ruticina	Bernabo	Argentina	–
Tisquibron	Bryan	Spain	–
Venzoquimpe	Quimpe	Spain	–
Vigocina	Europa	Spain	–

Raw Materials

6-[D(-)-alpha(aminophenylacetamido)] penicillanic acid (ampicillin)
Sodium bicarbonate
Formaldehyde

Manufacturing Process

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

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

References

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

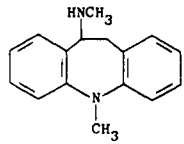
METAPRAMINE

Therapeutic Function: Antidepressant

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

Common Name: –

Structural Formula:



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

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

Raw Materials

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

Manufacturing Process

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

The aqueous acid solution is rendered alkaline by adding 2N sodium hydroxide solution. After extracting with diethyl ether (3 times 100 cc), drying the extracts over potassium carbonate, treating them with decolorizing charcoal, filtering and evaporating the ether, a yellowish oil (0.9 g), identified as 5-methyl-10-methylamino-10,11-dihydro-dibenzo[b,f] azepine, is obtained in a yield of 37.5%.

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

References

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

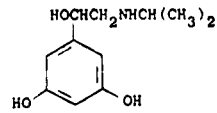
METAPROTERENOL SULFATE

Therapeutic Function: Bronchodilator

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

Common Name: Orciprenaline sulfate

Structural Formula:



(base)

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

Trade Name	Manufacturer	Country	Year Introduced
Alupent	Boehr. Ingel.	W. Germany	1961
Dosalupent	Boehr. Ingel.	Italy	1963
Alupent	Badrial	France	1966
Alupent	Boehr. Ingel.	U.S.	1973
Metaprel	Dorsey	U.S.	1973
Alotec	Tanabe	Japan	–
Astmopent	Polfa	Poland	–
Astop	Rafa	Israel	–
Lenasma	Ravasini	Italy	–
Novasmasol	Zambeletti	Italy	–

Raw Materials

3,5-Diacetoxyacetophenone
Isopropylamine
Bromine
Hydrogen

Manufacturing Process

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

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

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

References

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

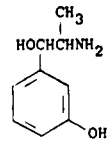
METARAMINOL

Therapeutic Function: Hypertensive

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

Common Name: m-hydroxynorephedrine; m-hydroxypropadrine; metaradrine

Structural Formula:



Chemical Abstracts Registry No.: 54-49-9

Trade Name	Manufacturer	Country	Year Introduced
Aramine	MSD	U.S.	1952
Pressoral	Travenol	U.S.	1963
Pressonex	Winthrop	U.S.	1963
Aramine	MSD-Chibret	France	1963
Araminium	Sharp & Dohme	W. Germany	—
Araminon	Merck-Banyu	Japan	—
Icopal B	Bayer	—	—
Levicor	Bioindustria	Italy	—
Metaraminol	Bristol	U.S.	—

Raw Materials

m-Hydroxyphenylethyl ketone
Butyl nitrite
Hydrogen

Manufacturing Process

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

10.8 parts of the meta ketone is dissolved in about 125 parts of absolute alcohol containing 5.6 parts of hydrogen chloride. The solution is agitated with a catalyst such as the palladium catalyst above described in an atmsophere of hydrogen until no more hydrogen is absorbed. This requires from 60 to 90 minutes or more. When reduction is complete the catalyst is filtered off and the filtrate evaporated to dryness by being placed in a desiccator at ordinary temperature.

The residue is the hydrochloride of m-hydroxyphenyl-α-aminoethyl ketone. This is purified by recrystallization from absolute alcohol. It is then dissolved in 200 parts of water and agitated with a further quantity of the palladium catalyst in an atmosphere of hydrogen until saturated. The product thus recovered from the solution is the hydrochloride

of m-hydroxyphenylpropanol amine. After recrystallization from absolute alcohol this melts at 177°C. The corresponding free base can be prepared from the hydrochloride by treatment with ammonia, according to U.S. Patent 1,995,709.

Metaraminol is often used in the form of the bitartrate.

References

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

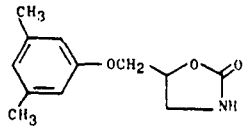
METAXALONE

Therapeutic Function: Skeletal muscle relaxant

Chemical Name: 5-(3,5-dimethylphenoxymethyl)-2-oxazolidinone

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 1665-48-1

Trade Name	Manufacturer	Country	Year Introduced
Skelaxin	Robins	U.S.	1962

Raw Materials

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

Manufacturing Process

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

References

Merck Index 5785
Kleeman & Engel. p.571

PDR p. 783
OCDS Vol. 1 p. 119 (1977)
I.N. p. 606
REM p. 927
Lunsford, C.D.; U.S. Patent 3,062,827; November 6, 1962; assigned to A.H. Robins Company, Inc.

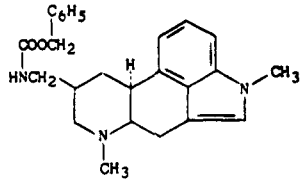
METERGOLINE

Therapeutic Function: Analgesic

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

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

Structural Formula:



Chemical Abstracts Registry No.: 17692-51-2

Trade Name	Manufacturer	Country	Year Introduced
Liserdol	Farmitalia	Italy	1970

Raw Materials

1-Methyl-dihydro-lysergamine
Carbobenzoxy chloride

Manufacturing Process

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

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

References

Merck Index 5790
I.N. p. 606

Camerino, B., Patelli, B. and Glaesser, A.; U.S. Patent 3,238,211; March 1, 1966; assigned to Societa Farmaceutici Italia, Italy

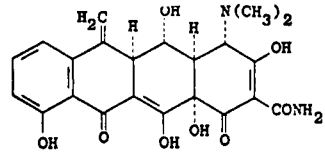
METHACYCLINE

Therapeutic Function: Antibiotic

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

Common Name: 6-methylene-5-hydroxytetracycline

Structural Formula:



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

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

Trade Name	Manufacturer	Country	Year Introduced
Metagram	Zanardi	Italy	–
Metilenbiotic	Coli	Italy	–
Microcilina	Biotrading	Italy	–
Mit-Ciclina	Von Boch	Italy	–
Molciclina	Molteni	Italy	–
Optimicine	Biochemie	Austria	–
Ossirondil	Gazzini	Italy	–
Paveciclina	I.B.P.	Italy	–
Physiomycine	Roland-Marie	France	–
Piziacina	Farmochimica	Italy	–
Plurigram	Lafare	Italy	–
Prontomicina	Tosi-Novara	Italy	–
Quickmicina	Panthox & Burck	Italy	–
Radiomicina	Radiopharma	Italy	–
Rindex	Sidus	Italy	–
Rotilen	Amelix	Italy	–
Sernamicina	Pharma Williams	Italy	–
Stafilon	A.G.I.P.S.	Italy	–
Tachiciclina	C.T.	Italy	–
Tetrabios	Ausonia	Italy	–
Tetranovo	Totalpharm	Italy	–
Tiberciclina	Tiber	Italy	–
Ticomicina	Benedetti	Italy	–
Treis-Ciclina	Ecobi	Italy	–
Valcin	Chemil	Italy	–
Vitabiotic	Pharmex	Italy	–
Wassermicina	Wassermann	Italy	–
Yatrociclina	Italfarmaco	Italy	–
Zermicina	Pulitzer	Italy	–

Raw Materials

Oxytetracycline
Sulfur trioxide
Hydrogen fluoride

Manufacturing Process

To a stirred solution of 4.6 g (0.01 mol) of anhydrous oxytetracycline in 40 ml of dry tetrahydrofuran is added 3.5 g (0.021 mol) of pyridine-sulfur trioxide complex. After 16 hours of stirring at room temperature, the resulting suspension is filtered, and the solid is slurried with 25 ml of 2% hydrochloric acid for 10 minutes, filtered and thoroughly washed with methanol followed by ether. The pale yellow crystalline 5-oxytetracycline-6, 12-hemiketal-12-sulfuric acid ester melts at 210°C.

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

References

Merck Index 5798

Kleeman & Engel p. 567
PDR p. 1881
OCDS Vol. 2 p. 227 (1980)
DOT 1 (1) 10 (1965)
I.N. p. 603
REM p. 1205
Blackwood, R.K., Rennhard, H.H., Beereboom, J.J. and Stephens, C.R., Jr.; U.S. Patent 2,984,686; May 16, 1961; assigned to Chas. Pfizer & Co., Inc.
Blackwood, R.K.; U.S. Patent 3,026,354; March 20, 1962; assigned to Chas. Pfizer & Co., Inc.

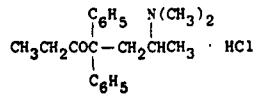
METHADONE HYDROCHLORIDE

Therapeutic Function: Narcotic analgesic

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

Common Name: Amidone hydrochloride

Structural Formula:



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

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

Raw Materials

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

Manufacturing Process

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

References

Merck Index 5799
Kleeman & Engel p. 573
PDR pp. 1048, 1061, 1571

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

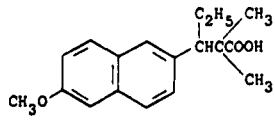
METHALLENESTRIL

Therapeutic Function: Estrogen

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

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 517-18-0

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

Raw Materials

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

Manufacturing Process

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

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

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

(A) Obtaining a β-Ketonic Ester by Reacting Ethyl Bromoisobutyrate with Cyanonerolin: 9 g of cyanonerolin are heated in a reflux apparatus for 40 minutes with 7 g of zinc and 19 g of ethyl bromoisobutyrate in the presence of 150 cc of anhydrous benzene. After cooling, the mixture is filtered to eliminate unreacted zinc and is hydrolyzed by stirring for one hour with dilute sulfuric acid (10 cc of sulfuric acid to 200 cc of water). The benzene layer is washed, dried and the solvent is eliminated. It is purified by recrystallization in methyl alcohol. 12.5 g of ketonic ester (MP = 72.5° to 73.5°C) are thus obtained in the form of large prismatic crystals.

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

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

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

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

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

References

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

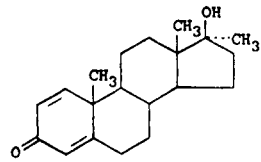
METHANDROSTENOLONE

Therapeutic Function: Androgen; anabolic

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

Common Name: Methandienone

Structural Formula:



Chemical Abstracts Registry No.: 72-63-9

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

Raw Materials

Bacterium *Didymella lycopersici*
17β-Methyl testosterone
Selenium dioxide

Manufacturing Process

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

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

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

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

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

References

Merck Index 5810
Kleeman & Engel p. 570
OCDS Vol. 1 p. 173 (1977)
I.N. p. 605
REM p. 998
Wettstein, A., Hunger, A., Meystre, C. and Ehmann, L.; U.S. Patent 2,900,398; August 18, 1959; assigned to Ciba Pharmaceutical Products, Inc.
Wettstein, A., Vischer, E. and Meystre, C.; U.S. Patent 2,929,763; March 22, 1960; assigned to Ciba Pharmaceutical Products, Inc.

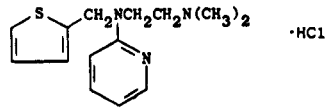
METHAPYRILENE HYDROCHLORIDE

Therapeutic Function: Antihistaminic

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

Common Name: Thenylpyramine hydrochloride

Structural Formula:



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

Trade Name	Manufacturer	Country	Year Introduced
Thenylene	Abbott	U.S.	1947
Pyrathyn	Davis Sly	U.S.	1947
Histadyl	Lilly	U.S.	1948
Semikon	Beecham	U.S.	1949
Lullamin	Reed Carnrick	U.S.	1954
Dozar	Tutag	U.S.	1956
Allergin	Myers-Carter	U.S.	—
Allerest	Pharmacraft	U.S.	—
Brexin	Savage	U.S.	—
Citra	Boyle	U.S.	—

Trade Name	Manufacturer	Country	Year Introduced
Ephed-Organidin	Wallace	U.S.	–
Excedrin P.M.	Bristol-Myers	U.S.	–
Histadyl	Lilly	U.S.	–
M.P.	Dymond	Canada	–
Sedanoct	Woelm-Pharma	W. Germany	–
Contac	Vonora	W. Germany	–
Co-Pyronil	Lilly	Italy	–

Raw Materials

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

Manufacturing Process

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

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

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

References

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

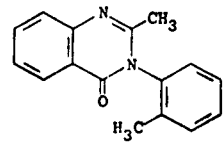
METHAQUALONE

Therapeutic Function: Hypnotic

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

Common Name: Metolquizolone; ortonal

Structural Formula:



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

Trade Name	Manufacturer	Country	Year Introduced
Quaalude	Lemmon	U.S.	1965
Sopor	Amer. Crit. Care	U.S.	1967
Somnafac	Cooper	U.S.	1968
Parest	Lemmon	U.S.	1969
Quaalude	Rorer	Italy	1969
Optimil	Wallace	U.S.	1972
Aqualon	Arcana	Austria	–
Cateudyl	Cavor	Belgium	–
Citexal	Draco	Sweden	–
Divinoctal	I.S.H.	France	–
Dormigoa	Scheurich	W. Germany	–
Dormir	Langley	Australia	–
Dormutil	Isis-Chemie	E. Germany	–
Hyptor	Bio-Chimique	Canada	–
Hyminal	Eisai	Japan	–
Mandrax	I.S.H.	France	–
Mequelon	Merck-Frosst	Canada	–
Meroctan	Sanwa	Japan	–
Methadorm	Eri	Canada	–
Metasedil	Cooper	Switz.	–
Mollinox	Asperal	Belgium	–
Motolon	Chinoin	Hungary	–
Nene	Sankyo	Japan	–
Nobadorm	Streuli	Switz.	–
Normi-Nox	Herbrand	W. Germany	–
Normorest	Doitsu-Aoi	Japan	–
Noxybel	Probel	Belgium	–
Oblioser	Gamaprod.	Australia	–
Optinoxan	Robisch	W. Germany	–
Parmilene	Chiesi	Italy	–
Paxidorm	Wallace	U.S.	–
Pexaqualone	Therapex	Canada	–
Pro-Dorm	Schurholz	W. Germany	–
Revonal	Merck	U.K.	–
Rouqualone	Rougier	Canada	–
Sedalone	Pharbec	Canada	–
Sleepinal	Medichem	Australia	–
Somnium	Fargal	Italy	–
Sovelin	Weifa	Norway	–
Sovinal	N.D. & K.	Denmark	–
Spasmipront	Mack	W. Germany	–
Tiqualone	Barlow Cote	Canada	–
Tualone	I.C.N.	Canada	–

Raw Materials

Anthranilic acid
o-Toluidine
Acetic anhydride
Hydrogen chloride

Manufacturing Process

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

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

References

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

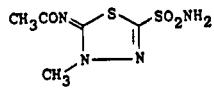
METHAZOLAMIDE

Therapeutic Function: Carbonic anhydrase inhibitor

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

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 554-57-4

Trade Name	Manufacturer	Country	Year Introduced
Neptazane	Lederle	U.S.	1959
Neptazane	Theraplix	France	1961

Raw Materials

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

Manufacturing Process

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

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

References

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

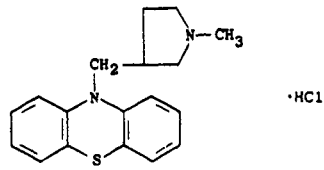
METHDILAZINE HYDROCHLORIDE

Therapeutic Function: Antipruritic

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

Common Name: –

Structural Formula:



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

Trade Name	Manufacturer	Country	Year Introduced
Tacaryl	Westwood	U.S.	1960
Dilosyn	Duncan Flockhart	U.K.	–
Disyncran	Allard	France	–
Tacryl	Pharmacia	Sweden	–

Raw Materials

1-Methyl-3-pyrrolidylmethyl chloride
Phenothiazine
Hydrogen chloride

Manufacturing Process

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

References

Merck Index 5826
Kleeman & Engel p. 577
PDR p. 1895
OCDS Vol. 1 p. 387 (1977)
I.N. p. 611
REM p. 1129
Feldkamp, R.F. and Wu, Y.H.; U.S. Patent 2,945,855; July 19, 1960; assigned to Mead Johnson & Company

METHENAMINE HIPPURATE

Therapeutic Function: Antibacterial (urinary)

Chemical Name: Hexamethylenetetramine hippurate

Common Name: –

Structural Formula: $C_6H_5CONHCH_2COOH{\cdot}(CH_2)_6N_4$

Chemical Abstracts Registry No.: 5714-73-8

Trade Name	Manufacturer	Country	Year Introduced
Hiprex	Merrell National	U.S.	1967
Hiprex	Riker	U.K.	1971
Hiprex	Kettelhack	W. Germany	1975
Hipeksal	Leiras	Finland	–
Hippuran	Orion	Finland	–
Lisogerm	Labofarma	Brazil	–
Urotractan	Klinge	W. Germany	–

Raw Materials

Hexamethylenetetramine
Hippuric acid

Manufacturing Process

179 g (1 mol) hippuric acid (benzoyl glycine) and 140 g (1 mol) hexamethylenetetramine were heated under reflux in 500 ml methanol. The small amount of water necessary to give a clear, homogeneous solution was added to the resulting reaction mixture which was then evaporated to dryness. The residue soon crystallized, a procedure that could be greatly accelerated by seeding with crystals of hexamethylenetetramine hippurate from a previous preparation. The resulting solid product was broken up and pulverized. Hexamethylenetetramine hippurate is stable on exposure to air and is soluble in water and alcohol. It melts at 105° to 110°C.

References

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